Vitamin D deficiency and its role in chronic nonspecific musculoskeletal pain

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THESIS SUMMARY

BACKGROUND

Pain is a universal and costly medical health problem. It is estimated that approximately one in ten individuals develop chronic pain each year. Chronic pain is among the top 10 complaints for which individuals seek help from primary care health professionals. In spite of its prevalence, doctors report a lack of confidence in managing chronic painful conditions. Moreover, the use of opioids for non-malignant chronic pain has increased recently and has become more regulated. Not surprisingly there is a high demand for alternative treatment options for managing chronic pain.

Chronic nonspecific musculoskeletal pain (CNMP) is a type of chronic pain, marked by the absence of a clear patho-physiological or anatomical origin. CNMP causes major disruption to patients' lives, relationships, and functionality. A rising prevalence of CNMP is observed in the general population but especially in children and adolescents. A diagnosis of CNMP early in life is recognized as a predictor for disability later. The limited information on its etiology, diagnosis and management perplexes doctors and patients alike.

There is a growing body of evidence that suggests vitamin D deficiency may play an important role in the etiology of CNMP. The discovery of vitamin D receptors in most tissues and cells in the human body and the identification of non-classical functions support the potential involvement of vitamin D in multiple chronic painful conditions including CNMP. In addition, vitamin D deficiency, by itself, is also reported as a major public health concern. Therefore because vitamin D supplementation is cheap and safe, it is increasingly being used as a management option. However the evidence base for such treatment is limited.

The management of CNMP, its perceived relationship with vitamin D deficiency and advice about using vitamin D supplementation by GPs has not been described previously. Nor do we know if supplementing vitamin D deficiency might improve symptomatology for patients with CNMP. In addition, very little is known about patient's perspectives, beliefs and views of their chronic pain management, especially in relation to vitamin D testing and supplementation, pain education and the patient-provider relationship. Patient perspectives are fundamental for identifying areas of management which require improvement to achieve better treatment outcomes.

AIM

The overall aims of this thesis is to provide evidence about,

1. The diagnosis and management of CNMP in Australian general practice and the role, if any, of vitamin D deficiency and supplementation in its etiology and treatment respectively.
2. The perspectives of patients with chronic pain about their medical management, investigations and vitamin D supplementation.

The research objectives are:

Objective 1- What management strategies do GPs employ with patients presenting with CNMP?

Objective 2- How effective is vitamin D supplementation in the management of CNMP?

Objective 3- What demographic and pain-related factors are associated with; testing for vitamin D levels, vitamin D deficiency and intake of vitamin D supplement among people with chronic pain?

Objective 4- What perspectives do patients with chronic pain have about the patient-provider relationship, pain education and does it affect their pain intensity and perceived time to recovery?

METHODS

For the objective 1 focus groups were used to explore and contrast in-depth accounts of GP's experience in Australia. As GPs' are often the first medical experts to start management for CNMP patients, their perspectives are critical for improving diagnosis and management. We wanted to understand their approach to managing CNMP and the role, if any, of vitamin D testing and supplementation. Ethical approval was granted by the Human Research Ethics Committee, University of Adelaide (HS-2013-056). Individual informed consent was collected at the beginning of each focus group. Twenty-seven general medical practices of varying size and socioeconomic patient mix in Adelaide and surrounding areas were invited to participate. Five practices with 23 GP's consented and participated in the study. The focus groups were audio recorded, transcribed using Nvivo 10 and analyzed thematically.

For the objective 2, a systematic review of the literature and meta-analysis was undertaken of studies published up to November 2015. Only randomized controlled trials investigating vitamin D supplementation compared with placebo were included. Studies using other designs and concurrent interventions along with vitamin D supplementation were excluded in order to study the direct effect of vitamin D. Following PRISMA guidelines, PubMed, Embase, Web of Science, Cochrane, and Scopus electronic databases were searched for randomized controlled trials comparing vitamin D supplementation to a control or placebo in CNMP patients; the search was not limited by language or date. All studies were independently reviewed using a standardized form. Jadad score was used to assess the quality of the studies included. The main outcome (pain) was measured using visual analogue scale (VAS). The mean change in VAS from baseline was considered as the primary pain outcome measure.

Meta-analysis was performed using the mean and standardized mean difference which was computed with 95% confidence intervals and overall effect size was calculated. Both fixed and random effect models were used in meta-analysis to properly account for heterogeneity in the studies. metan software in STATA was used for estimating the combined and overall effect.

For the objectives 3 and 4, a cross-sectional study using Survey Monkey was conducted to understand the perspectives of individuals with chronic pain about their pain management. Ethical approval was granted by the Human Research Ethics Committee, University of Adelaide (HREC-2016-0712) and the University of South Australia (application id-0000035791). The survey was completely voluntary and anonymous. The survey collected demographic data and included questions about the following; the participant's medical history, pain-related factors (pain intensity, duration and characteristics of pain), pain education, goals from chronic pain management, patient's perception of recovery time and vitamin D supplement intake. The analysis was performed using STATA 14.1 Statistical software. A range of statistical approaches were used for analysis these include; descriptive analysis for depicting the profiles of patients, logistic regression for estimating odds ratio, and least absolute shrinkage and selection operator (LASSO) technique.

RESULTS

In the first study, five main themes were identified: the ambiguous etiology of CNMP; gender differences; developing the "right strategy"; patient centered care; and verifying vitamin D levels. GPs adopt a patient-centered approach tailored to individual patients' medical history, physical examination and psychosocial health. GPs' recommended vitamin D supplements in patients with CNMP if indicated by a patients' history.

In study two, 107 articles were identified on initial search, but 77 studies were excluded on initial screening of abstract. Thirty full text studies were retrieved for further evaluation, however twenty-seven studies did not meet our selection criteria and hence were excluded. Data from the remaining three studies was included in the meta-analysis. A forest plot was used to present the results from the meta-analysis. Moderate – quality evidence suggested no effect of vitamin D supplementation on pain relief (SMD: 0.004; 95% CI: -0.248 to 0.256) in CNMP patients. Because only a small number of moderate quality studies were identified, better designed, large, double blind RCTs conducted over longer periods of time and capturing short, medium and long term effects are called for.

In study three, the estimated sample size was (n) 384 respondents to the survey to have power of 90% and have 5% uncertainty in the effect estimate. A simple prediction model was developed from the data collected using the LASSO regression technique. The findings from this study showed that older age was consistently associated with testing, vitamin D deficiency and intake of vitamin D. Unemployment, being on leave due to pain or in part time employment and being resident of Australia were also associated with vitamin D testing. Higher mean pain intensity score ≥6 on an 11 point numerical rating scale was associated with vitamin D deficiency; and being diagnosed with vitamin D deficiency was associated with intake of vitamin D. Being vitamin D deficient and unemployed on leave or part time employed due to pain were associated with doctor advised vitamin D supplementation.

Using the data collected in the survey study, the effect of pain education and patient-provider relationship on patient-reported pain intensity and recovery was examined using univariate and multivariate logistic regression. The findings from this study showed that individuals aged 40 years and above and female were more likely to report higher pain intensity and poor perception of recovery. Being in part-time employment was also associated with pain intensity and recovery. Pain education and patient-provider relationship did not show an association with

pain intensity and recovery. A separate regression analysis showed that individuals who received pain education were more likely to report changes in pain cognition and management of pain. We therefore hypothesize that pain education has an indirect relationship with patient-reported pain intensity and recovery induced by change in pain cognition and management of pain. The findings also show that individuals who reported good patient-provider relationship were more likely to report positive changes in pain cognition and management of pain.

CONCLUSION

General practitioners in Australia adopt a holistic approach to managing patients' with CNMP. They appear recommend vitamin D deficiency based on a person's history but the role of vitamin D deficiency in CNMP is unclear. The literature contains many studies examining the relationship between vitamin D deficiency and CNMP but only a few that could be included in a meta-analysis. The results demonstrated no evidence of benefit but more studies should be undertaken. Finally, using data from a cross sectional survey, it appears that several demographic and pain-related factors available to doctors are associated with vitamin D deficiency, testing and supplementation and these could be used in a predictive model for patients with chronic pain to rationalize testing and supplementation. More importantly, the pain management strategies for individuals with chronic pain should include education directed towards improving their understanding of pain and individual management.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other institution and affirms that to the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text of thesis. In addition, I certify that no part of this work will, in the future be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signed .....

Manasi Murthy Mittinty

(Candidate)

Date:

Publications contributing to this thesis

1. Gaikwad M, Vanlint S, Mittinity M, Moseley GL, Stocks N. Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis. Clinical rheumatology. 2016 Feb 9:1-8.

2. Gaikwad M, Vanlint S, Moseley GL, Mittinty MN, Stocks N. Understanding patient perspectives on management of their chronic pain–online survey protocol. Journal of Pain Research. 2017;10:31.

3. A qualitative exploration of GPs' perspectives on managing chronic non-specific musculoskeletal pain in Australian general practice- A Focus group study. Family Medicine and Community Health, *in press.*

Conference presentation arising from this thesis

1. Gaikwad M, Vanlint S, Alyward P, Stocks N. Chronic nonspecific musculoskeletal pain management: A Doctor's perspective. The 8th Annual Faculty of Health Postgraduate Research Conference. University of Adelaide, 25th September 2014, Adelaide, Australia.

2. Gaikwad M, Vanlint S, Alyward P, Stocks N. GP's perspective on managing Chronic Nonspecific Musculoskeletal Pain. The 2015 Australian Pain Society 35th Annual Scientific Meeting, 15-18th March 2015, Brisbane, QLD, Australia

3. Gaikwad M, Vanlint S, Mittinty M, Stocks N. Vitamin D and chronic non-specific musculoskeletal pain: a systematic review. The 2015 New Zealand Pain Society 40th Annual Scientific Meeting, 25-29th March 2015, Auckland, New Zealand.

4. Gaikwad M, Vanlint S, Mittinty M, GL Moseley, Stocks N. Does Vitamin D alleviate chronic non-specific musculoskeletal pain: a systematic review and meta-analysis? The 2016 Australian Pain Society 36th Annual Scientific Meeting, 13 – 16th March 2016, Perth, WA, Australia.

5. Gaikwad M, Vanlint S, Mittinty M, GL Moseley, Stocks N. Does Vitamin D alleviate chronic non-specific musculoskeletal pain: a systematic review and meta-analysis? The 2016 European Pain School, University of Sienna, 5th – 12th June, Sienna, Italy.

6. Gaikwad M, Vanlint S, Mittinty M, GL Moseley, Stocks N. Association of Vitamin D Supplementation and Chronic Non-Specific Musculoskeletal Pain: A Systematic Review and Meta-Analysis. The 16th World Congress on Pain, International Association for the Study of Pain, 25th – 30th September 2016, Yokohoma, Japan.

Research Translation (Media Coverage) arising from this thesis

1. "Vitamin D for Pain Relief? It Depends", MedPage Today, 7th February 2017. (**http://www.medpagetoday.com/resource-center/Osteoporosis/Vitamin-D/a/62981**)

2. "Standardising an approach to use of Vitamin D supplements in chronic pain relief" , ehospice, 7th November 2014 (**http://www.ehospice.com/australia/Default/tabid/10688/ArticleId/12949**)

3. "GPs should prescribe Vitamin D to treat chronic musculoskeletal pain", The Lead, 6th November 2014 (australia.com.au/industries/health/gps-should-prescribe-vitamin-d-to-treat-chronic-musculoskeletal-pain/)

4. Vitamin D should be prescribed by doctors to treat chronic musculoskeletal pain, according to research, Inquisitr, 7th December 2014. (http://www.inquisitr.com/1661168/vitamin-d-should-be-prescribed-by-doctors-to-treat-chronic-musculoskeletal-pain-according-to-research/)

5. "GP guidelines should include Vitamin D" National Seniors, 6th November 2014 (http://nationalseniors.com.au/be-informed/news-articles/gp-guidelines-should-include-vitamin-d-say-researchers)

Awards arising out of this thesis

1. Awarded the prize for best poster from the School of Population health at the 8th Annual Faculty of Health Postgraduate Research Conference.
2. Received travel award to attend the 2015 Australian Pain Society 35th Annual Scientific Meeting, Brisbane.
3. Selected among the top 6 posters presented at the 2015 New Zealand Pain Society 40th Annual Scientific Meeting, Auckland.
4. Received travel award to attend the study at the 2016 Australian Pain Society 36th Annual Scientific Meeting, Perth.
5. Selected among top 30 participants around the world to attend and present work at European Pain School, June 2016, Italy.
6. Awarded School of Medicine travel award to attend the European Pain School 2016, Italy.
7. Received travel award and free registration to attend the 16th World Congress on Pain, International Association for the Study of Pain 2016, Yokohoma, Japan
8. Received Walter and Dorothy Duncan Trust travel award for attending the 16th World Congress on Pain, Japan.

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If we knew what it was we were doing, it would not be called research, would it?

- *Albert Einstein*

To me that sums up my PhD journey really well! Though I'm full of gratitude for this journey and experience, it is not one without its peaks and valleys. At the final corner of my PhD candidature, I would like to sincerely thank the following people for their guidance, contribution and support.

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Finally, I dedicate my thesis to the visionaries who paved the way for girl education and social justice for women in India, namely Dr B.R. Ambedkar and Jyotirao Phule.

Abbreviations & Acronyms

ABS	The Australian Bureau of Statistics
ACPA	Anti-citrullinated protein antibody
ACR	The American College of Rheumatology
ANZBMS	Australian and New Zealand Bone and Mineral Society
BMD	Bone mineral density
BMI	Body Mass Index
BoD	Burden of disease
BOKS	Boston Osteoarthritis of the Knee Study
Ca	Calcium
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
CI	Confidence Interval
CNS	Central nervous system
CNMP	Chronic nonspecific musculoskeletal pain
CRH	Corticotrophin-releasing hormone
CWP	Chronic widespread pain
DAS 28	Disease Activity Score
DWL	Deadweight losses
DBP	Vitamin D binding protein
ESR	Erythrocyte sedimentation rate

FM	Fibromyalgia
FGD	Focus group discussion
FPS	Functional Pain Score
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPA	Hypothalamic- pituitary-adrenal axis
ICD	The International Classification of Diseases
IASP	The International Association for the Study of Pain
K/L scale	The Kellgren-Lawerence grading scale
LASSO	Least absolute shrinkage and selection operator
NHS	National health Survey
NHMRC	The National Health and Medical Research Council
NRS	Numerical rating scale
OA	Osteoarthritis
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	Parathyroid hormone
QOL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial

SS	Symptom severity scale
SOF	The Study of Osteoporotic fractures
SRQR	Standards for Reporting Qualitative Research
TasOAC	The Tasmanian Older Adult Cohort
TENS	Transcutaneous electrical nerve stimulation
TUG	Timed up and go test
VAS	Visual Analog Scale
VDR	Vitamin D receptor
UCLA	The University of California, Los Angeles activity scale
WPI	Widespread pain index
WOMAC	The Western Ontario and McMaster Universities Arthritis Index
1,25(OH) D	1, 25-dihyroxyvitamin D
25(OH)D	25-hydroxyvitamin D

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CHAPTER 1

Introduction

1.1. Introduction

According to the National Pain Strategy (1), "One in five Australians, including children and adolescents, will suffer chronic pain in their lifetime and up to 80% of people living with chronic pain are missing out on treatment that could improve their health and quality of life" (p. 7).

The impact of chronic pain on an individual goes beyond their physical suffering, it causes emotional distress, social isolation, and impacts society through the financial burden of disease via loss of income, medical expenses, and the monetary cost of the disability pension. The economic burden of chronic pain to society is enormous, with current estimates of $150 billion and $200 billion per annum in the USA and Europe, respectively (2). Management of chronic pain still perplexes health professionals and scientists alike due to its complex presentation and multiple co-morbidities (3). For many years chronic pain was considered as either a symptom of underlying disease (4) or a secondary consequence of other medical conditions (5, 6). However, chronic pain is now widely recognized as a condition in its own right (5). Hence, it is warranted to explore the mechanisms that underlie the development of chronic pain independent of other conditions.

The estimated prevalence of chronic pain in Australia is approximately 20% (7) which is similar to estimates for adult Europeans (8, 9). However, prevalence estimates of chronic pain can often be inaccurate due to differences in the definition of chronic pain (10-13), methods used for data collection (8, 10, 14, 15), if the focus is on a body part or function (11, 16) or pain being associated with a specific condition (12, 17).

Musculoskeletal conditions are reported to be the most common cause of chronic pain (7), with the reported high prevalence of chronic nonspecific musculoskeletal pain (CNMP) ranging between 30-70% (8, 15, 18, 19). According to Pfizer Australia (20), 13% of the Australian

population who live with chronic pain have no medical explanation for it. An alarming 20% have considered suicide with 5% attempting it because of their chronic pain (20).

Chronic pain management forms a significant part of the workload for general practitioners (GPs). GPs are often the primary contact for individuals experiencing pain (21, 22); GPs provide referrals to pain clinics and also the ongoing pain management following discharge from pain clinics (6). Predictably chronic pain is among the top 10 complaints for which individuals seek primary care (7, 23). However, primary care physicians report reduced confidence (24-26) in managing non-malignant chronic pain. They report lack of training and a perceived risk of side effects, substance misuse and concerns about addiction from opioid therapy (24-27). In the past 20 years, the prescription and consumption of opioids for managing chronic pain have increased fifteen-fold in Australia (28-30). This increase is attributed to GPs prescribing opioids for managing non-malignant chronic pain (31). An analysis of 4666 GP visits in Australia (30, 32) found that 43.9% of opioids were prescribed for chronic pain, 3.5% for malignant neoplasia and the remainder for non-chronic pain and other causes. This rise in opioid prescription by GPs may be due to lack of specialist support, shortage of proven therapies (33, 34), a wish to avoid patients going untreated (34) and to the Medicare model of funding which limits longer consultations (34) which might allow alternate strategies to be discussed and used. The increasing concern about the use of opioids for non-malignant chronic pain has led to heightened vigilance (32, 35), with doctors' failure to comply with the state legislative requirements for opioid prescription sometimes resulting in disciplinary action (36).

For the above reasons, there is a need for alternative therapies which could help relieve chronic painful conditions. A growing amount of evidence suggests that vitamin D deficiency may play an important role in the pathophysiology of CNMP (37). Vitamin D deficiency is also reported as a major public health concern in Australia with nearly one-third of Australians reported to have low levels (38). Low vitamin D levels have a direct effect on musculoskeletal health (37,

39, 40) and may often present as diffuse muscle pain, muscle fatigue, arthralgia, deep bone pain and muscle weakness (41-44). These symptoms are nonspecific and fit the criteria for CNMP. Vitamin D supplementation could alleviate some nonspecific pain and because it is easily available, and inexpensive it could be a safe method of managing CNMP.

The management of CNMP by GPs' and its perceived relationship with vitamin D deficiency has not been described previously. Nor do we know if correcting vitamin D deficiency could actually improve the pain experienced. This thesis provides evidence about the diagnosis and management of patients with CNMP and the effectiveness of vitamin D supplementation, which may potentially bridge the knowledge gap and help improve treatment outcomes. Moreover an attempt has been made to obtain insights from patients suffering with chronic pain, about their current pain management strategies and perceived recovery time.

1.2. Thesis Aim

The overall aims of this thesis are to provide evidence about

1) The diagnosis and management of CNMP in Australian general practice and the role, if any, of vitamin D deficiency and supplementation in its etiology and treatment.

2) The perspectives of patients with chronic pain about vitamin D supplementation and their medical management and investigations.

The research objectives are:

Objective 1- What management strategies do GPs employ with patients presenting with CNMP?

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Objective 4- What perspectives do patients with chronic pain have about the patient-provider relationship, pain education and does it affect their pain intensity and perceived time to recovery?

1.3. Thesis Outline

The remainder of the thesis is organized as follows. Chapter 2 provides the relevant literature that describes context of the specific aims, introduced above. The review covers common chronic painful musculoskeletal conditions, including CNMP, that are seen in Australian general practice. It also examines what role vitamin D deficiency and supplementation may have in each of these conditions. Chapter 3 addresses the first research question, which describes Australian GPs' decision-making processes when managing CNMP in practice using a focus group study design. This chapter is accepted for publication as a research article in peer-reviewed journal Family Medicine and Community Health.

Chapter 4 addresses the second research question, which examines the effects of vitamin D supplementation on CNMP using a systematic review and meta-analysis of randomized controlled trials (RCTs). This chapter was published as a research article in a peer-reviewed journal (45) (Attached as Appendix).

Chapter 5 presents the methods for a cross-sectional survey of patients with chronic pain, the variables selected to examine patients' perceptions, views, and beliefs on vitamin D testing, deficiency and supplement intake; pain education; patient-provider relationship; pain intensity and their perception of recovery. Chapter 5 describes in detail the objectives and methodology

used in designing and conducting the survey. Chapter 5 is published as a research article in the peer-reviewed Journal of Pain Research (Attached as Appendix).

Chapter 6 addresses the third research question, which examines the patients' views and beliefs about vitamin D testing, deficiency and supplement intake and the factors associated with medically advised vitamin D supplementation and patients' perception of recovery. Chapter 6 is under review as a research article in a peer-reviewed journal.

Chapter 7 examines patients' views and beliefs about patient-provider relationship and pain education, and if there is an association between the patient-provider relationship and pain education and patient reported pain intensity and perception of recovery. This chapter will be prepared for submission to a peer-reviewed journal after completion of the Ph.D.

Chapter 8 provides a summary from the overall thesis, synthesis of the findings, and a proposed plan for future research.

CHAPTER 2

Literature Review

The structure of this chapter is as follows. Section 2.1 describes the background on vitamin D, its synthesis, metabolism and guidelines on interpreting vitamin D levels in clinical practice. Section 2.2 reviews pain, and the journey from the Biomedical model to the current Biopsychosocial model of pain. Section 2.3 describes the effects of vitamin D on chronic pain conditions such as osteoarthritis (OA), rheumatoid arthritis (RA), chronic widespread pain (CWP), fibromyalgia (FM) and chronic nonspecific musculoskeletal pain (CNMP), and on how vitamin D levels might relate to or modulate CNMP.

2.1 Vitamin D

In 1919, Sir Edward Mellanby proposed a deficiency of a fat-soluble vitamin or accessory food factor (46) as the cause for the development of rickets in children. He fed a diet consisting only of oats to a group of dogs restrained indoors without any sun exposure. He produced rickets in these dogs through the restrictive diet. He then fed the dog's cod-liver oil, which is not present in oats, and the dogs were cured of rickets. He attributed the treatment success to vitamin A present in the cod liver oil. In 1922, McCollum and associates performed a test of bubbling oxygen through cod liver oil, which burned out the vitamin A, leaving behind a "new substance" that remained effective in treating rickets. They labelled this new substance in the oil - "vitamin D" following sequential alphabetical designations (47). Labelling of this substance as a vitamin is often questioned, as vitamin D acts more like a hormone than a vitamin. Also unlike any other vitamins, vitamin D can be synthesized in the human body. It is acknowledged as a fat-soluble hormone precursor, which is produced by exposure to adequate sunlight. In 1928, a German structural chemist Adolf Windus won the Nobel Prize for the chemical identification and synthesis of vitamin D (48). Two forms of vitamin D are recognized

namely; vitamin D2 [ergocalciferol] found in plants and some fish and vitamin D 3 [cholecalciferol] synthesized in the skin from direct exposure to the sunlight (49).

2.1.1. Synthesis of Vitamin D

Cutaneous synthesis of vitamin D

On exposure of the skin to sunlight (UV-B rays), pre-vitamin D3 is synthesized in the skin from 7-dehyroxycholesterol (see Figure 2.1). Multiple factors such as the amount of UV exposure (290-315 nm wavelength), skin pigmentation and thickness, age, latitude, season, and level of sun protection used (including clothing, shade, and sunscreen) regulate this step. Previtamin D3 is isomerized to vitamin D3, which binds to the vitamin D binding protein (DBP) (48) and is transported into the liver. In the liver, it is hydroxylated by the 25-hydroxylase enzyme to 25-hydroxyvitamin D [25(OH) D] which is the inactive form. Subsequently, in the proximal convoluted tubules of the kidneys, 25-hydroxyvitamin D is hydroxylated by the enzyme 1 α-hydroxylase to 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$], the physiologically active form (50-52). This cutaneous synthesis of vitamin D supplies 80-100% of the daily requirement of vitamin D (53).

Exogenous synthesis (synthesis of dietary vitamin D)

Vitamin D can be ingested from food sources such as eggs, oily fish, liver, unfortified butter and fortified foods like milk, margarine, cereals, juice, and yoghurt (54). This orally ingested vitamin D2 also binds to DBP and is transported to the liver from where it follows the path of cutaneous synthesis (48).

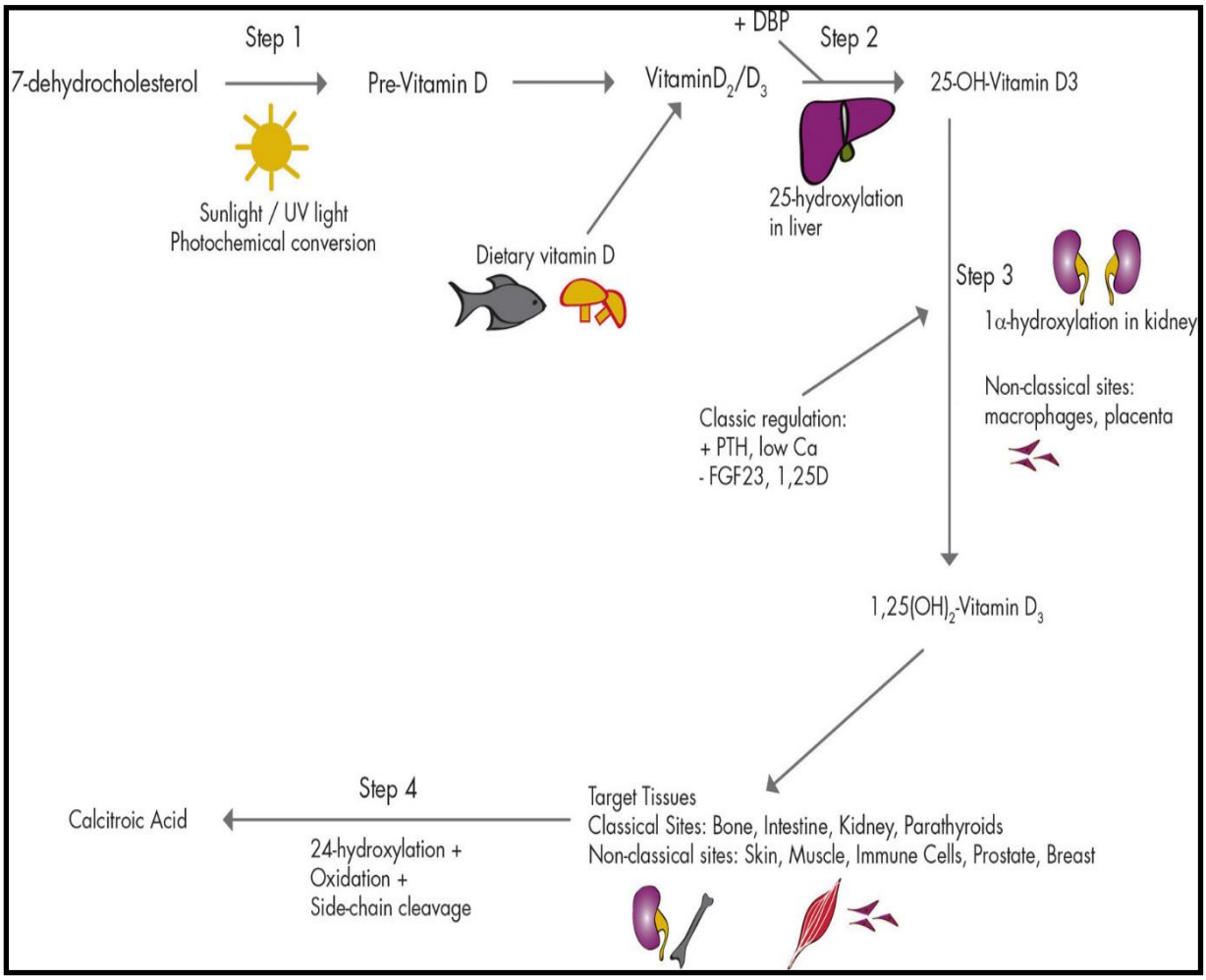

Figure 2.1 Synthesis of Vitamin D (48)

Both 25 (OH) D and 1, 25(OH) D undergo 24-hydroxylation to form 24, 25 (OH) D and 1, 24, 25 (OH) D respectively (56), which is the initial stage of biodegradation that ends in the formation of water-soluble calcitroic acid (56, 57). The hydroxylation of vitamin D in the liver is almost unregulated therefore serum level of 25(OH) D can reflect either cutaneous production in the skin or dietary intake and is hence used as the marker for vitamin D status (57, 58). The only regulated step in the synthesis of the active form of vitamin D is the production of 1, 25(OH) D by the kidney (51).

The wide-ranging effects of vitamin D are also attributed to the extra-renal expression of the enzyme 1 α-hydroxylase in tissues of skin and brain (50) and also in the cells of osteoclasts, macrophages (59), breast, colon, prostate (60) and smooth muscle (61). They can locally synthesize the active form of vitamin D (61). This pre-vitamin D3 is biologically inert and needs to undergo two successive hydroxylation's to become biologically active (see Figure 2.2).

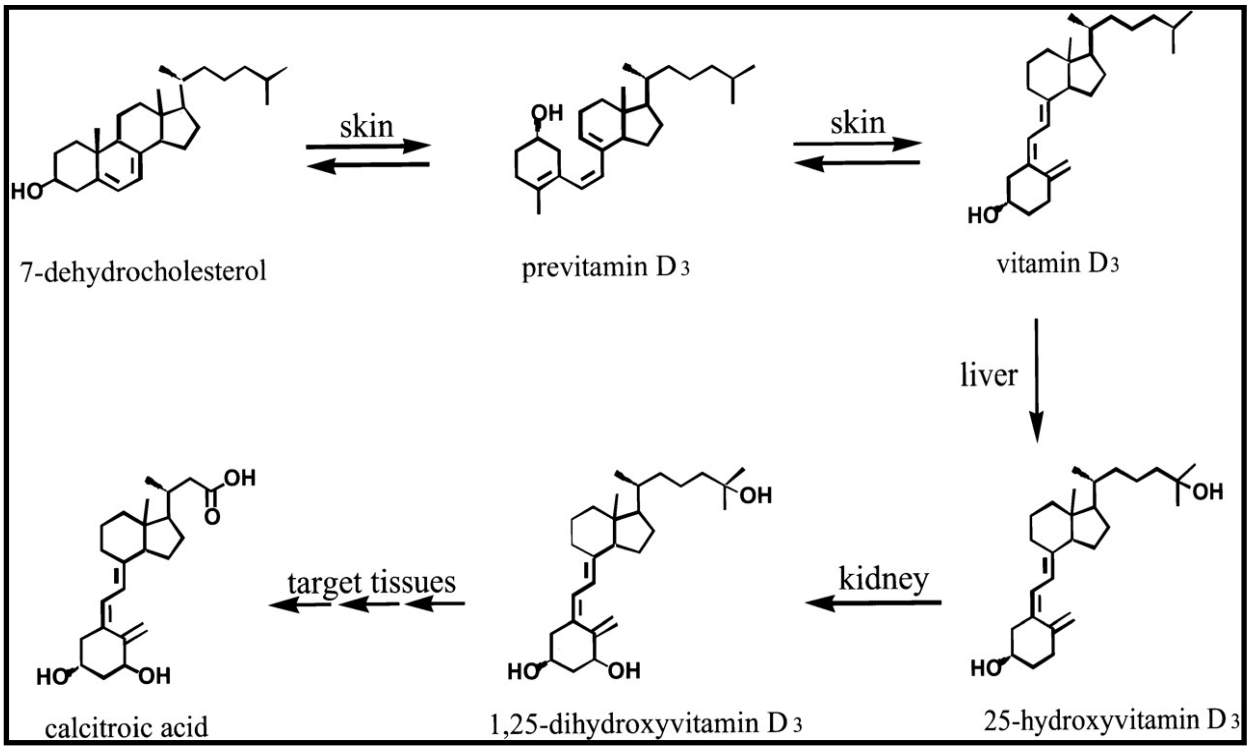

Figure 2.2 Vitamin D synthesis, activation and catabolism (55).

2.1.2. Calcium homeostasis

A flux of calcium between bone, kidney, intestine and extracellular fluid regulates plasma concentration of calcium. This flux is predominantly controlled by 3 major hormones:

parathyroid hormone (PTH), calcitonin and 1, 25-dihyroxyvitamin D. These hormones also form a negative feedback control for maintaining calcium levels (62). The parathyroid hormone (PTH) is regulated by the serum calcium (Ca), phosphorus (P) levels (61), growth hormone and prolactin (63). The normal concentration of PTH, phosphate, and calcium regulate the central point in vitamin D metabolism - the renal hydroxylation of 25- hydroxyvitamin D to 1,25- dihydroxyvitamin D. Though decrease in PTH and phosphate levels independently increase 1,25-hydroxyvitamin D production, PTH is the most potent stimulus (64). Rising levels of 1, 25-dihydroxyvitamin D increases the plasma concentration of calcium and phosphate by increasing the absorption of calcium and phosphate from the gastrointestinal tract (50-52). It also increases osteoclastic reabsorption of calcium and enhances the effects of PTH in the nephron to promote renal tubular calcium reabsorption. Thus, 1,25-dihydroxyvitamin D regulates calcium and phosphate deposition and release from bone (64).

2.1.3. Vitamin D receptors

There are two known forms of the vitamin D receptor (VDR), namely nuclear VDR and membrane bound VDR. The most thoroughly described are the nuclear VDR, an intracellular polypeptide from the steroid-thyroid-retinoid acid receptor superfamily (65). The discovery of the nuclear VDR in 1969 enhanced the knowledge about various functions of vitamin D (66). The nuclear VDR gene contains 9 exons and 8 introns and is present on chromosome 12q12-14 (67, 68). Nuclear VDR initiates biological functions or suppression of gene transcriptions, by binding to the DNA of target cells as VDR/VDR homodimers or VDR/RXR heterodimers and synthesizing RNA encoding proteins (65).

The membrane-bound VDRs are located in the cells of various tissues including parathyroid, pancreas, special nerve cells, keratinocytes, macrophages and renal tubular cells (51), brain, vascular smooth muscle, prostate, and breast (69). These membrane-bound VDRs induce 'rapid responses' leading to the formation of second messengers and phosphorylation of intracellular proteins and regulating approximately 3% of the human genes (70).

2.1.4. Evaluating Vitamin D status

The circulating levels of 25(OH)D is measured to evaluate vitamin D status- sufficiency, insufficiency, deficiency or toxicity in an individual (71, 72). Even though 25(OH) D is not the biologically active form of vitamin D, it is used because it gives the sum of both cutaneous and exogenous synthesis (71, 72). It also has a half-life of approximately 2-3 weeks, as compared to 4-6 hours of 1,25 (OH)D (73). As a consequence, circulating serum levels of 25(OH)D are a thousand fold higher than 1,25(OH)D (73). Moreover, in the case of vitamin D deficiency, renal production of 1,25(OH)D increases (71, 72) due to PTH regulation of calcium metabolism, which can give false positive results for the 1,25(OH) D assay, making it less reliable.

2.1.5. Level of Vitamin D in Australian Population

An approximate exposure of 10-15 minutes to a midday sun in summer in Sydney is considered equivalent to taking a 15000 IU (375 µg) of vitamin D supplement orally (74). However, due to the increased prevalence of skin cancer in Australia, previous public health messages have discouraged people from this level of exposure to sun rays when UV radiation is high (75). It now appears that almost 1/3 of the Australian population has low serum levels of vitamin D

(38). Studies have also observed that nearly 43% of young women and 23% of the general population (76, 77) in Australia are vitamin D deficient during winter. Moreover, children and adolescents have poor vitamin D status particularly those from the cooler regions of Tasmania (78) and New Zealand (79).

2.1.6. Interpretation of circulating vitamin 25 (OH) D levels

Current evidence, based on a working group commissioned by the Australian and New Zealand Bone and Mineral Society (ANZBMS) and Osteoporosis Australia, classifies circulating levels of serum 25(OH)D as follows (80):

1. Vitamin D adequacy: > 50 nmol/L at the end of winter (10–20 nmol/L higher at the end of summer, to allow for seasonal decrease).
2. Mild vitamin D deficiency: 30–49 nmol/L
3. Moderate vitamin deficiency: 12.5–29 nmol/L
4. Severe vitamin D deficiency: < 12.5 nmol/L

The working group recommended a target level of 50 or 60 nmol/L for maintaining bone health and muscle function. An analogous range between 50 and 62.5 nmol/L was recommended by the 14th vitamin D workshop (81) to prevent adverse musculoskeletal outcomes such as fractures and falls. However, the serum level of vitamin D necessary for prevention of other diseases is still unclear.

The knowledge of non-classical effects of vitamin D which included immune modulation, cellular regulation, apoptosis, anti-inflammatory, anti-microbial, insulin secretion and neuroprotection (51, 61) advocated its potential role in multiple conditions. Along with the rising prevalence of vitamin D deficiency worldwide (82), vitamin D supplementation is being

used in the management of wide range of conditions including chronic pain. The past decade has seen an explosion in studies regarding the underlying role of vitamin D deficiency and/or supplementation for the management of the chronic musculoskeletal conditions. However, in order to understand the potential role of vitamin D deficiency in painful conditions and their treatment, it is important to first understand the evolution of pain models up to the current Biopsychosocial model.

2.2. Chronicles of Pain

To heal does not necessarily imply to cure. It can simply mean helping to achieve a way of life compatible with their individual aspirations—to restore their freedom to make choices—even in the presence of continuing disease.

—Rene Dubos (1978)

Pain is a universal and costly medical health problem (83). Though there has been an explosion of research on pain (84), it still remains difficult to diagnose and manage and also difficult to explain. Chronic pain is especially demoralizing; its continuous presence limits the individual's personal, social and professional activities, often making them adopt the sick role (85). Research has shown that solely tissue-based explanations for symptoms fail to explain chronic pain (83). Although physical pathology and pain may be related, physical pathology does not predict the severity of pain nor the level of disability. Similarly, the severity of pain cannot fully predict the level of psychological distress or the degree of associated disability (83). The question that remains to be answered is how to provide an optimal level of management and care for the patients suffering from chronic pain. There are a number of theories that have tried to address this complex situation. Earlier theories focused on tissue damage and the associated pain. However, recent theories put greater emphasis on the sensitivity of nociceptive system (86), non-nociceptive sensory inputs, associative learning (87), and cognitive and behavioral processes that link fear of pain, activity avoidance and catastrophizing (88). The biomedical concept of chronic pain has given way to the biopsychosocial concept of pain (89, 90), which posits that pain, and how people respond to it, is influenced not only by the biological factors but also by the belief's, attitudes and social and cultural environment of the patient (91, 92). This Biopsychosocial model supports an integrated multi-disciplinary treatment approach (93). Although it is beyond the scope of this thesis to review the theories in depth, a concise

discussion allows a framework for evaluating the possible role of vitamin D in the chronic painful conditions.

2.2.1. The Biomedical model of pain

Ever since the revolutionary writings of Descartes, the idea that pain runs along a channel has been popular and has guided treatment (94). Descartes viewed the physiology as a "hydraulic system" that runs directly from the receptor on the skin to the brain (Figure 2.3). His drawing depicted a man with fire near his foot; the fire activates the 'pain receptor' stimulating the hydraulic system to ring a bell in his head. This model ruled the management and study of pain for many centuries and is, arguably, still popular to this day.

Figure 2.3 Descartes model of pain (94)

The Biomedical model provides a framework for disease and health based on reductionism, which suggests that all diseases occur due to a biological defect or pathogen, and dualism, which suggests that mind and body are two separate entities (95). Health was judged by the mere presence or absence of symptoms or disease. This Biomedical model was also applied to diagnosing and managing painful conditions. It focused solely upon nociception, the sensing of a harmful stimulus without essentially taking emotional aspects of pain into consideration (96). Thus, overlooking how past experiences, social and cultural background shape the whole experience of pain (96).

The Biomedical model was criticized for promoting an impersonal, cold, technical style of clinical practice which overlooked the human dimension of suffering and compassion (89, 97) and disregarding the interaction of diverse social and individual factors that form a major part of an individual's experience. Engel recommended a more holistic approach as an extension to the Biomedical model known as the Biopsychosocial model (98) which is described in section 2.2.6.

2.2.2. The Specificity Theory

The Specificity theory of pain was proposed by Max von Frey in1894 (99). He postulated that there are four main types of sensations: pain, touch, heat, and cold, and all of the other skin sensations are derivatives of these main types. Each of the four sensations was suggested to have distinctive receptors and pathways that carry the stimulus from periphery to spinal cord and then to specific centers in the brain (Figure 2.4). Thus, each sensation was perceived to have a specific central and peripheral set of mechanisms that also determined the intensity and nature of the sensation (pain, heat, cold and warmth) generated. Although the theory aptly explained many characteristics of pain such as sensory receptors that respond to specific

nociceptive stimuli, for example, the A - delta and c-nerve fibers, it did not account for neurons which respond to both non-nociceptive and nociceptive stimulus, nor the many vagaries in the relationship between stimulus and response in the nociceptive range (100). The Specificity theory also could not explain pain without ongoing tissue injury or stimulus (101), for example phantom limb pain where the pain seems to arise from an absent limb.

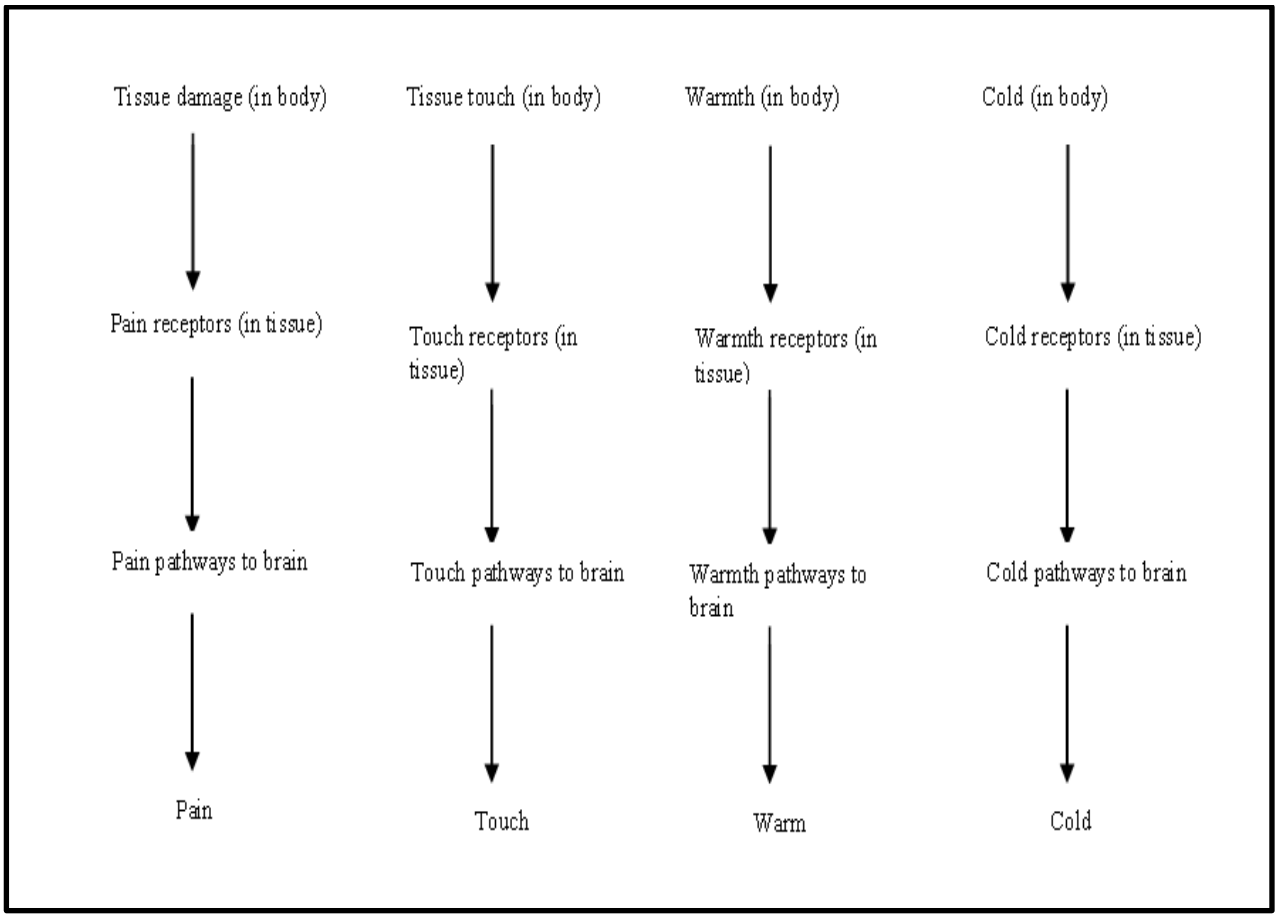

Figure 2.4 Schematic representation of the Specificity theory (102)

2.2.3. The Pattern theory

In 1920 Goldschneider proposed the 'Pattern theory' (103) which disregarded the Specificity theory and suggested that all senses including pain shared receptors and that there was no special system for perceiving pain. The theory advocated that a peripheral sensory input, damaging as well as non-damaging both can give rise to painful or non-painful experience depending on the difference in the patterns of the signals sent through the nervous system (Figure 2.5). For example, being hit hard feels painful because it produces different patterns of neural activity but being caressed does not, although they belong to same sense modality. The difference in the patterns determined the quality of sensation. The major success for the Pattern theory was that it identified the neurophysiological mechanism of encoding and processing sensory information thus accounting for painful conditions such as neuralgia (104). However, it also had limitations; such that it did not acknowledge any control of the brain over the perception of pain and the role of various psychological factors that could affect the perception of pain.

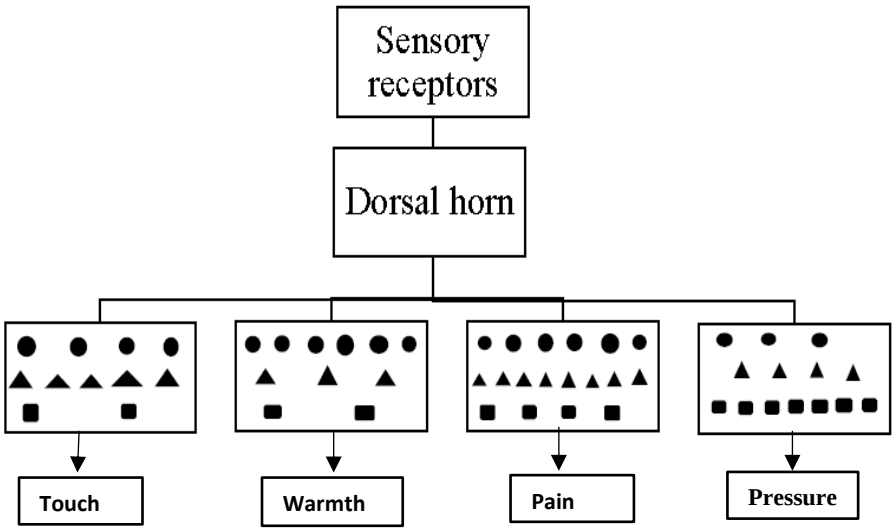

Figure 2.5 Schematic representation of the Pattern theory (102)

2.2.4. The Gate Control Theory of Pain

The Gate Control theory proposed by Ronald Melzack and Patrick Wall (105) was the first theory to postulate the top-down brain influences on the experience of pain and related behaviors. This theory postulated that signals produced in primary afferents following stimulation of skin are transmitted to three regions within the spinal cord; the substantia gelatinosa, the dorsal horn and a group of cells termed as 'transmission cells' (Figure 2.6). The transmission of sensory information from the primary afferent neurons to transmission cells of the spinal cord was moderated by the substantia gelatinosa in the dorsal horn which functions like a 'pain gate'. The activity in the small nerve fibers (A-delta and C fibers) acts to open the gate, whereas the activity in large nerve fiber (A- beta) closes the gate, thus limiting the pain experience. The gate can also be modulated by input from descending fibers that originate from supraspinal centers and project to the dorsal horn; if the nociceptive information exceeds the threshold of inhibition it can open the gate and activate pathways that lead to the pain experience. As described by Melzack in 1993 (106), the Gate Control theory forced scientists to acknowledge the central nervous system as an essential component in pain processes; with the brain and dorsal horn capable of modulation, inhibition and excitation of sensory inputs and altering the pain processes. The Gate Control theory is the first major theory to recognize the close interaction between psychosocial and physiological processes affecting pain (94), although its focus was arguably on the influence of non-nociceptive input over nociceptive input. More recent development of the Gate Control theory have posited that an individual's thoughts, feelings, and behavior could affect the transmission of the nociceptive signal by opening or closing the gate. Negative thinking, focusing on pain and nonconstructive thinking; feelings such as sadness, helplessness, anger, hopelessness, and stress; behaviors such as poor nutrition, inactivity, smoking, sleep deprivation – could potentially "open" the gate whereas, positive thoughts, feelings, and behaviors could prevent the gate from "opening" (94). The

wide acceptance of the Gate Control theory led to the development of treatment strategies such as transcutaneous electrical nerve stimulation (TENS), which aims to close the gate by selectively stimulating A beta (large diameter) nerve fibers (107). However, the inadequacies in the Gate Control theory became evident with an improved understanding of the significance of higher central nervous system (CNS) levels in the modulation of nociception (108, 109) and its failure to explain chronic pain states in the absence of tissue injury.

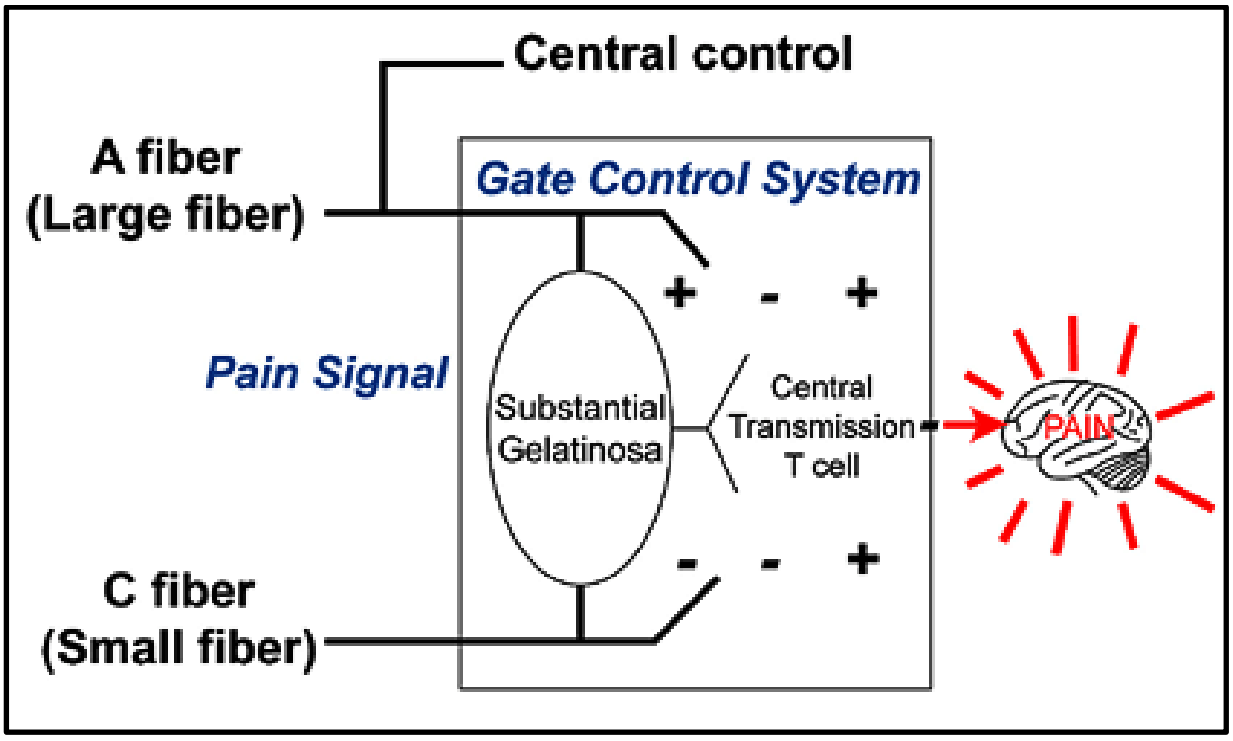

Figure 2.6 The Gate Control theory (105)

2.2.5. The Neuromatrix model of Pain

Although the Gate Control theory mention's descending influence on the 'gate', there was not much detail given about this component. Twenty-five years later Melzack proposed the Neuromatrix model as an extension of Gate Control theory (110). This theory promotes pain as a multidimensional experience, initially produced by the specific pattern of nerve impulses generated by neural network or neuromatrix, which is widely distributed and can be activated in the presence of peripheral sensory stimulus or centrally without stimulation. According to this model, every individual has an exclusive neuromatrix, formed by an individual's genes, sensory and learning experiences (Figure 2.7) which help to understand why individuals experience pain differently (111).

The Neuromatrix model is widely recognized for its contribution to managing chronic pain states after resolution of the primary injury or when the pain shifts from the primary site (112). The Neuromatrix model was recognized as a clinical breakthrough for its application to phantom limb pain and pain after spinal cord resection (113). However, the Neuromatrix model was criticized for its lack of specificity, as it did not specify the biological or neurochemical substrates for its basis (114). Another criticism of the Neuromatrix model was that it did not add more to our understanding of the mechanisms of pain relief from the Gate Control theory and was deemed more suitable for understanding brain functioning than pain itself (114).

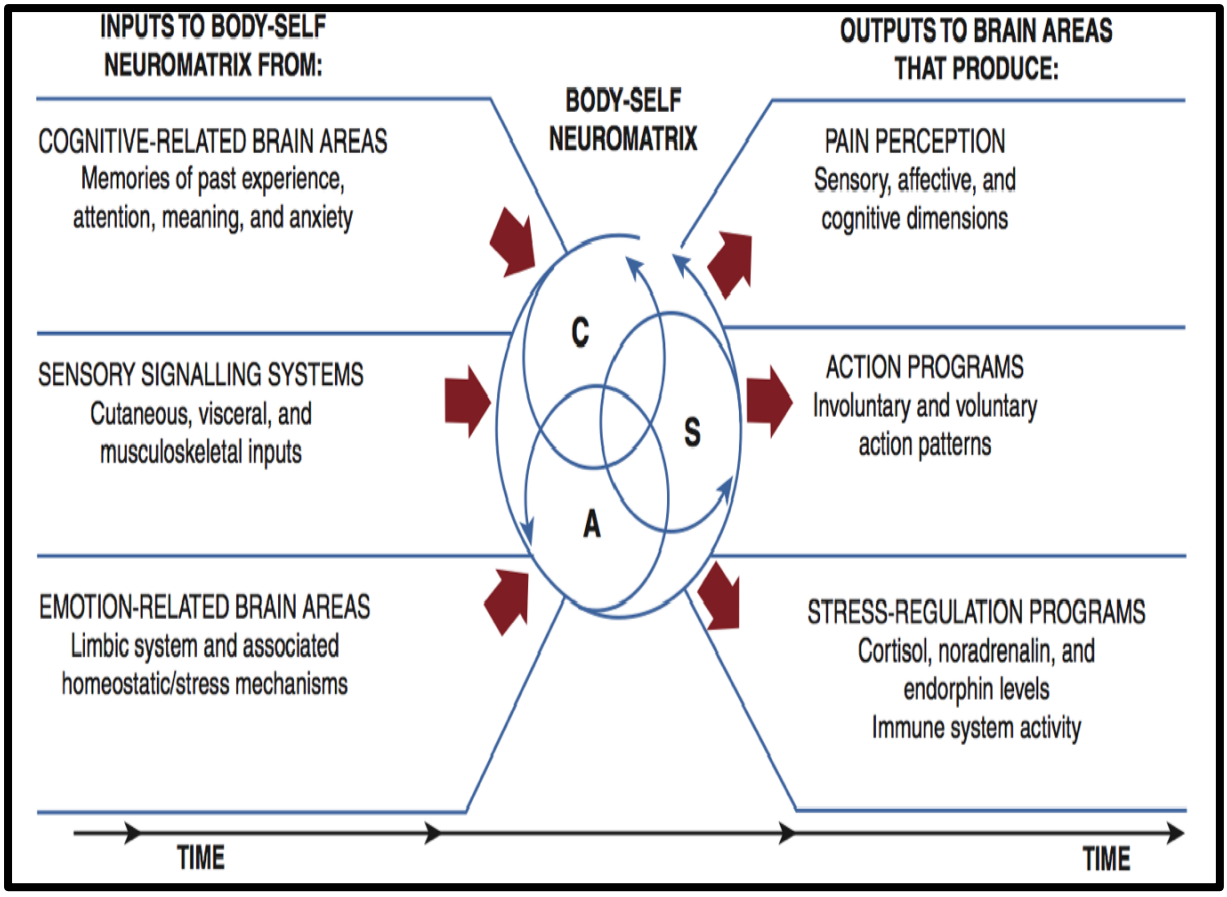

Figure 2.7 The Neuromatrix model of pain (115)

Pain-stress response

Melzack incorporated the role of the hypothalamic- pituitary-adrenal axis (HPA axis) (111) in the maintenance of chronic pain in the Neuromatrix model. He proposed that an injury or painful stimulus disrupts the homeostasis, inducing the HPA axis starting with the secretion of Corticotrophin-releasing hormone (CRH) from the hypothalamus (Figure 2.8). CRH activates pituitary gland to secrete adrenocorticotropic hormone, which stimulates adrenal cortex to secrete cortisol (111). To meet the high demand of cortisol during stress, blood sugar levels rise, the breakdown of muscle protein increases and replacement of calcium in bones is also inhibited (111). Melzack emphasized that prolonged stress and homeostatic imbalance could exhaust this adaptive response also known as Selye's General Adaptation Syndrome (116).

Prolonged stress also activates the limbic system, which is important for emotion, motivation and cognitive process (116). In addition, once the pain is established, it could act as a stressor itself, maintaining the disruption to homeostasis thereby forming a vicious cycle which continues to preserve and contribute to the pain-stress process.

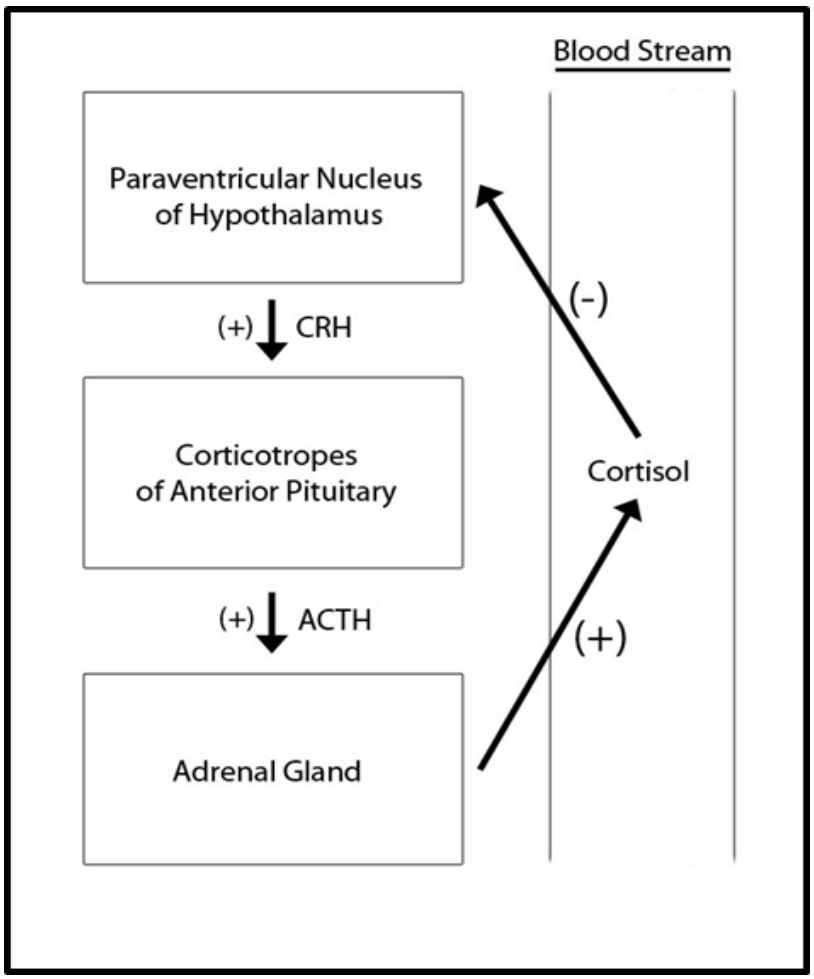

Figure 2.8 The Hypothalamic Pituitary Adrenal Axis (111)

2.2.6 The Biopsychosocial Model

In his criticism of the Biomedical model Engel recommended a more holistic approach as an extension to the Biomedical model known as the Biopsychosocial model (98). This model accredited equal importance to biological, psychological and social factors (Figure 2.9) in the diagnosis, prevention, and management of disease (89). It prompted clinicians to broaden their gaze, support multidisciplinary treatment and disease control and helped to improve the patient and health care provider relationship.

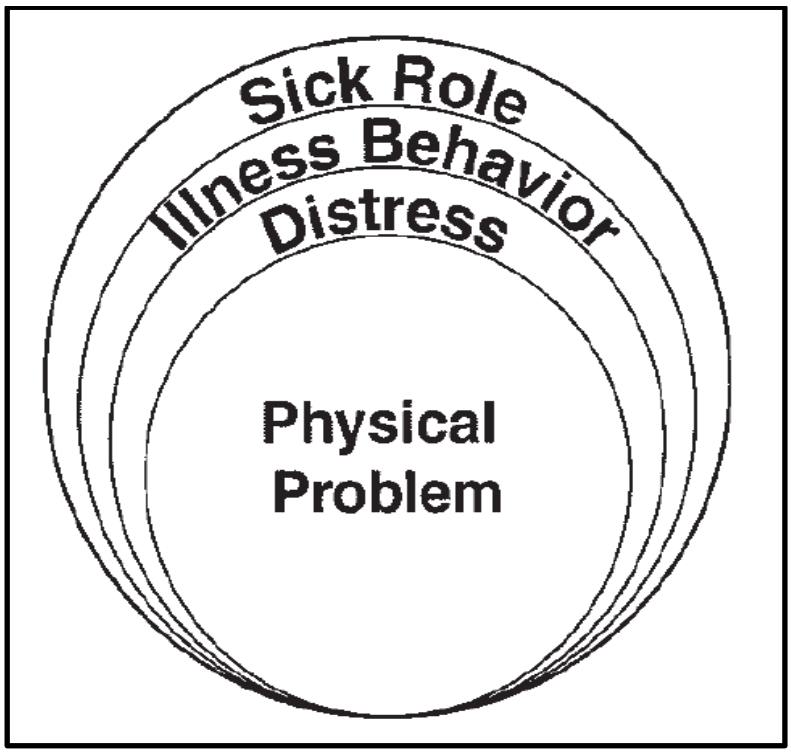

Figure 2.9 Engel's conceptual model of illness (117)

In 1982, Loeser applied the Biopsychosocial model to the understanding and management of pain. He added four dimensions closely associated with pain (90): a) nociception, b) pain, c)

suffering, and d) pain behavior. He defined nociception as stimuli, either: chemical, mechanical or thermal that act on peripheral receptors producing activity in the nerve fibers; pain as the sensation that results due to the nociception; suffering as the unpleasant emotional response and pain behavior as the actions used to communicate about the pain (Figure 2.10). This model emphasized how an individual's past experiences and anticipation of recovery could impact their suffering and pain behavior. This model successfully highlighted the intricate nature of chronic pain and the complex interactions between the psychological, social and economic factors, in forming the pain experience and its maintenance.

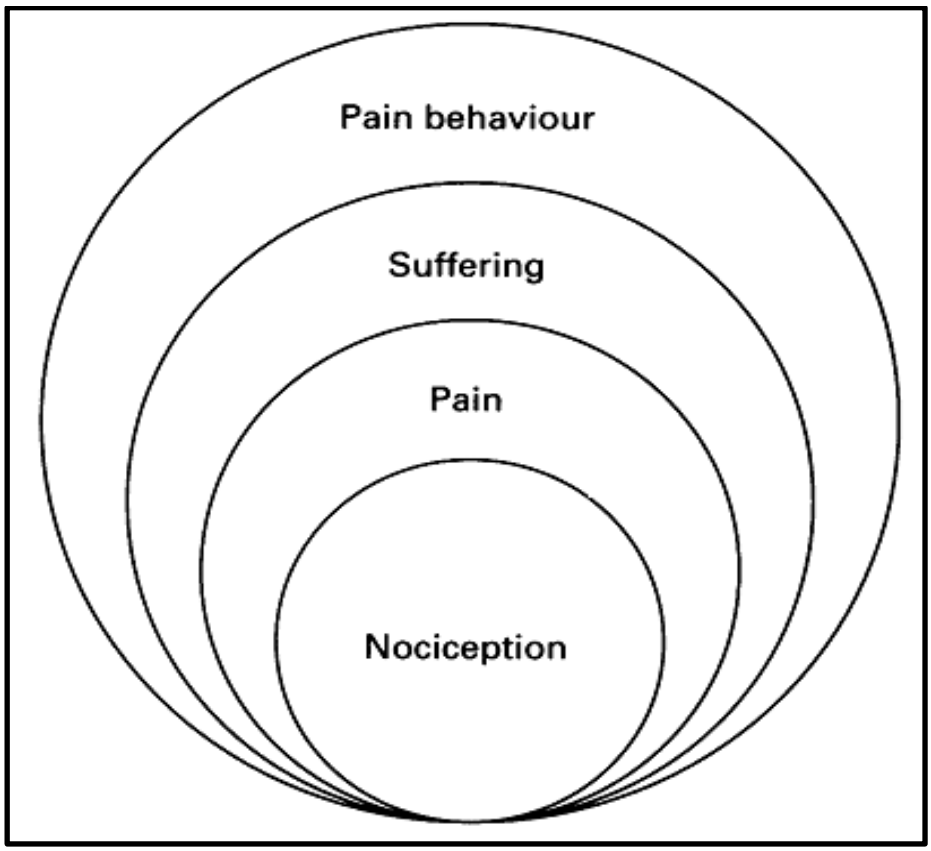

Figure 2.10 Loeser's conceptual model of pain (90)

The biopsychosocial perspective recognized pain as a complex phenomenon that results from interactions between the physiological, psychological and social factors (90). It further recognized the interaction of different emotional, psychological, social and economic factors and its effect on individual's experiences of pain, reporting of symptoms and associated disability (94). The major strength of the Biopsychosocial model is that it acknowledges the role played by psychological and social factors in pain.

The Biopsychosocial model considers pain to be a physical illness that is influenced by physiological, psychological, and social factors that interact and or exacerbate the clinical presentation. Even patients with identical medical diagnosis differ in their psychosocial and behavioral characteristics, which influences their treatment outcome.

2.2.7. Current theoretical concept of pain

Today our understanding of pain has further evolved from "being the outcome of nociception" to pain being an emotional and sensory experience that serves to protect our body (87, 118). Pain is acknowledged as the "output" that can be modulated by an individual's biological, psychological and social factors which explains why every individual experience pain differently. While, nociception is defined as the activity in high-threshold primary neurons A-delta or C fibers most often due to noxious stimulus. Unlike nociception, pain can always be sensed and it informs us to protect the body part. It is also the only protective mechanism we are necessarily aware of, thus making self-report the best measure of pain.

2.2.8. Mechanism of Pain

Peripheral Sensitization

Damage or inflammation of tissue changes the chemical environment of the peripheral nociceptors (119). Injury and inflammation release intracellular contents such as ATP, K^+ ions; and produce inflammatory cells such as cytokines, chemokines, and growth factors; neutrophils which secrete Cox-2 which promotes PGE2 production (119). These factors can directly affect the nociceptive terminal and stimulate it (nociceptor activators), while others can sensitize the terminal making it hypersensitive to succeeding stimulus (nociceptor sensitizers) (119). This is known as peripheral sensitization (120). Peripheral sensitization decreases the excitation threshold of polymodal nociceptors (121) and also increases the responsiveness of peripheral end of nociceptors (120), which transfer the input from target tissues via the spinal cord to the brainstem (120). Following sensitization, even a harmless stimulus can evoke pain while noxious stimulus can evoke an even stronger response (120). For example, primary allodynia (120) where previous non-painful stimulus such as hot water (showering) becomes painful after a sunburn.

Central Sensitization

A nociceptor input can generate long-lasting excitability of neurons in central nociceptive pathways, which is reversible. This phenomenon is known as central sensitization. The concept of "central sensitization" was first proposed by Woolf and colleagues in 1983 (122). It is also described as activity-dependent plasticity due to increase in the synaptic strength by N-methyl-

D-aspartic acid glutamatergic receptors. The "conditioning input" can also amplify subsequent responses to other non-stimulated non-nociceptor or nociceptor fibers (123). Central sensitization can also be elicited by the diminished inhibitory transmission or loss of inhibitory neurons (124). Once established it augments nociceptive sensitivity and remains highly plastic (125); new nociceptive input aggravates it, however, in the absence of new nociceptive input it does not resolve but is sustained (126). Recently Woolf also integrated all forms of pain sensitization and reduction in pain threshold beyond the receptor field of spinal nociceptors into central sensitization. This new integration promotes that central sensitization can be detected in other CNS locations and can have multiple drivers that can change a period of time (86). Thus, psychological, social and biological factors all can influence neuronal activity-they can all generate central sensitization. This is central understanding the change in pain hypersensitivity seen in clinical syndromes such as fibromyalgia, which does not have clear tissue injury (119, 123).

2.2.9. Peripheral nerve injury

In the event of peripheral nerve injury, three additional mechanisms have been suggested which are ectopic excitability, disinhibition, and structural reorganization in the dorsal horn of the spinal cord.

Ectopic excitability

Following a nerve injury, the distribution of sodium and potassium ion channels is altered which leads to increase membrane excitability. It can also produce ectopic impulses in the absence of peripheral stimulus. This is known as ectopic excitability and is a major contributor to spontaneous neuropathic pain seen in diabetic peripheral neuropathy (127).

Structural reorganisation

The central terminals of nociceptor sensory neurons terminate in the superficial laminae of the dorsal horn, while low threshold sensory fibers terminate in the deep laminae of the dorsal horn. The physical arrangement of this circuitry is reorganized following a peripheral nerve injury. However, although this structural rewiring has been identified in rodents it still remains to be observed in patients (128).

Disinhibition

Peripheral nerve injury causes substantial loss of inhibitory currents especially the ones mediated by GABA. This is due to the selective death of GABAergic inhibitory interneurons (129). Following the nerve injury, neurons in the dorsal horn begin to undergo apoptosis due to excessive glutamate release, failure of glutamate uptake or result from the release of tumour necrosis factor from activated microglia (129).

2.3. Musculoskeletal conditions and the role of vitamin D

2.3.1 Osteoarthritis (OA)

Background

The term “osteoarthritis” (OA) comes from Greek meaning bone and joint inflammation. It is a progressive degenerative disorder of synovial joints characterized by gradual loss of cartilage, changes in subchondral bone with subsequent development of bony spurs and cysts on the joint margins. It may affect a single joint, few joints or can be generalised (130). The main symptoms of OA are joint pain, stiffness, locomotor restriction and varying degrees of functional impairment (131). The symptoms, especially pain, tend to be worse in the morning and improve in 1-2 hours, followed by worsening during late afternoon and evening again to be improved after a few hours (132). If night pain is present it often interferes with the sleep pattern causing fatigue and enhancing sensitivity to pain (133).

The pathophysiology of pain in OA is not fully understood. The hyaline cartilage covering the articular surfaces of bones in the synovial joint is aneural, which means it is not nociceptively competent – it cannot generate a nociceptive signal. There are nociceptive fibres and mechanoreceptors present in the synovium of the subchondral bone, periosteum, tendons, capsule and ligaments (133) and in the OA affected bone marrow lesions and synovitis (134, 135) so these tissues are obviously more implicated. Both central and peripheral sensitization are reported to play a part in the maintenance of the pain (133).

Diagnostic guidelines for Osteoarthritis

The American College of Rheumatology (ACR) criteria (68) can be used to diagnose OA of hand, hip, and knee. However, a clinical diagnosis of OA can be made without laboratory or radiographic investigations in the presence of typical signs and symptoms on clinical grounds in patients above the age of 45 years (136).

The ACR criteria for osteoarthritis of the hand (137):

i) hand pain, aching or stiffness

ii) Hand tissue enlargement of two or more joints

iii) Fewer than three swollen metacarpophalangeal joints

iv) Hand tissue enlargement of two or more distal interphalangeal joints

v) Deformity of two or more joints

The ACR criteria for osteoarthritis of the hip (137):

i) Hip pain plus at least two of the following:

ii) ESR of less than 20 mm per hour

iii) Femoral or acetabular osteophytes on radiographs

iv) Joint space narrowing on radiographs

The ACR criteria for osteoarthritis of knee (137):

i) Knee pain plus osteophytes on radiographs and at least one of the following;

ii) Patient age older than 50 years

iii) Morning stiffness lasting 30 minutes or less

iv) Crepitus on motion

Vitamin D and osteoarthritis

OA is often associated with vitamin D deficiency especially in elderly people (138, 139) and affects the health-related quality of life in the older population (140). Vitamin D deficiency affects bone mineral density, articular cartilage turnover and osteoblastic activity (141) and also enhances the activity of metalloproteinase and proteoglycan synthesis (142) which leads to cartilage loss and can, therefore, theoretically precipitate OA (143). It is also possible that the reduced mobility in OA patients affects the time they spend outdoors and their activity levels leading to reduced UV exposure thus causing diminished vitamin D synthesis.

Some studies show a moderate to a strong association between vitamin D levels and knee OA. However, it is unclear if this association is applicable across all age groups. An observational study (143) separated 80 elderly women with knee OA (diagnosed following ACR criteria) into two groups based on their serum vitamin D levels tested by ELISA. Group 1 consisted of 54 patients with vitamin D level <50nmol/l and group 2 consisted of 26 patients with vitamin D level > 50nmol/l. The Kellgren-Lawerence (K/L) grading scale was used for determining the clinical grade of knee OA and the Lequesne Algofunctional Index was used to assess the pain and physical function, with a total score ranging from 0 to 24. A score of < 7 corresponds to mild-moderate, 8-13 severe and > 14 to extremely severe functional impairment. Patients in group 1 showed higher K/L grades- 2, 3 and 4 ($p<0.001$) and also significantly higher score in Lequesne test ($p<0.001$) when compared to group 2. This study showed that vitamin D status correlates with disease severity and worsening especially in women aged 65-80 years diagnosed with knee osteoarthritis (143). However, contrasting findings were observed in another cross-sectional study (144), which compared serum vitamin D levels of 148 patients aged 45- 60 years, diagnosed with knee OA with 150 age-matched controls. The study found

that the overall mean serum 25(OH) D levels in participants with OA were not significantly lower than the controls (p=0.28). However, subgroup analysis showed that the mean 25 (OH)D levels in OA patients aged <60 years was significantly lower than the controls (p=0.01) thus, suggesting a significant association between serum vitamin D and knee OA in patients aged <60 years (144).

Two main symptoms of OA, pain and physical activity, have been widely investigated for the effect of vitamin D supplementation. A retrospective cohort study (145), involving 182 OA patients scheduled for knee or hip replacement surgery, investigated the role of vitamin D levels on pre-operative physical activity. The University of California, Los Angeles (UCLA) activity scale was used to measure patients' physical activity. A score of >3 was considered as mild functional disability and a score <3 as a major functional disability. The study found that patients with 25(OH)D levels <50 nmol/L compared to patients with 25 (OH)D levels >50 nmol/L were three times more likely to report UCLA activity scale scores of <3 (Odds ratio (OR) 2.79; 95% CI,1.72-9.17) suggesting an association between serum level of vitamin D and pre-operative physical activity score (145). These findings are in line with previous studies which reported an association between vitamin D levels and muscle strength and performance (146, 147) thus affecting overall physical activity in OA patients. The Tasmanian Older Adult Cohort (TasOAC) (148) examined, the correlation between vitamin D levels and the difference in the knee and hip pain. Radioimmunoassay was used to measure 25(OH)D levels at baseline and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire was used to measure pain at baseline, 2.6 and 5 years, from 769 randomly selected adults aged 50-80 years. This was the first study to demonstrate that even moderate vitamin D deficiency could predict the incidence, anatomical changes and worsening of knee pain over 5 years and

hip pain over 2.4 years (148). This suggests that maintenance of vitamin D status may attenuate knee or hip pain and the decline in QOL in older populations with knee OA.

In 2012 a cross-sectional study (149) found that inter-racial differences in experimental pain are mediated by differences in vitamin D levels. The study compared 45 black Americans and 49 white Americans diagnosed with symptomatic knee OA. The study used quantitative sensory testing, including measures of sensitivity to heat and mechanically induced pain. Black Americans showed significantly lower levels of vitamin D, demonstrated a higher level of pain and greater sensitivity to heat and mechanically induced pain than the white Americans. This suggests that deficiency in vitamin D levels may be a risk factor for increased knee OA pain in black Americans (149).

Another widely researched area is structural changes in OA patients (determined by radiographs) and the effect of vitamin D. Presence of cartilage loss, osteophytes and narrowing of joint space have been shown to be relatively reliable radiographic indicators of progression of OA (150). The K/L scale is widely used to classify the progression of OA using the above radiographic indicators. The K/L scale ranges from 0 to 4; 0=no osteophytes or joint space narrowing, 1=questionable presence of joint-space narrowing or osteophytes or both, 2=definite presence of either osteophytes or joint space narrowing, 3=definite moderate (approximately 50%) joint space narrowing usually with osteophytes present and 4=severe joint space narrowing.

Using this technique MacAlindon et al. (150) studied participants from the Framingham Study who had been followed for more than 40 years. The participants received anteroposterior weight-bearing radiography of the knee at baseline and a follow-up examination. The K/L scale

was used, with a score of 2 and above classified as OA. The study found that participants with low intake and low serum levels of vitamin D, approximately 75 nmol/L, had 3 fold increased risk of radiographic worsening of pre-existing knee OA than participants with high intake and serum levels (150). Similar results were replicated in hip OA patients. Lane et al selected 237 women from the random sample of the Study of Osteoporotic fractures (SOF) (151), who had a baseline and follow-up (8 years) data on serum vitamin D levels and hip radiographs and performed logistic and linear regression to examine the association between vitamin D levels with radiographic changes. The study reported that participants with low serum levels of vitamin D (defined as between 19-54 nmol/l) were nearly 3 times more likely to develop incident hip OA, defined as the development of definite narrowing of the joint space. Most studies consider serum level of vitamin D >50 nmol/l to be sufficient, it is not clear as to the reason for defining deficiency even above 50 nmol/l level. This study also did not investigate the effects on progression of OA.

Although these studies investigating how radiographic indicators of OA interact with vitamin D levels show similar outcomes, only one study supports the effect of vitamin D on disease incidence (151) while others support its role only in disease progression and not incidence (150). Moreover, MacAllidon et al. used the full extension anteroposterior radiographs which have limited accuracy in evaluating the joint space without fluoroscopic positioning (150). A follow-up study in 2007 (152) used data from two longitudinal cohort studies which included the Framingham Offspring Cohort (offspring of the original Framingham study participants) and Boston Osteoarthritis of the Knee Study (BOKS). They found no association between vitamin D status and risk of joint space or cartilage loss in knee OA patients. The study included 715 and 277 subjects respectively from each cohort with baseline mean vitamin D level of 50 nmol/L. The study used radiographic assessment for joint space narrowing, MRI for cartilage

loss, and radioimmunoassay for measuring vitamin D levels at baselines and follow-up, 9.5 years for the Framingham Offspring Cohort and 30 months for the BOKS study. The cohort studies showed 20.3 % and 23.6% worsening of the knees respectively, with most knees showing no evidence of OA at baseline thus negating any association between vitamin D levels and incidence or disease progression of OA (152).

These findings are in line with randomized double-blind placebo-controlled clinical trials. An RCT (153) randomised 146 participants diagnosed with symptomatic knee OA to receive either oral cholecalciferol 2000 IU/day or placebo for 2 years. The treatment and placebo group showed no significant differences in the increase in serum vitamin D levels ($p<0.001$), knee pain ($p=0.08$), knee function ($p=0.04$) and cartilage volume loss ($p=0.96$) indicating that vitamin supplementation for 2 years, as compared with placebo, did not reduce knee pain or cartilage volume loss in patients with symptomatic knee OA.

Another 2016 multicentre RCT (154) in Tasmania and Victoria randomised 413 participants with symptomatic knee OA and low vitamin D levels to receive 50,000 IU vitamin D3 or an identical placebo monthly for 2 years. The study found that level of vitamin D increased in the treatment group more than in the placebo group ($p<0.001$). However, there were no significant changes in the tibial cartilage volume ($p=0.13$) as measured by MRI, or the WOMAC knee pain score ($p=0.10$) over 2 years among participants receiving the supplementation as compared to the placebo. Thus, failing to show any association between vitamin D levels and progression of OA. However, these RCTs included participants with vitamin D levels between 12.5 - 60 nmol/L, which is below the optimal vitamin D level of 50 nmol/L in winter and 10-20 nmol/L higher in summer for musculoskeletal health as described by the Australian and New Zealand (AUNZ) position statement (80). This raises the question of how many patients

in the treatment group reached optimal vitamin D levels, which could be the reason why the group did not benefit from additional vitamin D.

In conclusion, although though there is some evidence supporting the role of vitamin D in the development and progression of OA, the heterogeneity of trial outcomes and lack of effect shown in prospective RCTs means that at present there is no clear indication for regular use of vitamin D in OA patients. A systematic review (138) appraising the evidence regarding the effect of vitamin D on OA, identified the lack of evidence regarding the association of vitamin D and OA in hip or hand. However, for OA of the knee, there is a moderate level of evidence linking vitamin D levels with the progression of knee OA, and strong evidence linking vitamin D levels with cartilage loss. This review suggests that vitamin D may have affected the structural changes of knee OA rather than the symptoms.

2.3.2 Rheumatoid arthritis (RA)

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown aetiology (155) characterized by systemic features and joint involvement (156). It affects nearly 1% of adults worldwide (157). RA exhibits periods of flare-ups which are characterised by pain, inflammation, and restriction in the movement and remission (158). The inflammation can also damage the joints if left untreated (158).

Diagnostic guidelines for Rheumatoid arthritis

Again, the ACR criteria are used for the definitive diagnosis of RA (159). There are 3 main criteria:

i) The confirmed presence of synovitis in at least 1 joint,

ii) Absence of an alternative diagnosis that better explains the synovitis,

iii) A total score of 6 or more out of 10 in the categories described below in A-D;

A. Joint involvement (159):

- 1 large joint – score 0
- 2- 10 large joints (shoulders, elbows, hips, knees, and ankles) - score 1
- 3 small joints (metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists) with or without involvement of large joints - score 2
- 4- 10 small joints with or without involvement of large joints – score 3
- >10 joints (at least 1 small joint)- score 5

B. Serology (at least 1 test result is needed for classification) (159)

- Negative rheumatoid factor and negative anti-citrullinated protein antibody (ACPA) - score 0
- Low-positive RF or low-positive ACPA- score 2
- High-positive RF or high-positive ACPA – score 3

C. Acute-phase reactants (at least 1 test result is needed for classification) (159)

- Normal CRP and normal ESR- score 0
- Abnormal CRP or abnormal ESR - score1

D. Duration of symptoms (159)

- < 6 weeks- score 0
- > 6 weeks- score 1

Vitamin D and Rheumatoid arthritis

Vitamin D has multiple immunomodulatory actions (160, 161) such as inducing immune tolerance (162), decreasing antigen presentation (163), inhibiting pro-inflammatory T helper cells (164), producing regulatory T cells and suppressing proliferation and differentiation of B-cell precursors into plasma cells (165). 1,25-(OH)D inhibits the differentiation of monocytes to dendritic cells reducing the number of antigens presenting cells that stimulate the T cells which are vital in RA (166). Evidence supports the role of vitamin D deficiency in the development and progression of multiple autoimmune conditions, such as RA (167), type 1 diabetes mellitus, multiple sclerosis (168), polymyositis (169), and systemic lupus erythematosus (SLE) (169).

Because vitamin D has immune modulatory actions, its possible role in the development of RA and the associated pain have been studied extensively. A systematic review and meta-analysis (170) investigated if there was an association between vitamin D intake and the incidence of RA and vitamin D levels and RA activity. For the analysis, of the former association, data was collected from 3 cohort studies including 215 and 757 participants and 874 incident cases of

RA. The study found that individuals in the higher vitamin D intake group had a 24.2% lower risk of developing RA than the lower intake group. In the sub-group analysis, the study found that vitamin D supplement intake also lowered the risk of developing RA by 23.6%. The meta-analysis showed a significant association between vitamin D intake and RA incidence (p=0.047). For the second analysis, data was collected from 8 studies, six cross-sectional and two case-control studies. Seven of the eight studies indicated that RA activity was inversely correlated with serum vitamin D levels. However, as noted by the authors the results of the analysis should be interpreted cautiously as the data on vitamin D levels and RA activity from all studies could not be combined because of high heterogeneity between the individual study designs and outcomes (170). These results are in contrast to another study conducted by Baker et al. (171) which found no association between vitamin D intake and risk of RA.

Very few studies investigating the risk of developing RA have actually examined the nutritional and dietary intake of the participants prior to the onset of RA. One such study, a prospective cohort study (172) who followed participants for 11 years reported that higher intake of vitamin D was associated with lower risk of RA, especially in elderly women. The cohort reported on data collected from 29,368 women aged between 55-69 years with no prior history of RA. The study followed these participants for 11 years, estimated their dietary and supplemental intake of vitamin D as reported from the respondents' responses to a baseline food frequency questionnaire and examined the incidence of RA. The study confirmed 152 cases of RA in the 11 years follow-up period. The inverse association was evident for dietary and supplementary vitamin D intake and risk of development of RA (Relative risk (RR) 0.67, 95% CI, 0.44-1.00, p=0.05). Despite the large sample size and long follow-up, only 152 cases were identified during the follow-up period of 11 years and as a result, could not establish a statistical significance (172). These findings are in contrast to the two cohort studies conducted by

Costenbader and colleagues (173) who found no association between vitamin D intake and the risk of developing RA. The first cohort included 91,739 women from the Nurses' Health Study (1980-2002) and the second study included 94,650 women from the Nurses' Health Study II (1991-2001).

The relationship between vitamin D and disease activity of RA has been researched considerably. A cohort study (167) which compared 44 patients diagnosed with RA to age and sex-matched controls (n=44) found that vitamin D deficiency was highly prevalent in patients with RA and influenced disease severity. The study measured serum vitamin D levels, parathyroid hormone levels, C-reactive protein and erythrocyte sedimentation rate along with the 28-joint Disease Activity Score (DAS28) in both the groups. Vitamin D levels were found to be negatively correlated to the DAS28 score, CRP and ESR the correlation coefficient being -0.084, -0.115 and -0.18 respectively. This suggests that vitamin D has a role in modulating disease activity in RA (167). Similar findings of an inverse association between vitamin D status and disease activity in RA were observed in studies conducted by Cutolo and colleagues (174) who studied the association between serum 25- hydroxyvitamin D levels and the DAS28 score in female RA patients from Italian and Estonian background during winter and summer. The study found that in both IP and EP the variation in 25(OH)D levels between winter and summer was significant ($p=0.0005$). However, a negative correlation between 25(OH)D and DAS 28 was found in summer only in IP ($r= -0.57$, $p<0.0001$) and in EP in winter ($r= -0.40$, $p <0.05$).

Similar findings were observed in studies conducted by Rossini and colleagues (175) in 2010 ($p=0.001$) and Haque and Bartlett (176) in 2010 ($p=0.001$). A recent systematic review and meta-analysis also found an inverse association between vitamin D and disease activity as

measured by the DAS28 (r=-0.13, 95% CI, -0.16- -0.09). The latitude-stratified subgroup analysis showed a relatively stronger negative correlation between vitamin D levels and DAS28 in low-latitude areas and also in developing nations (156). The stronger negative correlation in low-latitude areas was attributed to the moist weather condition in low-latitude areas, which tend to cause higher arthritis pain resulting in higher DAS28 scores. Some of the limitations of this meta-analysis is that it has a small sample size (n=3489) and it does not address heterogeneity within the selected studies. Some studies have also linked vitamin D deficiency with disease activity in RA (177, 178). However, other studies did not find an association between vitamin D deficiency and disease activity in RA (171, 179, 180).

Many studies have also proposed that vitamin D deficiency also leads to RA associated osteoporosis. This was first suggested by Olezner and colleagues in 1998 (181), who investigated 96 RA patients and found that lower levels of serum vitamin D accelerated negative calcium balance and inhibition of bone formation which lead to an increase in the disease activity and predisposed them to osteoporosis (181). Deal and colleagues (182) have also observed that RA patients are more susceptible to osteoporosis (182). Hence, vitamin D supplementation along with anti-rheumatic drugs have been proposed for patients with RA not only for its effect on disease activity (157) but also for the prevention and treatment of osteoporosis (183).

The findings from the above studies provide some support for the role of vitamin D in the development and progression of RA suggesting that vitamin D measurement and supplementation should be considered as an option in the management of RA patients. However, due to the limited number of studies investigating the association between vitamin D and RA, there is clear need for well-designed RCTs with long-term follow-up.

2.3.3 Chronic widespread pain

Background

Chronic widespread pain (CWP), is a global musculoskeletal disorder, with an estimated prevalence of 10% to 24% in the general population (184, 185). The pathophysiology of CWP is unclear, but it is believed that somatization, altered pain perception, functional changes in pain receptors and hyperexcitability of central and peripheral nervous system play important roles. Although multiple individual, social, psychological and occupational risk factors influence the development and progression of CWP, other potential risk factors for developing CWP are smoking status (186), poor education (187), low physical activity (188), low income (189, 190) and poor social life, relationship status- married, divorced or separated (185). CWP is characterized by reduced pain threshold, fatigue, disturbed sleep, problems with cognition and feelings of stress, depression and anxiety, headaches and irritable bowel syndrome (191).

Chronic widespread pain often overlaps and even resembles other musculoskeletal and pain syndromes such as CNMP (192), chronic fatigue syndrome (193), fibromyalgia and irritable bowel syndrome (193). These conditions are often grouped as "medically unexplained symptoms" (194) and are recognised in specialist clinics (195). However, this often leads to the interchangeable use of these terms, especially chronic widespread pain, fibromyalgia and CNMP in practice (196-198). FM is now recognised as one of the sub-group of patients who have CWP where CWP forms a cardinal feature of FM (191).

The interchangeable use of terms was first observed by Rohrbeck and colleagues (193) who discovered that the estimated frequency of fibromyalgia was much higher than the annual prevalence of diagnosed fibromyalgia in the primary care setting in UK population. Therefore,

they examined the consultation pattern over a 5-year period and identified 148 cases consulting for various musculoskeletal pains and 524 controls who had not consulted for musculoskeletal pain during the same period. The review showed that patients seeking medical care for multiple regional pain syndromes exhibited similar attributes to those associated with CWP and FM. Also, the GPs were rarely using the diagnostic label of "fibromyalgia" and were not necessarily applying the ACR criteria for fibromyalgia when making the diagnosis (193). Similar findings were supported by another UK primary care study (199). The known differences between CWP and FM are that patients with CWP do not exhibit tender points (191) and are linked to higher consumption of drugs, and use of disability pensions compared to FM patients. Still, there is not enough information on other sub-categories of CWP, which could potentially improve patient care.

Diagnostic guidelines for chronic widespread pain

According to ACR criteria, CWP is classified as pain persisting for more than 3 months that affects both sides of the body, above and below the waist, including some part of the axial skeleton (200-203). In 1996 Macfarlane et al. (204) proposed a coding system for classifying CWP pain as pain with a strong association with psychological disturbance, fatigue, sleep problems and tender points. They named it the "Manchester definition". Though this definition is used in clinical and epidemiological studies it is not clear if this definition is better than the ACR criteria. Future research should compare the classification based on these methods, with or without tender points.

Vitamin D and chronic widespread pain

Multiple studies demonstrate that CWP is associated with low levels of vitamin D (37, 200-203). This relationship is often attributed to the development of osteomalacia associated with low vitamin D levels, of which musculoskeletal pain is a feature. Moreover, CWP and low vitamin D levels have common risk factors such as smoking (186), low physical activity (188) and depression (187) which may partly explain their association. It is equally possible that CWP will affect physical activity and subsequent sun exposure thus affecting vitamin D levels.

Some studies show evidence of low vitamin D levels in women experiencing CWP, while in men it is unrelated to vitamin D levels. It is not clear why there was a gender difference, however, it is important to note that these studies mostly include participants of Caucasian origin which may not translate to non-white ethnic groups (200, 205).

In a large cross-sectional study (202), the European Male Aging Study data from 3075 men aged between 40-79 years was collected. The participants with CWP had lower vitamin D levels than the pain-free participants ($p<0.05$). The findings suggest a moderate level of association between vitamin D levels and CWP indicating vitamin D levels to be a predictor of the onset of CWP. In a follow-up analysis (203), data was collected from the original participants of the EMAS study. The study assessed baseline as well as follow-up vitamin D levels, the course of pain, and presence of CWP using the ACR criteria. Of the 2313/3369 respondents, 151 developed new CWP at follow-up and 577 remained pain-free at both time points. The participants at the upper quantile of serum 25(OH)D level (≥ 90.6 nmol/l) as compared to those in lower quantile (<38.9 nmol/L) were more likely to have developed CWP (OR=1.93; 95 % CI,1.0-3.6) at follow-up. These results (203) suggest that men with very low

levels of vitamin D (below 38.9nmol/L) at the beginning of the study were at an increased risk of developing CWP at follow-up, mediated by depression (OR=1.77; 95 % CI,0.98-3.21), and obesity (OR=1.67; 95 % CI,0.93-3.02).

Similar results were observed in various reports which suggest an association between low vitamin D and CWP in a specific group (201). These findings contrast with a population-based study (200), which observed an association between serum vitamin D levels and CWP, in women but not in men, although men reported similar rates of pain (11.4% for men, 12.5% for women). This study included 9377 men and women born in the 1st week of 1958 who had a biomedical assessment at the age of 45 years. The mean vitamin D levels in women who reported CWP were 46.6 nmol/l and men were 53.1 nmol/l respectively (200). The analysis showed the interaction between 25(OH) D levels and gender in relation to CWP (p=0.006). This interaction was independent of lifestyle and social factors. Similarly, a 2015 meta-analysis (205) of data from 12 studies giving a total of 1,854 patients and 7850 controls, found a crude association between low levels of vitamin D and CWP. In the unadjusted analysis, CWP patients showed higher risk of hypovitaminosis D (OR= 1.63; 95% CI, 1.20–2.23, p=0.117, I2=37.8%). The subgroup analysis based on gender did not find a significant difference in the ORs. Although the individual studies included in the review suggested a relationship between hypovitaminosis D and CWP, the pooled analysis failed to establish any association.

Studies investigating the effect of vitamin D supplementation on pain often separate the pain categories with five commonly being used: chronic, widespread, non-specific, persistent or musculoskeletal pain. Hence, studies reporting an effect observed with supplementation are listed under the section of chronic non-specific musculoskeletal pain.

2.3.4 Fibromyalgia

Background

In 1904, Sir William Govers first coined the term "fibrositis", a term commonly used to describe muscular pain, tension or psychogenic rheumatism. The current concept of fibromyalgia was proposed by Smythe and Moldofsky in 1977-1978 (206), which represents it as pain condition (-algia) and not just inflammation of connective tissues (-itis). Fibromyalgia (FM) (207) is a major type of non-inflammatory myalgia (208), commonly seen in rheumatology clinics (209). The prevalence of CWP and FM in developed countries is reported to be 10% - 24% (185, 197) and 0.5%- 4% (210) respectively in the adult population. It is characterised by chronic widespread pain and multiple tender points for which no definitive cause is identified (211). It is associated with a range of other symptoms, like sleep disorder, psychological stress, fatigue and mood disorders (193). The muscle pain and tenderness in FM is attributed to central sensitisation and amplification of nociception (208). When fibromyalgia was first proposed, it was controversial, however now with extensive research in the area our understanding has improved.

Diagnostic guideline for Fibromyalgia

The following criteria are used for the diagnosis of FM. A patient should satisfy all three conditions listed below for a diagnosis of FM (212):

i) Widespread pain index (WPI) > 7 and symptom severity (SS) scale score >5 or WPI 3-6 and SS scale score >9.

ii) Symptoms should be present at a similar level for at least 3 months.

iii) The patient does not have a disorder that would otherwise explain the pain.

Widespread pain index (WPI) -

WPI is used as a quantitative measure (213) to record the presence of pain in the listed nineteen body parts. The presence of pain in each is scored 1, a score of > 7 is considered diagnostic.

Symptom severity (SS) scale –

SS is a two-part scale (213) which is used to indicate the level of symptom severity over the past week. In part (a) fatigue, waking unrefreshed and cognitive symptoms are scored 0 (no problem), 1 (slight/mild problems), 2 (moderate level of the problem) and 3 (severe, life disturbing problem) each. In part (b) a list of other symptoms such as muscle pain, muscle weakness, headache, dizziness, constipation, diarrhoea, irritable bowel syndrome, insomnia, heartburn, nausea, vomiting, loss of appetite, rash etc. are checked. SS scale is scored between 0 to 12 by adding the scores in the parts (a) and (b).

Vitamin D and Fibromyalgia

According to the 1990 ACR criteria for FM an individual should have a history of CWP and presence of 11 out of 18 tender points, which are grouped in 9 paired regions of the body (211). Women are 1-2 times more likely to experience CWP, but about 10 times more likely to meet criteria for FM (210). This gender difference between CWP and FM is solely attributed to the ACR criteria requiring 11/18 tender points, which is observed 11 times more commonly in women than in men (214, 215). This tender point criterion made FM more exclusive to females as they are more likely to exhibit tender points than men. Therefore, excluding this criteria would make it far more generalised in all gender groups (216). This is reflected in studies

investigating the incidence of vitamin D insufficiency or deficiency in FM patients. Screening 40 female patients (217) with FM attending an outpatient department of the Civil Hospital, Karachi , showed that 32 were vitamin D deficient (serum vitamin D levels <50nmol/l) and 8 patients were vitamin D insufficient (serum vitamin D levels between 52.5-72.5 nmol/l). Similar, findings were observed in a 2003 case-control study (218) comparing the vitamin D levels of 38 pre-menopausal women to age and gender matched controls. The study found that 17 women from the FM group as compared to 7 women from the control group had a serum vitamin D concentration <20 nmol/l. ($p<0.015$) supporting the observation that there is a higher proportion of vitamin D deficiency in FM patients (218). However, another case-control study (219) did not observe a significant difference in vitamin D levels between the patient and control group ($p>0.05$), the incidence of vitamin D deficiency was also similar between the two groups (67.5% vs 70%). The treatment group included 40 pre-menopausal women diagnosed with FM while the control group included 40 age and sex matched healthy controls. But, the study observed that in the FM group, vitamin D levels showed significant correlation with the intensity of pain ($r=-0.653$, $p=0.001$) as reported by the patients, suggesting that hypovitaminosis D may play a role in amplifying pain intensity in FM patients (219). These findings were similar to a 2010 cross-sectional study (220) which did not observe a significant difference in vitamin D levels in 87 fibromyalgia patients compared to 92 age and sex matched healthy controls and no association between vitamin D levels and pain intensity. These findings were similar to another case-control study conducted in the United States (192) that observed no effect on pain with vitamin D supplementation. Altogether, these studies do not make any conclusive findings regarding the association between vitamin D and FM, with some studies, reporting a positive association (217, 221, 222) and others a negative association (198, 220, 223). The major limitations of these studies were that most included only female participants

and most did not have long enough follow-up periods. There was also a lack of information regarding seasonal variations in serum levels of vitamin D and in pain intensity.

Multiple studies have investigated the effect of vitamin D supplementation in FM patients. In a case-control study (224), bone mineral density (BMD) and serum vitamin D levels were measured to examine the possible association between fibromyalgia and osteoporosis or hypovitaminosis D. The study collected data from 205 female patients (224) diagnosed with fibromyalgia and 205 gender and age- matched healthy controls. The study found no differences in BMD and vitamin D levels in the patients (cases) and controls. However, it was recorded that in summer, the patient group showed a lower rise in vitamin D levels than controls, indicating a relative vitamin D insufficiency among FM patients. The lower rise in vitamin D levels could be due to reduced outdoor time as a result of fatigue and soreness in the patient group. However, as the study did not follow these patients further, there are no data to show if the reduced vitamin D levels during summer altered the pain intensity of these patients (224). Another study (213) screened vitamin D levels and calculated WPI of 30 consecutive female patients (both veiled and non-veiled) diagnosed with fibromyalgia. This study found all the FM patients had severe vitamin D deficiency (mean level was 11.8+- 3.6 nmol/L) with a significant inverse correlation between vitamin D levels and WPI ($p=0.08$). The study supplemented all participants with either single dose (600,000 IU) vitamin D3 intramuscular injections or oral vitamin D3 tablets 50,000 IU weekly for 8 weeks. Participants were re-evaluated by the clinical FM diagnostic criteria at follow-up, 1 month after the treatment with vitamin D injection or 2 months after treatment with vitamin D tablets. The study observed clinical improvement in all patients following treatment with vitamin D. In a 2014 study (225) 30 women with fibromyalgia and vitamin D levels <80nmol/L were randomized to receive 1200-2400 IU cholecalciferol per day. The treatment group observed a reduction in pain

irrespective of the dose given as compared to the control group. The major limitation of this RCT was its small sample size. Another study (222) found similar results in 139 patients with fibromyalgia. One hundred and three patients (74%) had low vitamin D level (38.9nmol/L); and were randomized to receive vitamin D3 injections (600, 000 IU i.m. single dose) or oral tablets (50,000 IU) for 8 weeks. Ninety percent of the patients in the treatment group reported complete resolution or a decrease in myalgia. This study also showed that vitamin D deficiency was highly prevalent in Arab (86%) and Pakistani patients (87%) (222) and least prevalent in Caucasian patients (8%) suggesting that the diagnosis of FM in Indo-Pakistani women could mean low levels of vitamin D. Limitations of this study were the lack of a control group and the short follow-up period. The study also did not provide any information regarding recovery time or variations for the two methods of supplementation used. The number of studies evaluating the effect of vitamin D supplementation on pain intensity in FM patients is limited, necessitating more focused research in the area to understand how low vitamin D may generate or maintain pain in FM patients.

2.3.5. Chronic non-specific musculoskeletal pain

Background

Chronic non-specific musculoskeletal pain (CNMP) is a complex idiopathic condition, characterised by localized or generalised pain and disability. The pathoanatomical and pathophysiological explanation for CNMP is unclear which often leads to a non-specific diagnostic label based on the presenting symptoms (226). It is a major health problem (227) with an increasing number of patients (217, 228), especially in children and adolescents (229, 230). However, there is a paucity of data on the prevalence of CNMP, mainly because of the lack of clear guidelines for identifying patients and different and often overlapping definitions of pain used in individual studies. Most of the studies reporting on prevalence use different terms of investigation such as, "chronic pain", "chronic widespread pain" or "nonspecific pain". According to de Vries and colleagues (231), in Western societies a high prevalence of CNMP is reported among patients seeking medical care resulting in reduced participation in work leading to a high socioeconomic cost. Chronic nonspecific musculoskeletal pain (CNMP) is an idiopathic condition with high prevalence reported among patients seeking medical care in general practice. The effects of CNMP extends beyond individual's physical and mental health, often affecting their family (232-234) and social life, working ability and performance (235) resulting in high levels of health care utilisation (236).

CNMP has a multidimensional biopsychosocial basis (84, 237), with patients exhibiting higher levels of anxiety and depression and poor physical activity and gross motor skills (226). Multiple factors such as psychological, physical, lifestyle (238) and social factors (84) interact to form a vicious cycle of pain (88) with management approaches reflecting this

biopsychosocial framework (118, 239). Meyer and colleagues (240) observed that in chronic musculoskeletal pain conditions, the sensitivity of central neurons input from unimodal and polymodal receptors is intensified. As a result, patients experience generalized or widespread hypersensitivity which resembles central sensitization. Management strategies should also put greater emphasis on the enhanced sensitivity of the nociceptive system (86), increased contribution of non-nociceptive sensory inputs and associative learning (241), cognitive mechanisms that emphasise perceived threat to body tissue and behavioural processes linking fear of pain, activity avoidance and catastrophizing (88) and de-emphasise ongoing tissue pathology or damage (87), with some exceptions, such as seronegative arthropathies.

Diagnosis of chronic non-specific musculoskeletal pain

CNMP is often used interchangeably especially with CWP and FM, because the pain presentation and associated co-morbidities such as mood disorders, sleep disturbances, and fatigue (211) are similar. However, it often differs from the ACR classification of CWP by more commonly affecting a single site rather than multiple sites (185). Due to the lack of diagnostic criteria, CNMP is often a diagnosis of exclusion. We do not know the clinical reasoning general practitioners (GPs) apply for diagnosing CNMP. There is a clear need for more research to understand the clinical presentations and diagnosis of CNMP in primary care.

Related research objective: To understand the clinical reasoning GPs' employ when diagnosing managing patients with chronic non-specific musculoskeletal pain.

Chapter 3 entitled ‘A qualitative exploration of GPs’ perspectives on managing chronic nonspecific musculoskeletal pain in Australian general practice’ aims to address this gap in knowledge.

Vitamin D and chronic non-specific musculoskeletal pain

There are mixed findings from studies investigating the role of vitamin D deficiency for patients with CNMP. A small number of studies suggest an association between low vitamin D levels and incidence of CNMP (37, 200), with one even reporting complete resolution of pain (213) on supplementation. However, there are also studies showing no effect of vitamin D supplementation (192, 198) and these contributed to the Cochrane systematic review (242) appraising evidence regarding the effect of vitamin D supplementation on all chronic painful conditions, concluding that there was insufficient evidence of a positive effect of vitamin D supplementation on pain. Thus, the link between vitamin D and CNMP remains unclear.

A cross-sectional study conducted by Plotnikoff and Quigley (37), was the first to demonstrate an association between vitamin D and nonspecific musculoskeletal pain, with nearly 96% of participants found to be vitamin D deficient. This study included 150 patients suffering from non-specific musculoskeletal pain with no history of FM, temporomandibular disorder, or complex regional pain syndrome. The study observed no differences in the level of vitamin D deficiency among the immigrant and non-immigrant groups. The risk of vitamin D deficiency was more pronounced in the younger compared to the older participants. Following this study, multiple studies were performed to investigate if gender and ethnicity affect vitamin D and

CWP. The results from these studies are conflicting. For example, the study by MacFarlane and colleagues (201) who conducted two population-based cross-sectional surveys, A and B in England, which compared subjects of South Asian origin (India, Pakistan and Bangladesh) with white Europeans. Survey A reviewed the occurrence of musculoskeletal pain among people aged 18-75 years while survey B was a screening survey of bone density in women aged 18-36 years using bone density scanning. The results from Survey A indicated a high incidence of widespread pain among South Asians (n=1945, OR=1.6, 95% CI, 1.3-2.1) compared to white Europeans (n=932). Survey B similarly showed a higher incidence of widespread pain among South Asians (n=137, OR=1.8, 9.5% CI, 0.7-4.7) and found that low levels of vitamin D (<10ng/ml) were more common among those with widespread pain (OR=3.5, 95% CI, 0.4-31.0).

These results not only show Asian ethnicity as a high-risk group but also suggests low levels of vitamin D to be a predictor of CWP. These results are consistent with a 2010 study (223) performed in an outpatient clinic in Iran. The study compared serum vitamin D levels of 276 patients referred to the clinic for the nonspecific musculoskeletal pain to 202 matched controls. The study (223) found a strong association between vitamin D and nonspecific bone pain, leg pain, arthralgia and widespread skeletal pain particularly in females (OR=2.1, 95% CI, 1.1–4.3, p=0.001). Another prospective observational study (243) performed in 2010 measured vitamin D levels in 100 female patients with CNMP of duration greater than 6 months, who were unresponsive to analgesic drugs. Eighty-four patients were detected as vitamin D deficient (serum vitamin D levels between 24-48 nmol/L) with 42 patients classified as severely deficient (serum vitamin D levels between 12- 20 nmol/L). All patients with deficient levels of vitamin D were given 1 α hydroxycholecalciferol 0.5-1μg with 800mg of calcium supplements orally daily according to the severity of the deficiency for 3 to 4 months. All showed noteworthy

improvement in their symptoms. The patients were thereafter given a daily supplement of 400IU vitamin D3 and 800 mg calcium carbonate along with a recommended 15 minutes of daily sun exposure, which maintained their improvement and treatment effect even after a year.

Several cross-sectional studies (244-246) and case reports (247, 248) and large intervention studies (192, 249, 250) support the beneficial effect of vitamin D supplementation on musculoskeletal diseases or complaints. These case series report on an unusual pain syndrome in vitamin D deficient patients, which shows improvement on supplementation (247, 248). These cases describe the pain pattern as nonspecific and sometimes localised to lower extremities, which may represent CNMP. But, due to limited information, it is difficult to be certain that this is the correct diagnosis. One of these reports observed complete resolution of symptoms with 50,000IU intake of vitamin D2 (247). However, the pain was reproduced if vitamin D deficiency recurred and could again be resolved with normalisation of vitamin D status. Another case study reported on wheelchair bound patients who regained their muscle strength within 4 to 6 weeks of treatment with vitamin D (248).

A small number of randomized controlled studies have investigated the efficacy of vitamin D supplementation on nonspecific pain. In 2012 Schreuder et al (250) performed a semi-crossover randomized controlled trial on 84 non-Western immigrants who were vitamin D deficient with complaints of persistent nonspecific musculoskeletal pain. The study evaluated the effect of high dose vitamin D3 on the pain patterns. Participants were randomized to either placebo or oral vitamin D3 150,000 IU single oral dose. At week 6, patients originally in the vitamin D group were randomised a second time to receive vitamin D again or switch to placebo, whereas patients originally in the placebo group were all switched to vitamin D. The outcomes were self-evaluated by patients based on the changes in their pain after the first 6 weeks. Patients in

the vitamin D group reported significant pain relief (p=0.04) and improved ability to walk upstairs (p=0.008), compared to their counterparts in the placebo group. The study found a small positive effect 6 weeks after high-dose vitamin D3 on non-specific musculoskeletal pain. This study used only a single strength of vitamin D with some participants receiving only 1 dose of vitamin D supplementation in 12 weeks which could have affected their outcome measures.

Another RCT (249) investigating the effects of a single a dose of 30,000 IU vitamin D administered orally or parenteral on nonspecific musculoskeletal pain in community-dwelling elderly subjects over 65 years of age observed similar effects. The study used a Visual Analog Scale (VAS) for pain assessment, Timed up and go test for measuring functional mobility, and SF-36 to measure the quality of life. The study assessed pain, functional mobility, quality of life and vitamin D levels before and after 4 weeks of treatment. In both the oral and parenteral (intravenous) vitamin D group, the TUG (p=0.0001, 0.0001) and the VAS (p=0.0001, 0.002) decreased significantly, whereas the SF-36 subtitles, physical functioning (p=0.0001, 0.0001), role physical (p=0.006, 0.001) increased. The single dose of vitamin D significantly improved the quality of life, decreased the pain and improved functional mobility in the elderly. This study added valuable information to the literature because of its randomized, placebo-controlled, double-blind study design and power analysis. This study excluded participants diagnosed with underlying chronic conditions such as Paget's disease, renal stones, fibromyalgia, thyrotoxicosis etc. that could potentially interfere with the effects of vitamin D supplementation.

These findings were not replicated in another RCT (192) including 50 patients with CNMP and vitamin D levels <50nmol/L. The study found no effect of 50,000 IU vitamin D

supplementations given once weekly for 3 months on the pain. The study used Functional Pain Score (FPS), and VAS to measure pain and serum immunoassay to measure vitamin D levels, at baseline and 3-month follow-up. There was no difference in, vitamin D levels (p=0.09), VAS (p=0.73), FPS (p=0.18) compared to 3-month post-treatment vitamin D levels (p=0.85), VAS (p=0.12), FPS (p=0.05). The study also observed no difference in pain scores between the treated groups. However, this study lacked proper blinding and randomization and included patients diagnosed with osteoarthritis (in whom pain is an integral part of their clinical diagnosis) in the control group. The current state of the evidence concerning vitamin D supplementation in CNMP pain is still unclear.

Related research objective- - What is the current evidence concerning the effect of vitamin D supplementation on pain associated with CNMP?

Chapter 4 – 'Does vitamin D alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis' aims to address this gap in knowledge.

2.3.6 How vitamin D can affect or modulate chronic nonspecific musculoskeletal pain?

The discovery of vitamin D receptors on muscle cells (251-253) led to many studies, as vitamin D supplementation could be an inexpensive and effective method to treat nonspecific musculoskeletal pain. It would be especially beneficial in non-Western immigrants, who are more prone to vitamin D deficiency than resident Caucasian people (201, 254-257).

In addition to calcium homeostasis, vitamin D is involved in many regulatory biological processes such as anti-inflammatory, anti-apoptotic and anti-fibrotic (51, 61) and it is believed to play a role in innate and adaptive immune system function as well (51, 61). People with vitamin D deficiency can present with nonspecific muscular pain and bone pain (258). It is proposed that the pain associated with hypovitaminosis D may be due to insufficient calcium phosphate (259) which affects the collagen matrix mineralisation causing it to become rubbery. As a result, the bone is not well supported which causes pressure on the periosteal covering innervated by sensory fibres (259). Even a gentle pressure on these bones can elucidate pain (259). Supplementation with vitamin D may exert non-genomic influence on the metabolism of muscle cells, growth of muscle fibres and nonspecific effect on central and peripheral nervous system (250).

Vitamin D deficiency could disturb the neuroimmunological process that subserves pain (260) due to the loss of its immune regulatory (51, 61), anti-inflammatory and anti-apoptotic function (51, 61). However, it is still unclear if pain associated with vitamin D deficiency is widespread or localised to arms, lower back or legs.

2.3.7 Characterising the testing, prescription, and taking of vitamin D supplements in people with pain.

Vitamin D supplements are taken by a large number of people, with and without pain. It is also considered as cost-effective (261, 262), easily available intervention (262) with minimal side effects (262). Remarkably, however, little is known about the demographic and clinical features that are associated with the testing, prescription and consumption of vitamin D supplements in people with chronic pain. There is a reasonable evidence that older age groups (263), female

gender (264), higher body mass index (265) and dark skin pigmentation (266) are associated with vitamin D deficiency.

However, one would predict that if the link between vitamin D deficiency and pain is based specifically on postulated biological mechanisms, such as the neuroimmunological process, then the characteristics of someone's pain neuropathic or non-neuropathic descriptors and the intensity of their pain, should also be considered when testing for, prescribing and taking vitamin D supplementation. Moreover, if vitamin D deficiency is suspected on the basis of biological mechanisms of effect, then factors such as where one lives should relate only insofar as differences in exposure to sunlight or diet exist.

Related research objective- What demographic and pain-related factors are associated with testing of vitamin D, vitamin D deficiency, and the prescription and taking of vitamin D supplements?

Chapter 6 – "Factors associated with testing, deficiency and supplementation of vitamin D: a predictive model" aims to address this gap in knowledge.

2.3.8 Patient's perspectives on pain education and their patient-provider relationship.

The first study of this thesis investigates, using a focus group design, the perspectives of GPs' on management of people with chronic pain. That study revealed certain features of the clinical interaction that were felt by GPs' to be important for the patient such as developing a good rapport. The final study of this thesis uses a survey design to compare and contrast the GPs'

perspectives with those of patients on the patient-provider relationship, the implications of pain education and their effect on pain intensity and perception of recovery. Patient perspectives on care has been studied in other contexts such as quality of care (267), cost of care (268), experience of care (269) among others. But it remains unknown as to whether patients with chronic pain and GPs are aligned in what they prioritise as important in their clinical interactions.

Related research objective- What are the experiences of people with chronic pain, of their health care interactions and pain education?

Chapter 7 – **"**Effect of pain education and patient-provider relationship on patient-reported pain intensity and recovery" aims to address this gap in knowledge.

2.4 Conclusion

There is some evidence of an association between vitamin D deficiency and musculoskeletal weakness and pain. However, it remains unclear if the pain associated with vitamin D deficiency is generalized or localized to a specific body part such as arms, lower back, and legs. It is also possible that another confounding factor may lead to both increased pain perception and lower vitamin D levels, or that they are simply associated but not causative. For example, individuals with musculoskeletal pain may have reduced exposure to sunshine because they walk less, which would lead to an association but would not necessarily mean that low vitamin D levels were causative. This would be applicable for all musculoskeletal pain types. It remains to be confirmed whether this association is causative or not.

This thesis seeks to identify the magnitude of any effect of vitamin D supplementation on nonspecific musculoskeletal pain. We then investigate the clinical understanding currently used by general practitioners when managing individuals who present with this complex condition. Further, for the first time, we try to understand the perspectives of patients' who experience chronic pain about their pain management. These studies will provide context-specific evidence that can contribute to the implementation of evidence-based management, to improve treatment outcome.

CHAPTER 3

A qualitative exploration of GPs perspectives on managing chronic nonspecific musculoskeletal pain in Australian general practice

3.1 Preface

This chapter comprises of the first study of the thesis, which examined objective 1 - What management strategies do GPs employ with patients presenting with CNMP?

In the Australian health care system, general practitioners (GPs) are usually the primary point of contact for medical advice (22). As a result GPs see the widest range of conditions of any specialty and are required to have a working knowledge of multiple conditions (270). Complaints of chronic pain arise in an estimated 15-20% of GP visits (23, 271). However compared to management of other chronic diseases physicians report a high level of dissatisfaction when managing chronic pain due to lack of training and resources (24-26).

This paper has been accepted as an original research article for publication in Family Medicine and Community Health.

Characteristics of Chronic Pain in Australia

Prevalence

According to the Australian Bureau of Statistics (ABS) National health Survey (NHS) data in 2007-2008 (272), 3.2 million people (1.4 million males and 1.7 million females) aged 15 years and over reported experiencing pain in the previous four weeks. In comparison to the 1995 data, the overall rates of body pain in Australia increased from 57% to 68%; and severe/very severe pain increased from 7% to 10% (272). It was also observed that 1 in 5 Australians with severe/very severe pain suffered from depression or other mood disorders which are 4 times the rate for people without pain (5%) and more than twice the national average (9%) (272).

The prevalence of chronic pain today is comparable or higher than that of the National Health Priority Areas such as cardiovascular disease, cancer, musculoskeletal diseases, injuries, mental disorder, asthma and diabetes (273). It is also estimated that the prevalence of chronic pain will increase from around 3.2 million in 2007 to 5.0 million by 2050 (273).

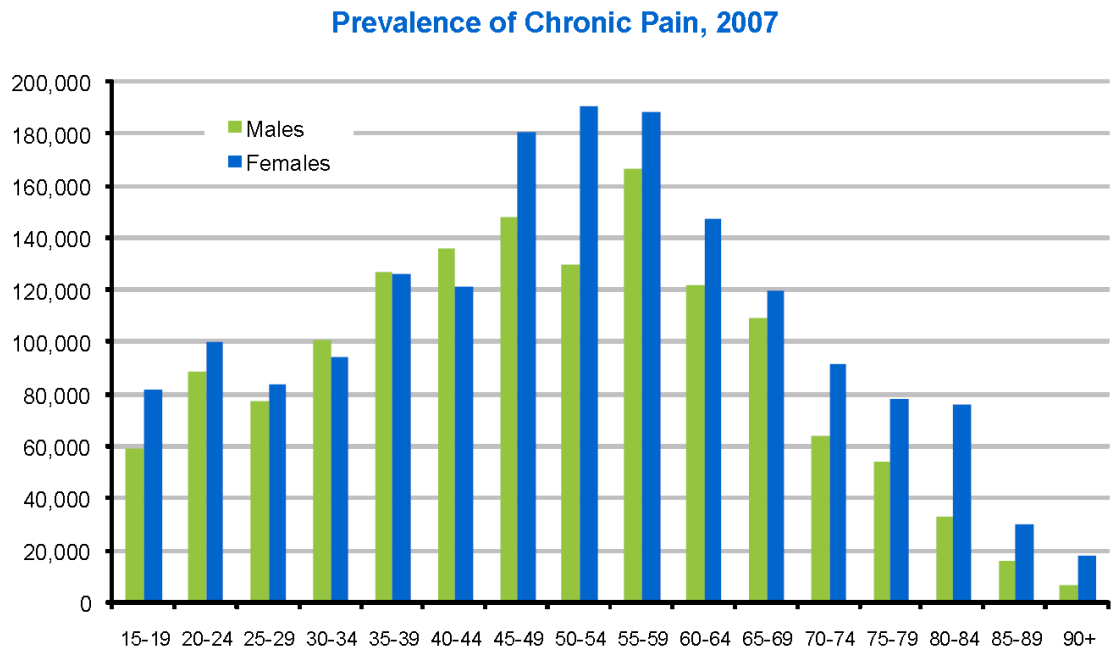

Figure 3.1 Prevalence Chronic Pain, Australia 2007 (273)

Economic Impact

On the Society:

The total cost of chronic pain was estimated in 2007 at $34.3 billion to the economy per year or $11,000 per person (273). The highest impact is seen on productivity costs with approximately $11.7 billion caused by chronic pain. The next largest share is associated with the burden of disease (BoD) at around $11.5 billion, followed by the costs to the health system at approximately $7.0 billion which captures the medical costs, the pharmaceuticals, other health care services and residential aged care (273). Comparatively, smaller costs are attributed to the opportunity cost (e.g. informal care, aids and modification and deadweight losses (DWL) (e.g. taxation revenue forgone, welfare payments, disability support pension, and NewStart allowance.

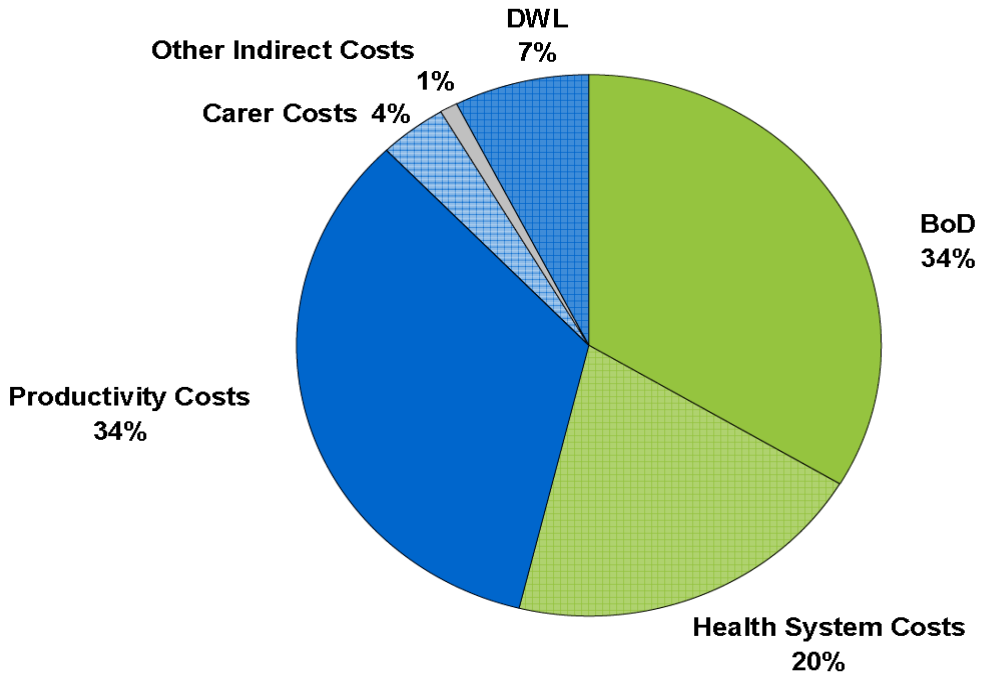

Figure 3.2 Total cost of Chronic Pain to society(273)

DWL: Deadweight loss; BoD: Burden of Disease

On the individual

Individuals suffering from chronic pain bear the largest share (55%) of the whole cost themselves, primarily due to the large burden of disease, followed by the Federal government which bears 22% of the total cost (273). While employers and the State Governments bear 5% each, followed by family and friends bearing 3%, and society bearing the remaining 10% of the cost (273).

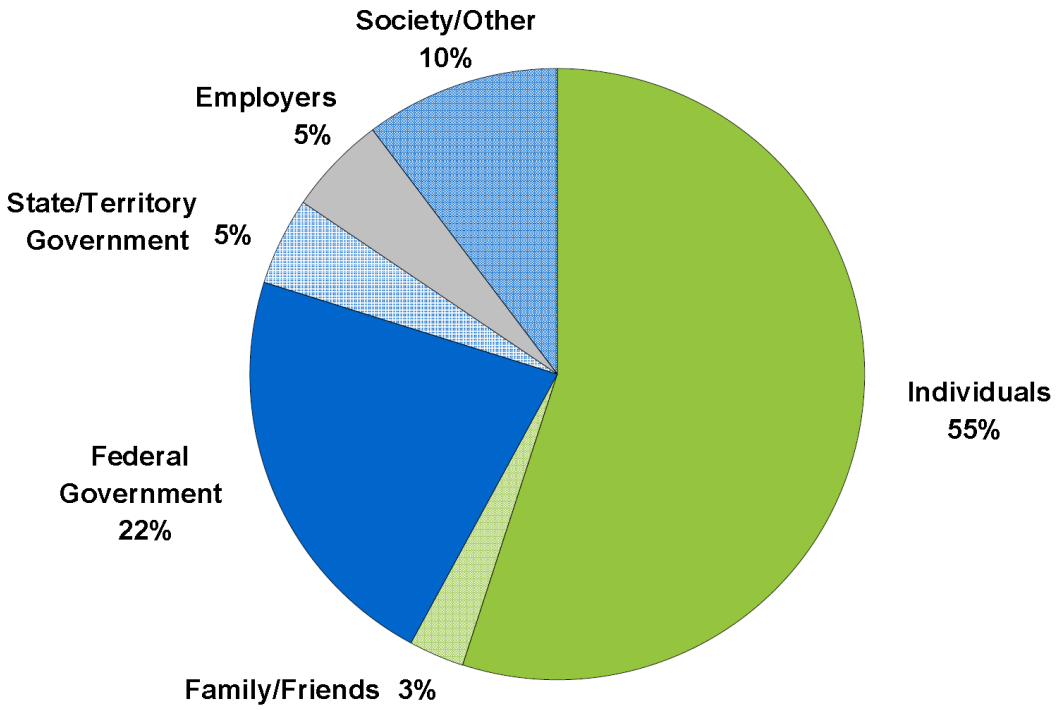

Figure 3.3 Total cost of chronic pain at an individual level (273)

Chronic nonspecific musculoskeletal pain

Chronic non-specific musculoskeletal pain (CNMP), is a type of chronic pain distinguished by the clear absence of pathophysiological or anatomical causes (226). It has a rising prevalence among patients seeking medical care in general practice. CNMP causes significant disruption to the sufferers' lives, relationships (226) and working ability (235). Multiple studies suggest that symptoms of CNMP in children and adolescent age groups is a predictor of poor quality of life and disability in adulthood (226, 274).

The International Classification of Diseases (ICD) does not provide diagnostic codes for an array of chronic pain manifestations (275) which includes CNMP. The lack of diagnostic codes hinders billing for health care expenses related to pain management and development of new therapies (276-278), which further complicates the management of CNMP for doctors. In the absence of both an ICD code and guidelines for management, it becomes imperative that we better understand how GPs are diagnosing and managing patients with CNMP currently.

As seen in chapter 2.3 CNMP has been linked with vitamin D deficiency, which is a major global public health concern (38, 279, 280), even in countries with abundant sunlight (280). It has been estimated that nearly one-third of Australians aged > 25 years are vitamin D deficient (38). Vitamin D supplementation for CNMP has produced inconsistent results (192, 249, 250, 281), with the benefits of screening for hypovitaminosis D being questioned (192, 282).

In the literature review, we found little information about how GPs manage CNMP, with no published studies undertaken in primary care. To address this, we conducted a qualitative study

with Australian GPs, aiming to understand their approach to managing CNMP. Bearing in mind, GPs role in primary health care for most individuals in Australia, their experiences and views can add valuable information to our understanding about the diagnosis and management of CNMP. This article addresses a significant gap in the literature by describing GPs clinical reasoning, experiences and views on managing CNMP in primary care setting.

Composition of Australian General Practice Workforce:

According, to the Australian Institute of Health and Welfare (AIHW) statistics, 102,805 medical practitioners were registered and 88,040 were employed in 2015. Of the employed practitioner's 27.2% were aged 55 years or older and 40.1% were women. The report also states that on average men practitioners worked 44.9 hours per week while women worked 38.6 hours (283).

Statement of Authorship

Title of Paper	A qualitative exploration of GPs' perspectives on managing chronic nonspecific musculoskeletal pain in Australian general practice-a focus group study
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Principal Author

Name of Principal Author (Candidate)	Manasi Mittinty nee Gaikwad		
Contribution to the Paper	Designed the study, conducted the study, performed analyses, interpreted the results and drafted the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/07/2017

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Simon Vanlint		
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Contribution to the Paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
Signature		Date	25/07/2017
Name of Co-Author	Nigel Stocks		
Contribution to the paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
Signature		Date	26/7/2017

3.2 Abstract

Objective: Chronic nonspecific musculoskeletal pain (CNMP) is a complex idiopathic condition which causes significant disruption to patients' lives, their relationships and functionality. The etiology of CNMP is not fully understood which makes diagnosis and management challenging. As general practitioners (GPs) are central to the management of chronic pain, their perspectives on managing CNMP is important.

Purpose: To explore the clinical reasoning GPs employ when diagnosing and managing patients with CNMP.

Methods: A qualitative study design using focus groups was conducted with Australian GPs. Five focus groups were conducted across Adelaide. All focus groups were audio recorded and transcripts were coded and analyzed thematically using NVivo software.

Results: The main themes remained consistent across the 5 focus groups: the ambiguous etiology of CNMP; gender differences; developing the "right strategy"; patient centred care; and verifying vitamin D levels.

Conclusions: The findings show that GPs use a patient-centered approach tailored to individual patients' medical history, physical examination and psychosocial health. There was general concern over low levels of vitamin D in patients with CNMP and vitamin D supplements were recommended if indicated by a patients' history.

Keywords

Qualitative research, Focus group study, general practitioner, chronic pain

3.3 Introduction

Chronic pain is Australia's third most costly health condition (273), with one in every five Australians experiencing chronic pain at some point in their life (284). Similar numbers are reported worldwide (285). Although pain is now recognized as a disease and is highly researched, its management perplexes the medical world. One of the reasons could be a poor understanding of the variations in the presentation of chronic pain.

Chronic nonspecific musculoskeletal pain (CNMP) is an idiopathic condition with high prevalence reported among patients seeking medical care in general practice (18) and rheumatology clinics (226, 286). CNMP is distinguished by the clear absence of an underlying anatomical or pathological cause (226). It is characterized by pain, distress, and disability (229). Besides poor physical health, it also causes mental and emotional suffering, social isolation (226, 229, 232), and reduced productivity (235). As the pathophysiology of CNMP is not fully understood, its management remains a challenge for medical doctors and patients alike.

General practitioners (GPs) are reported to be the preferred health professionals whom patients with chronic pain seek for medical care (21). Considering the central role of GPs in the management of chronic pain, their experience, perspectives and clinical reasoning about CNMP is fundamental to improving our understanding of the different variants of chronic pain. However, little is known about how patients with CNMP are currently being managed by GPs. To address this, we conducted a qualitative study with Australian GPs.

3.4 Purpose

The aim of this study was to explore the clinical reasoning GPs employ when diagnosing and managing patients with CNMP.

3.5 Methods

Ethics approval for the study was obtained from the University of Adelaide Human Research Ethics Committee (approval no: HS- 2013-056). Written consent was obtained from every participating GP prior to the focus group discussion.

Study Design

A qualitative methodology was selected for this study in order to enable an in-depth exploration of participant experiences, views, and understandings. The synergistic and serendipitous nature of focus groups has been well established (287, 288). Given that this is an under researched topic where unpredictable accounts or concerns could potentially arise, focus groups were considered the appropriate exploratory method. An additional advantage of the focus group method was that practitioners could potentially learn from each others' experiences during the discussion and thus explore the nature of best practice during (and potentially after) the focus group discussions.

A set of flexible semi-structured questions developed by the authors (two of whom are practicing GPs) to ensure coverage of research objectives across all focus groups was used as a guide for exploring GPs' views on management of patients with CNMP. Participants were encouraged to openly discuss the questions presented and any issues raised with the premise

of there being 'no right or wrong answers' in order to encourage both shared and contrasted contributions to be openly explored. The dynamics of a group were judged to be more likely to generate in-depth discussions where participants could also raise their own questions for collective consideration. Moreover, this flexible method enabled researcher interpretations to be iteratively explored during the group and the opportunity for any apparent emerging themes to be summarised for further critical participant input and revision. Emerging themes identified through initial thematic analysis of each focus group were introduced for further exploration and development in subsequent focus groups (289).

Twenty-seven practices were invited to participate in the study. Of which five practices agreed to participate. Twenty-three GPs were recruited via phone calls and emails to respective practice managers. Every participating GP was provided with an information sheet which included details about the proposed study and the procedure to be followed, ethics approval and consent. Five focus groups were conducted in each of the medical practices in Adelaide, providing varying size and socioeconomic mix of patients.

Data collection and analysis

Each focus group session lasting approximately an hour was audiotaped and later transcribed using the software Nvivo 10. Thematic analysis was performed on the transcribed data following the principles described by Braun and Clarke (290): (i) familiarization with data and transcription of verbal data; (ii) generating initial codes; (iii) searching for themes; (iv) reviewing themes; (v) defining and naming themes; and (vi) report production.

Each focus group discussion was conducted and audiotaped by MG. On completion of each focus group, transcription of the data was performed by MG, inserting memos to clarify

contextual circumstances where appropriate including intonation of the speaker. The initial coding was performed by MG who then 'fed back' her impressions to the team at the end for further discussion and validation against the transcript. The themes linking codes were initially identified by MG and SV, which were then periodically reviewed by PA and NS. Emerging themes were introduced to subsequent focus groups for further discussion and review.

Data Trustworthiness and Reflexive analysis

The dynamic and flexible nature of the focus group method allowed the moderator to share and iteratively expand upon her interpretations of discussions while they were taking place, both with supplementary questions and by providing summaries of issues raised with invitations for further contributions to expand and further shape these. This enabled a reflexive practice in that the moderator actively sought to question and reconstruct her own interpretations as part of the focus group activity. This was further enacted through the collective review of themes performed by the whole research team until a definitive consensus, grounded in the original data was arrived at.

3.6 Results

In reporting our qualitative findings, we have complied with the Standards for Reporting Qualitative Research (SRQR) (291).

Demographic data of participants

Five focus groups were conducted consisting of twenty-three GPs. Among the 23 GPs, 4 (17%) were female and 19 male (83%). Most GPs were aged 45-55 years (n=17, 74%) with only 2 (8.6%) being aged less than 40. The mean age was 50 years ± 8.7 and their years in general practice ranged between 3 - 43 years, with mean of 17.5.

Thematic Analysis Findings

Following thematic analysis, five themes were identified: ambiguous aetiology, gender differences, developing the "right strategy"; patient centered care; and verifying vitamin D levels.

Theme 1: Ambiguous aetiology

GPs reflected on the uncertainty of diagnosing and managing CNMP patients, particularly in the absence of any guidelines. CNMP was believed to have multifactorial etiology and pathophysiology which may often precede untreated injuries, falls, sprains, infections, and autoimmune disease. Uncertainty about the underlying etiology was a common theme. Some GPs linked the long-term use of medications like statins, benzodiazepines, and opioids to developing of CNMP in later stages. Some exemplar quotes for theme 1 are presented in Table 3.1.

Table 3.1 Exemplar quotes for Theme 1

Theme	Quotes
Theme 1 : Ambiguous aetiology	*"Usually patients with past medical history of untreated falls or fractures present nonspecific musculoskeletal pain"*
	"Patients with previously undiagnosed conditions like autoimmune disease, fibromyalgia often report chronic nonspecific musculoskeletal pain"
	"Many patients with old injuries related to sports, work later show nonspecific musculoskeletal pain symptoms"
	"Patients using statins long term can also develop nonspecific musculoskeletal pain."
	"Opioids, benzodiazepines dependency can often lead to chronic nonspecific musculoskeletal pain."

Theme 2: Gender differences

One of the topics discussed was the presence of gender bias. In general, there was consensus that more female patients are likely to be diagnosed with CNMP. This however, was attributed to their generally higher uptake of medical services. On the other hand, male patients were believed to seek medical advice for specific issues such as functional impairment due to pain. Some exemplar quotes for theme 2 are presented in Table 3.2.

Table 3.2 Exemplar quotes for Theme 2

Theme	Quotes
Theme 2 : Gender differences	*"Though more females present with non-specific variant, the reason could be that males rarely visit GPs."* *"Females to males ratio is 2:1, but then again females in general seek medical advice more frequently than males."* *"Males put a name to their pain, usually joints and muscle pain. They focus on the functional reduction and get it treated."*

Theme 3: Developing the "right strategy"

GPs emphasized that it was important to change the approach of diagnosis based on individual patient complaints, as patients with CNMP have diverse clinical presentations and needs. The "right strategy" was described as the process of identifying what would work best for an individual patient. The standard modus operandi – history taking, physical examination, and investigation was used, but tailored to the individual patient. Strong emphasis was placed on longer consultations as it helped to take a detailed medical history and also provided GPs an opportunity to develop a good patient-provider relationship. Arranging longer consults, however, was considered difficult due to financial and time constraints. Most GPs did not encourage repeating specialized investigations such as x-rays or CT scans as it was believed to add little or no value to the management, but instead drew patients' attention to general signs of wear and tear. Some exemplar quotes for theme 3 are presented in Table 3.3.

Table 3.3 Exemplar quotes for Theme 3

Theme	**Quotes**
Theme 3 : Developing the right strategy	"*Patients come with very different complaints hence it's difficult to have one approach"* *"Patient has an expectation of a thorough examination which needs to be matched. They need to be assured that the doctor cares and wants to help them".* *"Ideally longer consult would be perfect to build trust and confidence, but often not possible due to time and financial constraint."* "*Doing X-ray or ultrasound scan may make a patient feel great for doing it but adds little value to the diagnosis while increasing the costs and morbidity."* *"X-rays show signs of wear and tear. This is detrimental for patients, shifts their focus from the recovery to the physical aspect."*

Theme 4: Patient-centered care

Similar to diagnosis, management was also reported to be tailored to the individual patient. Setting realistic goals and managing the psychosocial health of patients' was reported as the framework for patient care. An important aspect for setting realistic goals was shifting patients' focus from complete recovery to improving their functional capacity, mood and overall quality of life. Managing psycho-social wellbeing (mood, stress, signs of depression) of patients was, at times, reported to be more pertinent to recovery than pharmacological therapy. Some GPs also reported limited or no improvement in patients if their psychological well-being was overlooked. However, most GPs observed a general resistance from patients in seeking psychological help, such as counseling or therapy, as this was attributed to the stigma attached to such treatments. Judging an appropriate time to introduce patients to these treatment options was considered crucial for their acceptance and continuity.

GPs also endorsed a multidisciplinary approach to management to increase the support network for the patients. This approach involved psychologists, exercise physiologists, nutritionists, physiotherapists, and massage therapists. In addition, some GPs advocated the use of relaxation techniques and meditation because they were thought to be beneficial to treatment outcomes. Some exemplar quotes for theme 4 are presented in Table 3.4.

Table 3.4 Exemplar quotes for Theme 4

Theme	Quotes
Theme 4: Patient-centred care	*"Patients are looking for quick fix need to set realistic goals."* *"It is important to set goals for your patient's especially functional goals."* *"There is always a psychological component with CNMP patients. Predominantly psychological support is important and often is more beneficial than drugs."* *"Increased stress or anxiety disorder makes CNMP worse and causes a bigger impact but patients are often resistant to diagnosis and need to be convinced tactfully."*

Theme 5: Verifying vitamin D levels

There was a general concern among GPs over vitamin D levels in chronic pain patients, mainly due to lower physical capacity and high body mass index. Although concerned over vitamin D levels, most GPs thought routine testing as avoidable. Instead GPs advised vitamin D supplements if indicated by a patients' history, activity levels, ethnicity, and diet. Vitamin D testing was also recommended for patients with a high-risk of developing deficiency, such as the elderly living in residential care or previously vitamin D deficient patients. Use of vitamin D supplements was reported to enhance the overall bone and musculoskeletal health, lessening of aches and pains and improving a general sense of well-being and mood in patients with CNMP. Vitamin D was also regarded as an economical, readily available adjunct therapy with minimal side effects. Some exemplar quotes for theme 5 are presented in Table 3.5.

Table 3.5 Exemplar quotes for Theme 5

Theme	Quotes
Theme 5 : Verifying vitamin D levels	*"Chronic pain patients are often at risk of vitamin D deficiency due to a sedentary lifestyle."* *"Patients are usually inactive with little to no outdoor activities, so the risk of deficiency increases."* *"It is cyclic they are not very active, spend less time in the sun, have lower levels of vitamin D end up having more aches and pain which makes them more scared of movement."*

3.7 Discussion

In this preliminary qualitative study, almost all participating GPs reported on the ambiguous etiology and variability in clinical presentations of patients with CNMP. It was believed that CNMP had a multidimensional biopsychosocial basis with patients exhibiting higher levels of anxiety and depression and poor physical activity. Despite its multidimensionality and unknown etiology, findings from our study show that GPs adopt a patient-centered approach to management tailored to individual patient needs. These findings, are similar to another study reporting on GPs management of medically unexplained symptoms. This study described that GPs applied similar strategies of tailoring treatments to patients for managing medically unexplained symptoms in the absence of guidelines (292).

GPs from our study also put special emphasis on spending more time with patients, developing a good patient-provider relationship, providing support systems and setting realistic goals for successful management which was consistent with other study findings (293, 294). Similar

strategies were also employed by Canadian clinical practitioners' (295), Dutch GPs (296) and Slovenian family physicians (297) when managing medically unexplained symptoms.

In addition GPs in our study were also concerned over low vitamin D levels in patients with CNMP and supported use of vitamin D supplements based on patients' history and lifestyle. Though, the underlying mechanism by which vitamin D levels might interact with chronic pain is not fully understood, literature suggests that vitamin D deficiency can often presents as non-specific bone and muscle pain (258). It is quite possible that vitamin D deficiency may closely resemble CNMP and could be overlooked. Therefore it is not surprising that there are many studies examining the role of vitamin D and supporting its potential use in various chronic painful conditions (298, 299).

Special emphasis was put on spending more time with patients, developing a good patient-provider relationship, providing support systems and setting realistic goals for successful management which was consistent with previous study findings (293, 294). In addition GPs in our study also reported concern over low vitamin D levels in patients with CNMP and supported use of vitamin D supplements based on patients' history and lifestyle. These views are not surprising given the number of studies examining the role of vitamin D and supporting its potential use in chronic painful conditions (298, 299).

It is reassuring that GPs in our study report similar strategies as Dutch GPs who, in an independent study, were asked about their approach to the treatment of patients with unexplained symptoms (296). Treatment strategies common to both these studies were developing a doctor-patient relationship and explaining to the patients the significant impact that their psychosocial health can have on their symptoms (296).

Strengths and weaknesses

This study is the first to qualitatively explore the management of CNMP in Australia. Being a qualitative study the number of participants was characteristically small. However, practices from various areas in Adelaide were selected in order to cover a diversity of patient populations and to subsequently obtain a spread of GP perspectives.

It is possible that the views and experiences shared by the GPs may have been influenced by their practice years, age or gender; it is noteworthy that younger female GPs did not participate in this study. While the GPs interviewed were not representative of the broader population of Australian GPs in a quantitative sense, the diversity of participating GPs in this study broadly reflects the demography of Australian general practice.

3.8 Conclusion

To our knowledge, this is the first qualitative study to examine the clinical reasoning GPs employ when diagnosing and managing patients with CNMP. Our key thematic findings were that GPs use a patient-centered approach to managing CNMP patients which is tailored to a patient's individual clinical presentation, needs, and psychological well-being. Besides, GPs may recommend vitamin D supplements depending on a patient's history and lifestyle. All GPs who advised vitamin D supplements perceived them as beneficial with none reporting side effects.

Acknowledgements

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Conflicts of Interest

The authors declare that they have no competing interests.

CHAPTER 4

Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis.

4.1 Preface

This chapter address the second objective of this thesis- How effective is vitamin D supplementation in the management of CNMP?

Findings from focus group discussions, Chapter 3, demonstrate that GPs consider vitamin D supplementation to be a potentially safe and effective method of management for patients with CNMP. In addition, findings from observational studies, as described in chapter 2 section 2.3, also indicate that low levels of vitamin D seem to be associated with several musculoskeletal disorders such as OA, RA, CWP, and FM. However, randomized controlled trials (RCTs), which are considered to be level II evidence by the National Health and Medical Research Council (NHMRC) provide mixed findings. RCTs are considered as level II evidence as they allow to make causal inference in the presence of unmeasured confounding and allow accounting for selection bias (300). In order to identify if the association (301) between vitamin D and CNMP is causal or otherwise conducting a systematic review was essential.

A Cochrane review (242) investigated vitamin D supplementation for the treatment of a range of chronic musculoskeletal conditions and concluded no substantial effect. Given the different pathophysiological origins of these conditions, such a finding was perhaps not surprising. The authors of the review suggested that specific conditions should be investigated individually. We contend that another aspect of that review may have contributed to its null findings: there was no attempt to confine source literature to direct comparisons between vitamin D and a control or placebo. This is important in this field because it is arguably very difficult to isolate the treatment effect attributable to vitamin D supplementation when it is instigated as a part of the multimodal intervention.

To address this gap in literature we conducted a systematic review of RCTs examining the effects of vitamin D supplementation on CNMP. Meta-analysis was conducted using the data from the systematic reviews, to estimate the "effect size" of vitamin D supplementation on CNMP. This chapter addresses the second aim of the thesis and has been published in the Clinical Rheumatology Journal (45) (Attached as Appendix).

What is already known on this topic?

Multiple studies report a strong association between low vitamin D levels and CNMP (302-304). However, these are mostly observational studies, which may not be able to fully control for all the confounding factors such as season, diet, age, latitude, body mass index, smoking, and physical activity. Moreover, they do not account for biases such as selection bias, unmeasured confounding bias, and measurement error (300). To reach conclusive outcomes, it is important that these findings are supported by evidence from RCTs.

Currently, only three RCTs satisfying our selection criteria, have examined the effect of vitamin D supplementation on CNMP symptoms. Results from these few studies are mixed, that is, some indicate a large effect and others show no effect ("statistically significant") of vitamin D supplementation on CNMP.

Although the best evidence synthesis of the effect of vitamin D supplementation on this condition is still not conclusive, there has been an exponential rise in vitamin D testing and supplementation worldwide (305-307). This has raised justifiable concerns about the evidence for vitamin D measurements and supplementation. In Australia alone, the use of vitamin D testing increased 94 fold between 2000 and 2010 (308). According to the current MBS reviews the number of claims and benefits paid for item numbers relating to vitamin D testing has

increased by 3587% in Australia over the last 10 years (282). Analysis of MBS data has raised concern about the unnecessary testing of vitamin D or repeated testing of vitamin D in the general population (282). The review noted that 98% of the vitamin D tests were requested for the purpose of screening/testing rather than monitoring. In order to promote quality use of testing, Medicare deleted the previous vitamin D testing item numbers 66608 and 66609 and split the testing into two types: i) 25-hydroxyvitamin D testing for high-risk patient groups, ii) 1,25- dihydroxyvitamin D testing for patients with severe conditions such as renal failure or hypercalcemia. Under the new rules, 25-hydroxyvitamin D testing is now restricted only to high-risk groups and cannot be used as a screening tool. The high risk patient groups were defined as the elderly or disabled people living residential care, house bound/ hospitalized geriatric patients, immigrants and people with dark complexion of either sex, people with chronic disease, obese people, people who avoid sun exposure and people who work in enclosed environment such as office, warehouses, taxi, night shift workers and factory. The testing of vitamin D outside this criteria is deemed to be private and requires the patient to bear the cost (282).

What this study adds?

To our knowledge, this is the only published systematic review and meta-analysis on the role of vitamin D supplementation on CNMP. This study was needed as it may help to answer the question, whether CNMP could be treated with vitamin D supplementation. Moreover, it is important to study if the low levels of vitamin D found in people with CNMP are causal or correlational. Meta-analysis of the collected data provides an opportunity to evaluate the treatment effect of vitamin D supplementation. We chose conducting a systematic review as it is considered Level I evidence by the NHMRC, Australia (282) (NHMRC Evidence Hierarchy

Table Attached as Appendix). This is because systematic reviews provide more data than the individual studies and meta-analyses increase the precision of the overall results, reducing the likelihood that the results are affected by chance (309).

Study design

This review was designed following PRISMA statement (310). The PRISMA checklist for our study is attached below. Only studies using randomized controlled or randomized double-blind controlled trial design were included as randomization and double blinding are known to minimize selection and confounding bias to a large extent thus allowing causal inference (311). Studies that combined vitamin D with other concurrent interventions were excluded, the reason for this being to isolate the unmediated treatment effect of vitamin D. This otherwise would be difficult if instigated as a part of multimodal intervention as there can be both direct and indirect effects of vitamin D. No restriction regarding the type, route, dose or frequency of vitamin D supplementation was enforced.

How the intervention might be useful?

Vitamin D supplementation increases blood levels of 25OHD (306) thereby correcting vitamin D deficiency. The details of how this might work (molecular mechanism, time to effect, and extent of reversibility of pain associated with vitamin D deficiency) are unclear at present (312). However, we propose that vitamin D deficiency is found to cause defects in bone mineralization causing widespread or localized bone pain or discomfort along with aches and pain in muscles and joints (313, 314) treating vitamin D deficiency may help relieve some of

the unexplained non-specific musculoskeletal pain. As there are vitamin D receptors in the central nervous system (315, 316), it is possible that they may modify pain perception. Vitamin D supplementation may also alleviate some of the nonspecific pain via its anti-inflammatory, anti-apoptotic and anti-fibrotic effects and restoration of calcium homeostasis (51, 61).

Interpreting the results

The results from the meta-analysis suggest that vitamin D has no effect on CNMP. However, it is necessary to interpret these results cautiously keeping in mind the heterogeneity within the study design and participant population and the relatively small sample size. There are paucity of RCTs comparing vitamin D supplementation to placebo. Moreover, within the studies selected there was heterogeneity because of differences in the dose and dose regimes of vitamin D supplementation used. It is also important for studies to have a long follow-up period as vitamin D levels show fluctuations based on seasonal variations. Future studies should try to improve the design of RCTs, including- increasing their sample size, to ensure clinically and statistically significant findings.

PRISMA checklist for the study

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	N/A
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 2-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5

Page 1 of 2

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 5-6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 6

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Statement of Authorship

Title of Paper	Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis.
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Publication Details	Clinical Rheumatology, February 2016

Principal Author

Name of Principal Author (Candidate)	Manasi Mittinty *nee* Gaikwad		
Contribution to the Paper	Designed the study, conducted the study, performed analyses, interpreted the results and drafted the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25.07.2017

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);

II. permission is granted for the candidate in include the publication in the thesis; and

III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Simon Vanlint		
Contribution to the Paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
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Contribution to the Paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
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Contribution to the Paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
Signature		Date	27/07/2017
Name of Co-Author	Nigel Stocks		
Contribution to the paper	Contributed to the study design, interpretation of results and reviewed the final manuscript.		
Signature		Date	27/07/2017

4.3 Abstract

Chronic nonspecific musculoskeletal pain (CNMP) is an idiopathic condition often seen in general practice and rheumatology clinics, the aetiology of which may include vitamin D deficiency. The objective of the present study is to evaluate the effectiveness of vitamin D supplementation in the management of CNMP through a systematic review and meta-analysis. According to PRISMA guidelines, PubMed, Embase, Web of Science, Cochrane and Scopus electronic databases were searched for randomized controlled trails comparing vitamin D supplementation to a control or placebo in CNMP patients; the search was not limited by language or date. Meta-analysis was performed using the mean and standardized mean difference which was computed with 95% confidence intervals, and overall effect size was calculated. Both fixed and random effects models were used in meta-analysis to account for heterogeneity in the studies. The initial search identified 107 studies, of which 10 were potentially relevant, with 7 studies excluded because they did not meet selection criteria. Three studies were included in the meta-analysis. We found no effect of vitamin D supplementation (standardized mean difference (SMD) 0.004; 95% confidence interval (CI) -0.248 to 0.256) on pain in CNMP patients. Forest plot is used to present the results from meta-analysis. Contrary to widespread clinical view, there is moderate level of evidence that vitamin D supplementation is not helpful for treating CNMP patients.

Keywords

Chronic nonspecific musculoskeletal pain, Meta-analysis, Systematic review, Vitamin D, Vitamin D supplementation

4.4 Background

Chronic non-specific musculoskeletal pain (CNMP) is an idiopathic condition which is a common presentation to rheumatology clinics (226, 286). CNMP is associated with decreased physical health, mental wellbeing, social life (18, 233), workability (234) and disability (235). Many sufferers become stuck in a descending spiral of economic, social, emotional and physical disadvantage (84, 230). CNMP is a significant burden to the economy (236). The aetiology of CNMP is not well understood and although many potential contributors have been identified (317), a clear nociceptive source has not, and empirical data concerning other contributors are lacking. As a result, CNMP is difficult to diagnose, prevent or treat. One potential contributor that receives substantial attention clinically and has been investigated in a range of clinical studies is vitamin D deficiency (37, 318).

Vitamin D is involved in many regulatory biological processes. In addition to calcium homeostasis, vitamin D is thought to have anti-inflammatory, anti-apoptotic and anti-fibrotic effects; it is thought to play a role in regulating blood pressure and in innate and adaptive immune system function (51, 61). This range of biological effects highlights the potential role of vitamin D deficiency in the development of symptoms associated with acute and chronic rheumatic diseases and it is biologically plausible that vitamin D deficiency contributes to the development and maintenance of CNMP. That people with vitamin D deficiency can present with nonspecific muscular pain and bone pain has been reported (258) and several studies have suggested a causative role (207, 303, 304). However, a recent Cochrane review (242) investigated vitamin D supplementation for the treatment of a range of chronic painful conditions and concluded no substantial effect. Given the different pathophysiological origins of the condition included, such as osteoarthritis, rheumatoid arthritis, and fibromyalgia, such a finding was perhaps not surprising. The authors of that review suggested that specific

conditions should be investigated individually. We contend that another aspect of that review may have contributed to its null findings: there was no attempt to confine source literature to direct comparisons between vitamin D and a control or placebo. This is important in this field because it is arguably very difficult to isolate the treatment effect attributable to vitamin D supplementation when it is instigated as a part of the multimodal intervention.

Despite the clinically topical nature of the issue and the substantial literature, no attempt has been made to conduct meta-analyses. Meta-analyses provide the obvious advantage of increasing power and estimating effect sizes, which can then be re-tested in subsequent studies (319). We aimed to fill these substantial gaps in the literature by using gold standard systematic review and meta-analysis methodology to evaluate the evidence concerning the effect of vitamin D supplementation, when compared in a randomized controlled trial to a placebo, on pain in people with CNMP.

4.5 Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (310) was followed for this review.

Inclusion criteria:

Only randomized controlled trial (RCT) or randomized double blind control study designs were eligible. For inclusion, RCTs had to compare vitamin D supplementation to a control or placebo and measure the pain outcome using Visual Analogue Scale (VAS). No restrictions were applied for the language but restricted the studies to those conducted on “humans”.

Exclusion Criteria:

Studies including patients previously diagnosed with an inflammatory joint disease, post-surgical patients or patients with experimentally induced pain were excluded.

Search strategy:

An electronic search was performed on 5 databases - PubMed, Embase, Web of Science, Cochrane, and Scopus. The search period was set from the time of commencement of these databases up to 3rd November 2015. The search strategies for each database are listed in Table 4.1. MG and SV independently searched for potentially eligible studies based on the study title and then read the abstracts and selected potentially relevant studies, from which studies not matching the selection criteria were excluded. Full articles of the remaining studies were reviewed for inclusion. The reference lists of selected studies were manually searched to find additional potential papers.

Table 4.1 Electronic search strategy tailored to each database

PubMed:				
Chronic [ALL] OR Persistent [ALL]	Nonspecific [ALL] OR Non-specific [ALL]	Musculoskeletal [ALL] OR Musculoskeletal pain* [ALL]	Pain [MH] OR Pain* [ALL]	vitamin D*[ALL] OR Cholecalciferol [ALL] OR Hydroxycholecalciferol* [ALL] OR Hydroxyvitamin D* [ALL] OR Ergocalciferol* [ALL]
Embase:				
Chronic OR Persistent	Nonspecific OR 'Non specific'	Musculoskeletal NEAR/4 pain*		"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR Ergocalciferol*
Web of Science:				
Chronic OR Persistent	Nonspecific OR 'Non specific'	Musculoskeletal NEAR/4 pain*		"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Ergocalciferol* OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3"
Cochrane Library:				
Chronic OR Persistent	Nonspecific OR 'Non specific'	Musculoskeletal AND pain*		"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR Ergocalciferol*
Scopus:				
Chronic OR Persistent	Nonspecific OR 'Non specific'	Musculoskeletal W/3 pain*		"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR Ergocalciferol* OR"Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR

Data extraction:

The final selection of the studies was collectively made by the group. Data extraction was performed by MG and MM using a standardized data extraction form similar to Table 4.2 highlighting the characteristics of selected studies. Data was extracted on sample size, characteristics of participants, intervention type; control group, main outcome, and adverse events. The review team was never blinded to authors' names or institutions, journal of publication and study results. MM provided the statistical support and help in performing the analysis. The manuscript was collectively written by the team and all authors' approved the final draft.

Table 4.2 Characteristics of Included Studies

Author/ Year	Design	Sample size	Participants	Main complaints	Intervention	Follow up period	Outcome	Jadad score
Sakalli et al. 2012	Randomised placebo controlled double blind trial	120	-Elderly patients aged > 65 years - Attended Rheumatology outpatient clinic.	nonspecific msk pain	Oral and intramuscular vitamin D	4 weeks	A single mega dose vit D decrease nonspecific msk pain. Improved QoL and improved functional mobility in elderly.	4
Schreuder et al. 2012	Semi-crossover randomized controlled trial	84	-age 18 to 60 years. - patients from 10 general practices in Delft, The Netherlands, non-western immigrants and their offsprings	Frequent, recurrent msk pain or pain lasting > 3 months without obvious cause (trauma, arthritis, sciatica).	-Oral vit D - 150,000IU in 7.5 ml oil OR placebo in 7.5 ml oil having same appearance and taste	6 weeks	A small positive effect on pain 6 weeks after high dose vit D supplementation	5
Warner et al 2008	Randomized Controlled Trial	288	-age group not specifed. - Rheumatology practice , Kansas City , Missouri.	Diffuse musculo-skeletal pain	50,000 IU ergocalciferol.	12 weeks	Vit D deficiency correction did not improve msk pain.	5

Quality assessment of selected studies

The 5-point Jadad score was used to assess the methodological quality of studies. Following, questionnaire formed the basis of scoring (320):

i) Was the study described as randomized?

ii) Was the study described as double blind?

iii) Was there a description of withdrawals and dropouts?

Each question is answered either yes or no, with each yes, the study is scored 1 point and no scored 0 points. For the well described method of randomization and blinding additional points are given respectively. However, 1 point each was deducted if the described method of randomization and blinding was incorrect. Clinical trials scoring more than 3 are considered as high quality (refer Table 4.3).

Table 4.3 Jadad Scores of included studies

Study	**Randomization (max points 2)**		**Blinding (max points 2)**		**Account of all patients (max 1 point)**	**Total Points**
Author/year	Randomization mentioned	Method of randomization appropriate	Blinding mentioned	Method of blinding appropriate		
Schreuder et al 2012	1	1	1	1	1	5
Sakalli et al 2012	1	1	1	1	0	4
Warner et al 2008	1	1	1	1	1	5

Data analysis

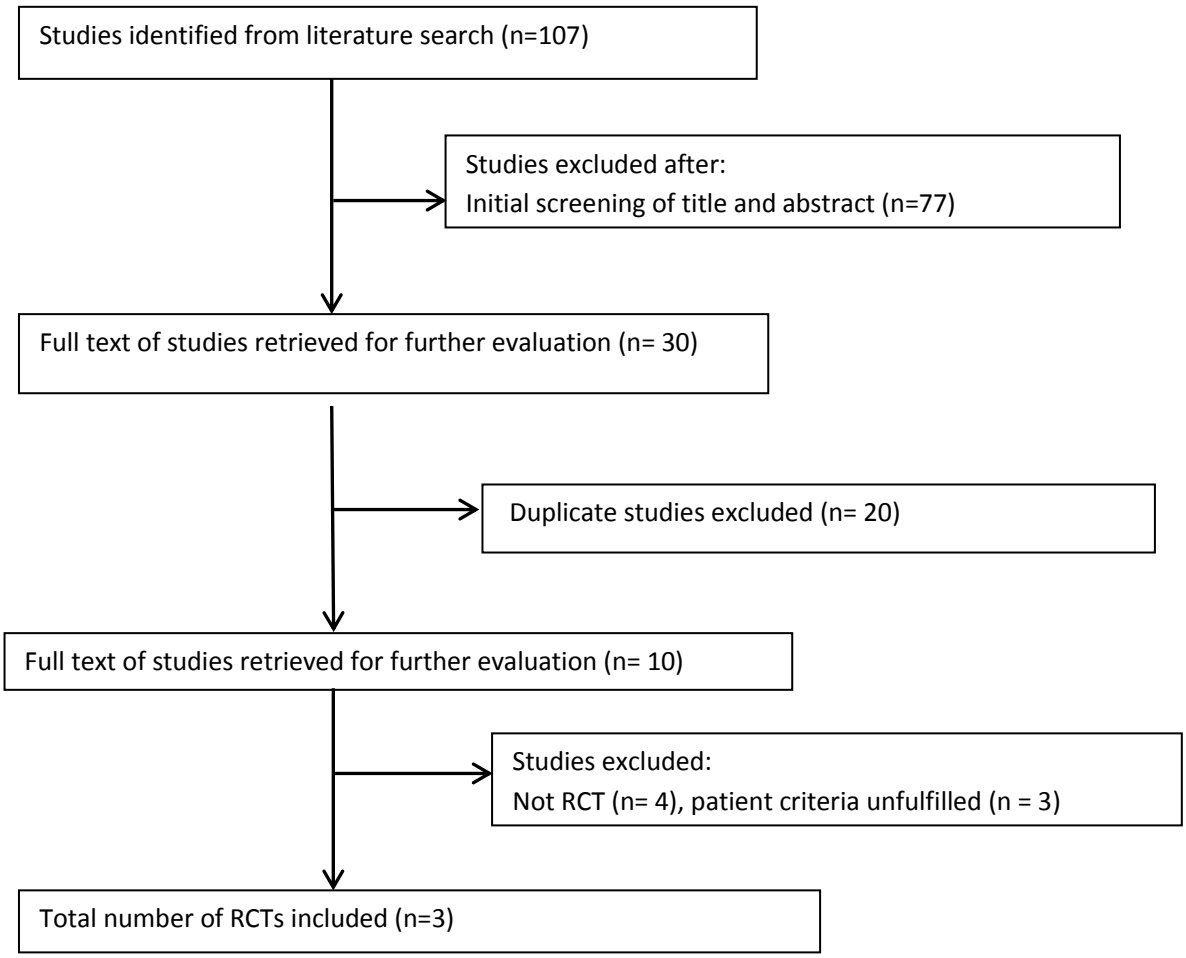
Meta- analysis of the standardized mean differences (SMD), and their standard errors, in VAS scores, was performed between vitamin D treated and placebo treated groups. SMD has several versions such as, Cohen's d (321), Glass'sΔ (322) and Hedges' g (323), however, we have used the simple SMD which is the ratio of the mean difference and the standard deviations. The value SMD less than 0.5 is considered to be a small effect, from 0.5 to 0.8 medium effect and greater than 0.8 large effect (324). Summary effect estimates were calculated with the fixed-effects models. Analysis was performed in Stata, version 12.1, software (StataCorp LP, College Station, Texas) using the metan commands (325). The heterogeneity between studies was assessed by computing the I2 statistics. A value of 0 inferred no heterogeneity and value above 50% is recognized as substantial heterogeneity (324). Following, Bailey (326) we used fixed effect model as the objective of this study is to test whether the intervention has produced an effect in a set of homogenous studies. In the fixed effects model we weighted the data by the amount of information (inverse of the variance of the study) that is captured by the study.

4.6 Results

The initial search located 101 studies from the databases (PubMed 14, Embase 20, Web of Science 19, Cochrane library 45 and Scopus 9). After reviewing the title, the abstract and removal of the duplicates, 10 studies were identified for potential inclusion (Figure 4.1). Full text of these articles was reviewed and assessed. Of these 10 articles, 7 were excluded because they did not meet our selection criteria of study design. Thus leaving us with only 3 studies, for conducting the systematic review (192, 249, 250). These three studies used an RCT study

design to investigate the effect of vitamin D supplementation (treatment group) compared to a placebo (control group) in CNMP patients.

Figure 4.1 Flow chart diagram of study selection



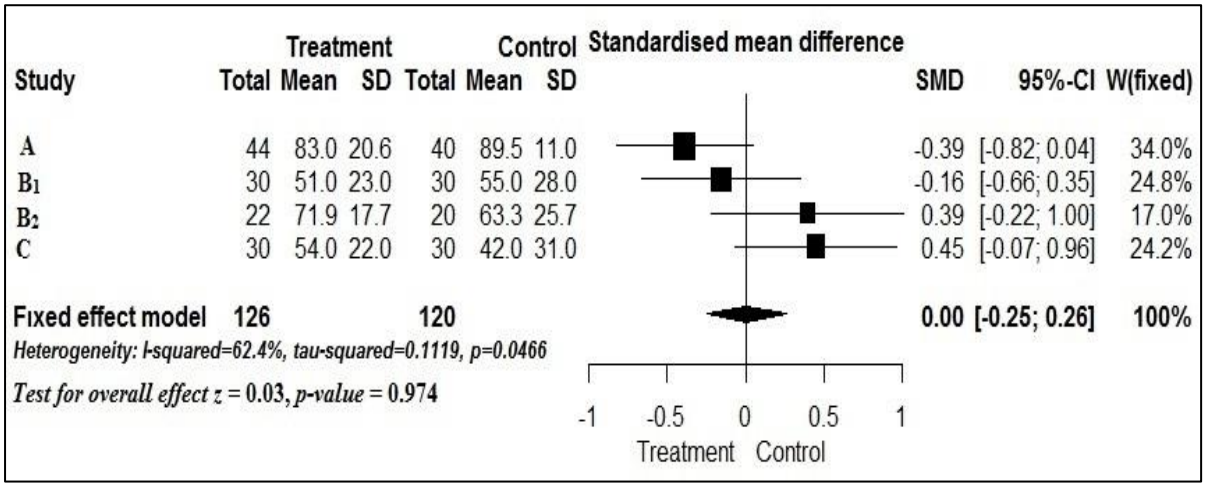
The characteristics of the selected studies are described in Table 4.2. The three studies included in the meta-analysis evaluated 492 participants in total. The participants were generally adults with their mean ages ranging from 41 to 76 years. The majority of participants in all studies were females. All studies measured pain, 1 study also measured functional mobility and quality of life. Study sample sizes ranged from 84 - 288 subjects. All 3 studies used VAS to measure changes in pain (outcome), in addition, studies also used the timed up and go test (249) functional pain scores (FPS) (192) and Likert scales (250). All studies used the oral route for administering vitamin D, except Sakalli et al study, which in addition also used the intramuscular route for administering vitamin D. This is reflected in Fig 2 which shows 4 studies namely: Study A- Schreuder et al. study, Study B_1 - Sakalli et al. oral vitamin D supplementation group, Study B_2- Sakalli et al. intramuscular vitamin D supplementation group and Study C- Warner et al. study. We did this to test if the mode of administration influenced the strength of the clinical effect. The trial period of selected studies was 4 weeks (249) and 12 weeks (192, 250). Of the 3 included studies, only 1 study reported that none of the participants experienced adverse events during the trial or in the follow-up period (250). In general, all studies scored highly on methodological quality with two studies scoring 5 and one study scoring 4 (Table 2).

Out of the three selected studies, two showed reduction in pain, following treatment with single mega-dose vitamin D supplementation (249, 250), and one showed no effect on pain following vitamin D supplementation (192).

Meta-analysis result:

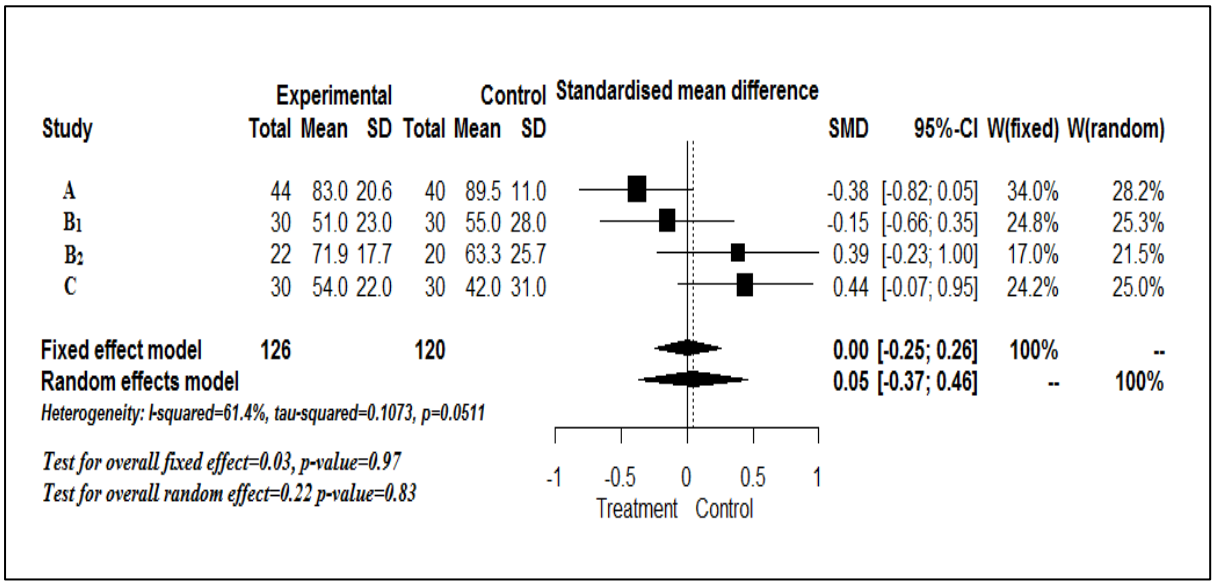
The results from meta-analysis are presented in the forest plot (Figure 4.2). The horizontal lines depict the length of confidence intervals, which for Study A and Study B_1 are on the treatment side, indicating a modest effect of the intervention on pain in CNMP patients. For Study B_2 and Study C the lines are on the control side, representing no effect of the intervention. The overall effect (represented by black diamond in Figure 4.2) lies on the line of no effect, indicating that the average effect size of the pooled analysis is 0. The I2 statistic is 62.4% indicating a moderate level of heterogeneity in the pooled analysis, which confirms that the variation is not due to chance. The overall pooled SMD was 0 with CI ranging between -0.25 to 0.26, p-value = 0.97 indicating that the intervention has no clinical effect on the CNMP (Figure 4.2). The test for overall effect is not statistically significant.

Figure 4.2 Forest plot using fixed effect model



To split the variance as within and between study variance, we also analyzed data using random effects model (Figure 4.3). The overall pooled SMD was 0.05 with CI ranging from -0.37 to 0.46, I2 = 61.4 and p-value = 0.05 reiterating no statistical significance.

Figure 4.3 Forest plot using random effects model



4.7 Discussion

We aimed to evaluate the evidence concerning the effect of vitamin D supplementation when compared in a randomized controlled trial to a placebo, on pain in people with CNMP. Our results are in contrast to the prevailing clinical opinion (286, 303, 327) insofar as they suggest that vitamin D supplementation does not decrease pain in CNMP when compared to a placebo. Our results also show, however, that robust randomized controlled trial data are perhaps more limited than would be assumed: despite a comprehensive search strategy, only three randomized controlled trials, with a total of 492 participants, satisfied our priori criteria. The included trials comprised of participants aged between 41-76 years with vitamin D levels of

20nmol/L or less. A range of doses of vitamin D were administered in each included trial, but there was no evidence of a dose-response relationship.

The current study raises new questions for the investigation of CNMP. Our results clearly suggest that vitamin D supplementation is not helpful for CNMP. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (328), we suggest there is low to moderate evidence (one high-quality study or several studies with some limitations but consistent results) (328) that vitamin D supplementation is not helpful for people with CNMP.

It is notable that the proposed mechanisms by which vitamin D deficiency might contribute to CNMP – disruption of calcium homeostasis, a loss of anti-inflammatory, anti-apoptotic or anti-fibrotic effects (51, 61) imply that the primary cause of CNMP lies within the tissues of the body. Although such mechanisms seem intuitive, they are not necessarily consistent with modern models of CNMP and other chronic pain conditions. Although vitamin D deficiency, through disruption of immune regulation (51, 61) could disrupt the neuroimmunological processes that subserve pain (260), the assumption that this would increase pain rather than decrease it remains to be properly tested. The prevailing theories with regard to chronic pain place greater emphasis on enhanced sensitivity within the nociceptive system (86), increased contribution of non-nociceptive sensory inputs and associative learning (241), cognitive mechanisms that emphasize perceived threat to body tissue and behavioral processes linking fear of pain, activity avoidance and catastrophizing (88) and de-emphasize ongoing tissue pathology or damage (with some exceptions, for example seronegative arthropathies) (87). Indeed, CNMP is widely considered to be influenced by a wide range of biological, physical, psychological and social factors (84) and management approaches reflect this biopsychosocial framework (118, 239). Perhaps vitamin D supplementation might play a more important role

in painful conditions that more obviously relate to tissue inflammation, for example, rheumatoid arthritis, although this remains to be determined.

The biological complexity of vitamin D effects leaves open the possibility that supplementation could offer benefit for people with CNMP and that the current research base is not sufficient to detect it. That is, protocols of the RCTs may have led to an inadequate rise in serum vitamin D levels post supplementation (329) due to non-compliance, although one might argue that such interventions are really 'advice to take a particular action' rather than the action itself (330). Different effects may also relate to the heterogeneity of body-mass index (BMI) between participants. Alternatively, standard doses of vitamin D supplementation may not always produce predictable increases in the vitamin D levels (329) or predictable rates at which vitamin D level changes (302), potentially masking positive effects. That other study designs, for example, clinical (286),observational (304), cross-sectional and case report studies (303), have demonstrated moderate benefit following supplementation, may reflect an advantage of tailored supplementation regimes (although considering the findings of such studies one should remember that these study designs are highly vulnerable and may overestimate true effects) (331).

The relative paucity of RCTs comparing vitamin D supplementation to placebo is surprising, considering the widespread clinical endorsement of the idea. The available data are also not very generalizable to all ages because most studies have investigated primarily postmenopausal women, and compared nonstandard doses for which there is little justification. Estradiol is recognized as a physiological predictor of vitamin D binding protein (332) and post-menopausal women show a higher natural decline in vitamin D levels than pre-menopausal women (333), suggesting that it would be important to investigate the variance in vitamin D levels in pre-menopausal women with depleting estradiol levels as well as in younger women

with normal estradiol levels. Furthermore, CNMP is highly prevalent in children and adolescents, but this group has not been investigated with regard to vitamin D.

There are several considerations, strengths, and limitations of the current study. We included the Warner et al study (192) even though they diagnosed participants with primary fibromyalgia, not CNMP. On closer appraisal, the participants in their study did not satisfy the ACR criteria for fibromyalgia but did satisfy criteria for CNMP. The strengths of this study are its focus on CNMP and inclusion of meta-analysis, as was recommended in a recent Cochrane review (242); the absence of language or publication restrictions, giving confidence that we did not miss important studies; the confinement of included studies to those that used a RCT design, because they provide the most rigorous method of verifying if a cause-effect relationship exists between the intervention and outcome (334). We used SMD score to evaluate the clinical relevance and CI for inference because it focuses on the probability and significance of the intervention and helps to establish the clinical and statistical significance of the findings (335). There are also limitations: the forest plot shows variability between the studies and broad 95% CIs shows the imprecision of the results, a common problem with small sample sizes (335). The most significant limitation is indeed the lack of source literature, which is particularly pertinent to the field because it contrasts with popular clinical belief.

This study shows that there is no proven effect of vitamin D supplementation on pain in people with CNMP when compared to a placebo. We conclude that there is GRADE C (96) to level B (moderate) evidence that vitamin D supplementation is not helpful for people with CNMP. Clearly, more robust and nuanced RCTs might have an important impact on our confidence in the estimate of effect (328).

CHAPTER 5

Understanding patient perspectives on management of their chronic pain – an online survey protocol

5.1 Preface

This chapter describes the study protocol and questionnaire used for conducting the final study of this thesis, which examined the perspectives of patients with chronic pain on their pain management. This chapter provides an overview of the study design, the process of data collection, and the methodological and the statistical approach used in the cross-sectional survey study. This chapter is published in the *Journal of Pain Research* (336) (Attached as Appendix).

Statement of Authorship

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Contribution to the Paper	Designed the study, conducted the study, performed analyses, interpreted the results and drafted the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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5.3 Abstract

Background:

It is widely recognized that both doctors and patients report discontent regarding "pain management" provided and received respectively. The impact of chronic pain on an individual's life resonates beyond physical and mental suffering; equal or at times even greater impact is observed on an individual's personal relationships, ability to work and social interactions. The degree of these effects in each individual varies, mainly because of differences in biological factors, social environment, past experiences, support, and belief systems. Therefore, it is equally possible that these individual patient characteristics could influence their treatment outcome.

Research shows that meeting patient expectations is a major challenge for health care systems attempting to provide optimal treatment strategies. However, patient perspectives and expectations in chronic pain management have not been studied extensively. The aim of this study is to investigate the views, perceptions, beliefs and expectations of individuals who experience chronic pain on a daily basis, and the strategies used by them in managing chronic pain. This paper describes the study protocol to be used in a cross- sectional survey of chronic pain patients.

Methods and analysis:

The study population will comprise of individuals aged ≥18 years, who have experienced pain for ≥3 months with no restrictions of gender, ethnicity, or country of residence. Ethics approval for the study was obtained from Humans Research Ethics Committees, University of Adelaide and University of South Australia.

Multinomial logistic regression will be used to estimate the effect of duration and character of pain, on patient's perception of time to recovery and supplement intake. Similar analysis will be conducted for estimating the effect of health professional support, pain education to family and employer on pain intensity and perception of time to recovery.

Discussion:

Knowledge about the perceptions and beliefs of patients with chronic pain could inform future policies, research, healthcare professional education, and development of individualized treatment strategies.

Keywords

Chronic pain, pain management, patient perspectives, survey, time to recovery

5.4 Introduction

The International Association for the Study of Pain (IASP defines chronic pain as "pain that persists beyond the normal tissue healing time, usually ≥ 3months", in the absence of an obvious underlying biological cause (337). With nearly 20% of the population affected worldwide, chronic pain has become a disease in its own right, rather than just being considered a symptom (7-9, 284). Furthermore, chronic pain is often associated with numerous physical and psychological complications such as disability, sleep disturbances, fatigue, depression and social isolation. The traditional approach for managing an injury or other illness of diagnosis and treatment offers little hope to individuals experiencing chronic pain by trapping patients with chronic pain in a vicious cycle of trial and error treatments. Both patients and their doctors struggle with "pain management" with studies reporting a feeling of inadequacy about providing optimal treatment among physicians (338-340) and dissatisfaction among patients concerning the treatments provided (341).

Studies show that between 40%-60% of the general population use dietary supplements to promote health and manage conditions (342-344). Approximately 33% of those who use supplements quote pain as the primary reason (343). However little is known about their benefits as perceived by patients with chronic pain. Moreover, pain is a subjective sensory emotional experience (337), which may be influenced by an individual's biological, environmental, social and psychological factors. Together with belief systems and expectations, these factors may also guide individual experiences, and influence treatment outcome(s). Even though studies (345, 346) report factors which predict chronic pain, their association with patients' perspectives of chronic pain and its management has not been studied extensively. In addition, meeting patients' expectations is an important objective for health care systems (347) as it appears to improve treatment satisfaction between 8% to 25% (348, 349).

Aligning patient expectations with a management plan can enhance treatment outcome and benefits.

Best practice insight recommends publishing a protocol prior to undertaking the study as it facilitates awareness of the research in progress (350). It also helps to maintain the transparency in reporting of the study (351, 352). This paper describes the protocol and the questionnaire used in a cross-sectional survey of individuals who experience pain for ≥ 3 months.

5.5 Aim & Objectives

The aim of this study is to investigate the views, perceptions, beliefs and expectations of individuals who experience chronic pain on a daily basis, and the strategies used by them in managing this pain. The objectives of this study are to investigate if duration and character of pain, education about pain affects chronic pain patients' perception of time to recovery and supplement intake. This study will also examine if health professionals support, pain education to family and employer is related to pain intensity and perception of time to recovery in patients with chronic pain.

5.6 Methods

Design

An online survey method was selected for this study as it is cost-effective and easy to administer; unlike face-to-face interviewing, a survey provides a standardized approach allowing uniformity of questions asked to all participants. It also provides access to individuals without geographical dependency thus allowing the collection of rich data (353). Although online surveys may limit participation from individuals without access to the internet (354) the advantages of this method have been shown to outweigh the disadvantages in terms of external validity (355).

A questionnaire was designed specifically for the study following the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) protocol (356) for the ethical reporting of surveys and will be administered online using Survey Monkey. Ethics approval for this study has been obtained from Human Research Ethics Committee of the University of Adelaide (approval no- HREC-2016-0712) and the University of South Australia (application id- 0000035791).

Recruitment

The survey will be advertised on multiple educational, basic and clinical science websites and on social media in different countries, including Australia, Ireland, India, New Zealand and The United States of America. Individuals accessing these websites will be invited to participate in the study if they met the inclusion criteria. The survey will be open for participants from all ethnicities and country of residence. It is anticipated that data collection

will cease by the end of October 2016. All participants activated an electronic consent prior to beginning the survey.

Inclusion criteria

Individuals for inclusion in the survey should be:

1. Currently aged 18 years and above.

2. Must have experienced pain ≥3 months' duration.

Exclusion criteria

Individuals are not eligible to participate in the survey if:

1. Their current age is below 18 years of age.

2. They suffer from acute pain of ≤ 3 months' duration

3. They do not consent to be a part of the survey study.

Consent & Confidentiality

Individuals who click the link provided to participate in the study are first taken to an information page. The information page describes the proposed study, its relevance and also outlines what type of information will be asked from the participants and the time required to

complete the survey. The information page notifies the participants that the survey is voluntary and their choice of participating or not participating will have no effect on their own pain management in any way. It also provides the participants with information regarding whom to contact in case of distress or if they have a complaint. The information page also explains that the survey is completely anonymous - information that could disclose the participant's identity will not be asked at any stage during the survey.

Data- storage & handling

The data will be stored on a secure computer owned by University of Adelaide, with password-controlled access. Only the research team (all authors listed above) will have access to the data.

Sample Size

Sample size calculations for estimation are based on three parameters, the variance or spread of the observations, the precision and the level of significance or probability of type-1 error.

$$n = \left(\frac{1.96^2 P(1-P)}{\delta^2}\right)$$

Where n= sample size, P = estimated population proportion, δ = precision of the estimate.

For this sample size estimation the values chosen were, P = 0.5 and δ = 0.05. Thus, giving us a sample size of 384 with 95% confidence interval and 80% power. This is the simple random sampling approach (357).

Questionnaire development

Currently, there are very few studies examining the perspectives and the expectations of individuals who experience chronic pain regarding their pain management. Due to the unavailability of validated scales of chronic pain patients' perspectives, this questionnaire was developed by the team of authors through discussions and literature search. The questionnaire (358) (Attached as Appendix) comprises of 5 sections and 39 items in total. A pilot study to verify the face and content validity of the questionnaire was conducted prior to finalizing it (359).

5.7 Analysis

Statistical analysis plan

All analysis analyses will be performed using STATA 14.1 Statistical software (325). Multinominal logistic regression will be performed to estimate the effect of duration and character of pain; education about pain and variation in supplement intake on chronic pain patient's perception of time to recovery. Univariate logistic regression will be used to examine the effect of support received from health professionals, family and employers on chronic pain patients pain levels, quality of life and physical goals. The analysis will be adjusted for confounding factors such as age, sex, education, employment and marital status.

Simple descriptive statistics such as mean, proportions and variances will be described for the entire sample. Participants will be described in terms of pain duration, average length of their

consulting time and frequency of visits, and satisfaction about their education and involvement in pain management.

5.8 Measures

Dependent variables/Outcomes:

1. Patients' perception of time to recovery

Information regarding participants' perceived time to recovery from their current pain problem will be collected.

2. Supplement intake

Information regarding each participant's intake of complementary medicines or dietary supplements (e.g. calcium, magnesium, fish oil) and alternative medicines (Chinese, herbal, Ayurvedic) will be collected, in addition to information regarding testing of vitamin D, vitamin D deficiency and vitamin D supplementation.

Independent variables/Confounders:

1. Demographic data

Information regarding each participant's age, sex, country of residence, education, employment and marital status will be collected.

2. Pain history

Information pertaining to each participant's history of current pain problem such as diagnosis received, duration, character and intensity of pain will be collected.

3. Pain education

Information regarding method of education received, provider of education and influence of education on understanding and management of pain will be collected.

4. Goals from pain management

The goals from pain management are classified into pain related outcomes; quality of life and physical functioning. Information pertaining to each classification will be collected.

5. Other variables.

Information regarding each participant's most recent health care consultation, as well as information regarding provision of pain education to their family and employers, and its perceived impact on their recovery time will be collected.

5.9 Dissemination

The results from this survey analysis will be included as a chapter in MG's thesis and published in peer-reviewed scientific journals as well as used for conference presentations. The results of the study will be made available to the public on the University of Adelaide and the Body in Mind website.

5.10 Discussion

To our knowledge, this is the first study to examine if patients' perspectives, views, and beliefs about their chronic pain management are associated, with perception of time to recovery and particularly with reference to testing and prescription of supplements. Moreover, the study has been promoted internationally and it is anticipated that the analysis will capture the variability of patients' perceptions and beliefs across countries (if the distribution of the sample obtained allows sub-group analysis). It is also expected that the results from the survey study will provide insight about what patients with chronic pain expect from their pain management and how these expectations are challenged by the duration of pain, the character of the pain, the quality of pain education, and support of health professionals. A deeper understanding of patients' perceptions with regards to their pain management will enable researchers, policy makers, and health professionals to design policies, interventions and prevention strategies which are tailored to individual patient needs and are intended to improve the treatment outcome.

This study will also provide information on intake of complementary and alternatives medicines, dietary supplements, non-pharmacological therapies, and educational sources most frequently used by the chronic pain patients for managing their pain. It is also anticipated that this evidence based knowledge will describe the self-management strategies most frequently implemented by chronic pain patients.

Conflict of interests

MG, SV, MM and NS declare that they have no conflict of interest. GLM—Noigroup Publications royalties, speaker's fees and Pfizer consultancy. This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

CHAPTER 6

Factors associated with vitamin testing, deficiency, intake and supplementation in patients with chronic pain

6.1 Preface

This chapter address the third objective of this thesis- What demographic and pain-related factors are associated with; testing for vitamin D levels, vitamin D deficiency and intake of vitamin D supplement among people with chronic pain?

This chapter presents the results from the analysis of data collected from the cross-sectional survey (Chapter 5). This chapter investigates the factors associated with vitamin D testing, deficiency and intake. As outlined in Chapter 3, findings from study 1 show that vitamin D supplementation is clinically endorsed by GPs for patients with CNMP. GPs considered vitamin D as improving the overall sense of wellbeing, musculoskeletal health and mood in patients with CNMP. It is also considered as a cost-effective (261, 262) and readily available intervention (262), with minimal side effects (262). Chapter 2 (literature review) describes in detail studies investigating the role of vitamin D in the etiology and management of chronic musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis, fibromyalgia, chronic widespread pain and chronic nonspecific musculoskeletal pain. However the factors associated with vitamin D testing, deficiency and intake in patients experiencing chronic pain are not yet widely researched. Hence the current study aimed to explore the demographic and pain-related factors associated with vitamin D testing, deficiency and supplement intake. Furthermore, we also examined the demographic and pain-related factors associated with vitamin D supplementation advised by doctors. This chapter is under review with a per-reviewed Journal for publication.

Statement of Authorship

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Contribution to the Paper	Designed the study, conducted the study, performed analyses, interpreted the results and drafted the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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6.2 Abstract

Vitamin D deficiency is a public health issue, with reports of six to twenty-five fold rise in vitamin D testing. It has been linked to many chronic diseases such as diabetes mellitus, cardiovascular disease, depression and chronic pain. Identifying factors associated with risk of deficiency in individuals with chronic pain will help minimize time and cost. This study aims to examine the factors associated with vitamin D testing, intake and doctor advised supplementation in individuals with chronic pain. Using a cross-sectional design, data was collected from 465 individuals with chronic pain. This data was analyzed using penalized logistic regression with the LASSO technique. 57% reported been tested for vitamin D, about 40% reported been diagnosed with vitamin D deficiency, and of those who had been tested, 60%, reported taking vitamin D supplementation. The findings suggest older age (*OR 3.12,CI 1.02-9.50*) and higher mean pain intensity score (*OR 2.02,CI 1.13-3.59*) increased an individual's chance of being vitamin D deficient. Unemployment or on leave due to pain (*OR 1.79,CI 1.03-3.11*), part-time employment (*OR 1.86,CI 1.02-3.39*), and being resident of Australia (*OR 2.32,CI 1.13-4.72*) increased chances of being tested for vitamin D. While, diagnosed vitamin D deficiency (*OR 6.67,CI 2.75-16.19*), unemployment or on leave due to pain (*OR 3.71,CI 1.25-11.00*) and in part-time employment (*OR 2.69,CI 0.86-8.38*) were associated with doctor advised vitamin D supplementation. Our results may have practical implications as identifying pre-test risk factors may assist, in identifying who is at risk of vitamin D deficiency, whom to test and treat.

Keywords

Vitamin D, Vitamin D supplementation, Chronic Pain, Supplements

6.3 Introduction

Vitamin D is unique compared to other vitamins as it is the only vitamin the human body can manufacture on its own with adequate exposure of the skin to sun (UVB rays) (360). Other vitamins need to be ingested via foods, for example vitamin C from fruits and vegetables. During synthesis in the skin it undergoes conversion into an "active form" known as 1,25-dihydroxyvitamin D which reaches target tissues (360, 361). For many years vitamin D was known as an essential compound important for strong bone and skeletal system. Promoting bone remodelling and maintaining calcium homeostasis (361) was believed to be its sole function in the human body. More than thirty years ago studies uncovered the presence of vitamin D receptors on almost every cell and tissue, which lead to the discovery of various genomic and non-genomic functions of vitamin D (362, 363). This also established the role of vitamin D in various chronic conditions such as diabetes mellitus, cardiovascular disease, depression, multiple sclerosis, many cancers (364, 365) and also chronic pain (37, 366, 367).

Vitamin D deficiency has been reported as a major public health problem worldwide (368, 369) with reports of increased vitamin D testing globally (370-372). In Australia, the Medicare Benefits Schedule expenditure on vitamin D testing was reported to be approximately $143.1 million in the year 2013-2014 (370). Similar figures are reported in Ontario, Canada (371) and the UK (372). Not surprisingly, a large increase in vitamin D supplementation has also been reported.

Vitamin D deficiency has been linked to chronic pain (37, 366, 367) which is the most burdensome non-fatal health condition in terms of years lived with disability (373) and the third most common health complaint presenting to Australian general practitioners (374). We

undertook a cross-sectional survey of patients with chronic pain to examine the factors associated with vitamin D deficiency, testing and supplementation. It is anticipated that the findings from this study will be beneficial for patients with chronic pain and physicians to guide who may be at risk of vitamin D deficiency, whom to test and when to treat.

6.4 Methods

Study design

The study protocol was published prior to collecting data (336). The cross-sectional study was an online survey of individuals aged 18 years and above who had experienced pain for more than 3 months with no restrictions on gender, ethnicity, or country of residence. Individual's aged less than 18 years, experiencing pain for less than 3 months and not providing consent for the study were excluded. The survey was advertised on multiple patient forum websites and linked social media in countries like Australia, New Zealand and the United States. The primary aim of the survey was to investigate the perceptions, beliefs and expectations of individuals who experience chronic pain on a daily basis, and the strategies used by them to help manage this pain. All participants gave electronic consent prior to beginning the survey.

Ethical Statement

This study was approved by the Human Research Ethics Committee of the University of Adelaide (approval no- HREC-2016-0712) and the University of South Australia (application id- 0000035791).

Survey Questionnaire

A specialized questionnaire was built in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (356). A review of literature was performed a priori to identify potential factors associated with vitamin D deficiency, information from this review was used for developing the questionnaire. The draft questionnaire was reviewed by two general practitioners (NS and SV), who approved the original draft with minor amendments to wording only. The survey was also piloted on three individuals diagnosed with chronic painful conditions to determine whether questions were easily understood and interpreted in the way intended by the researcher. The primary change following their feedback was simplifying some of the technical terms used in health research and making it more generalized to appeal a wider audience. Face and content validity was achieved by consensus among researchers conducting the survey.

Sample size

Sample size calculations for estimation were based on how wide a confidence interval (*CI*) we considered appropriate. This estimation depended on three parameters, the variance or spread of the observations, the precision and the level of significance or probability of type-1 error (357).

$$n = \left(\frac{1.96^2 P(1-P)}{\delta^2}\right)$$

Where n= sample size, P = estimated population proportion, δ = precision of the estimate.

As the estimated population proportion (P), was unknown we set P = 0.5 and δ, was set as 0.05 for the probability of type-I error = α=0.05. Using, this formula a sample size of 384 was estimated for effect size of 0.5 with 95% CI.

Statistical Analysis

To study the best predictors of described outcomes a common practice is to use a statistical model depending on the type of the variable (for example a linear model if the outcome is continuous). In case of binary outcomes univariate or multivariate logistic regression is used for estimating odds ratio (375). The multivariate logistic regression allows simultaneous identification of possible risk factors in one model, after adjusting for all predictors. Regular logistic regression estimation is carried out by maximizing the likelihood function. However, when we have many potential predictors and the sample size is small, then there may not be a meaningful way to estimate the coefficients. In order to overcome this, the usual practice is to use step wise regression. The trouble with stepwise regressions is that it uses unconstrained least-square estimation processes which either over/underestimate the effect sizes. To solve this issue, we used LASSO (Least absolute shrinkage and selection operator). LASSO is a regression technique that allows the selection of variables and estimation simultaneously in order to enhance the accuracy of the prediction and its interpretability (376). LASSO was initially designed for simple linear regression, but was extended for general linear models such as logistic regression (377). Estimation in LASSO is based on penalizing the likelihood

$$\widehat{\beta(\lambda)} = \underset{\beta}{\operatorname{argmax}}(l(\beta) - \lambda \sum_{j=1}^{p} |\beta_j|)$$

Where $\boldsymbol{\beta}$, is the effect size estimate using maximum likelihood, $\boldsymbol{\lambda}$ is the penalty parameter and *p* is the number of covariates in the model. The parameter $\boldsymbol{\lambda}$ controls the complexity of the model. In cases where $\boldsymbol{\lambda}$ is zero, the estimate will be same as the simple logistic regression. To obtain an optimal value of the penalty parameter we looked at the convergence of the likelihood. For some of the models the penalty value was 0.5, and for others the penalty was 2. The other benefit of using LASSO is it actually specifies the covariates whose effect sizes are exactly zero, thus allowing selection of variables. All the statistical analysis was done in STATA 14.1 (325). The LASSO logits regression were fitted using a special user written program in STATA [http://www.homepages.ucl.ac.uk/~ucakgam/stata.html].

Outcome measures

The outcomes were related to patient reported testing, prescription and consumption of vitamin D supplements. The following information was collected from the participants: i) had they been tested for vitamin D levels; ii) were their test results for vitamin D reported as deficient; iii) did they use vitamin D supplements for their pain; and iv) was the supplement advised by their doctor. All outcome responses are dichotomized and were coded as 1 if Yes and 0 if No.

Independent Variables

The independent variables were the demographic factors of the participants' which included age, gender, country of residence, marital status, education level and employment status.

Information regarding participants' pain experience was also collected. Participants were asked 'which of the following describe the characteristics of your pain? The choices given were aching, burning, sharp, pins and needles, throbbing and others. Participants were also asked if their pain was triggered by an injury, options provided were Yes and No. Participants also completed a numerical rating scale (NRS) anchored at left with 0 = no pain and at right with 10 = severe/worst pain in answer to the question 'what's the average severity of your pain?'

6.5 Results

The survey was conducted online from 29th August to 24th October 2016. 573 people in total participated however, 108 of these had incomplete information and hence were excluded from the analysis thus giving us a complete sample of 465 participants. All analyses were conducted presuming no participants completed the survey multiple times. Distributions of the demographic characteristics of 465 participants are presented in Table 6.1.

Table 6.1 Distribution of the demographic characteristics of the sample

Variable	Number (n)	Percentage (%)
Age (years)		
18-30	95	20
31-40	101	22
41-50	100	22
51-60	95	20
60+	74	16
Gender		
Female	403	87
Male	61	13
Prefer not to say	1	<1
Education Level		
primary and secondary	93	20
tertiary	174	38
post-graduate	177	38
others	19	4
Employment status		
Full-time employed	136	29
Unemployed/on leave because of pain	126	27
Part-time employment	93	20
Home duties	46	10
Student	53	11
Prefer not to say	11	3
Country of residence		
Australia	293	63
Europe	68	15
New Zealand	64	14
Others	40	9
Marital Status		
Married	216	46
Single	129	28
Partnered	88	19
Unmarried	27	6
Prefer not to say	5	2
Vitamin D deficiency		
Yes	191	41
No	84	18
Not applicable	190	41
Vitamin D testing		
Yes	267	57
No	198	43
Vitamin D intake		
Yes	204	44
No	261	56
Characteristics of pain		
1-4	128	28
5-8	173	37
>9	164	35
Is your pain triggered by an injury?		
Yes	152	33
No	313	67
How long have you had your pain problem?		
< 1 year	33	7
> 1 year	432	93

The age of participants ranged from 18 to 90 years, with almost equal number of participants from the age groups between 31- 40 years (22%) and 41-50 years (22%). Most participants were female and about two thirds were from Australia. Other countries which participated in the study were New Zealand, Europe, United States and India. Among the 465 participants, 57 % (n=267 /465) reported that they had been tested for vitamin D and about 40% were aware that they had been diagnosed with vitamin D deficiency. Of those who had been tested for vitamin D, 60% (n= 162/267) were in fact taking vitamin D supplementation.

To identify significant predictors of each outcome a simple logistic regression analysis was performed. In each of these, individual logistic regressions all the observed factors hypothesized, a priori, to be clinically useful for predicting the outcome, were entered simultaneously. In the simple logistic regression the factors significant for vitamin D testing were education, country of residence, employment status and gender. Similarly, the factors which were significant for predicting vitamin D deficiency were gender and mean pain intensity. Correspondingly the factors significant for vitamin D intake were age, gender, employment status, marital status, education and country of residence. All these factors which were entered in logistic regressions were re-entered into the LASSO model. Results from the penalized logistic regression with LASSO suggest that some of the predictors that initially showed association in simple logistic regression did not show association after penalizing.

The final model for the prediction of vitamin D deficiency consisted of six predictors: age, gender, country of residence, employment status, mean pain intensity and diagnosis for pain problem. For vitamin D testing additional predictors considered were: education level, pain related to injury, and duration of pain. For, vitamin D intake and doctor advised vitamin D supplementation, characteristics of pain, vitamin D deficiency, and vitamin D testing were considered.

The predictor's gender (gender 0= females, 1= males), pain related to injury (No= 0, Yes =1), mean pain intensity (0 = ≤ 5 or 1= ≥ 6 on 11 point numerical scale), duration of pain (0 = <1 year or 1 = > 1 year), vitamin D tested (No= 0, Yes =1) and vitamin D deficient (No= 0, Yes =1) were treated as binary variables. Due to fewer number of cases in each individual category the characteristics of pain were categorized into 3 groups; 0= 1-4 characteristics, 1= 5-8 characteristics and 2= >9 characteristics, which is used as the base category for LASSO. The categorical predictors were re-coded as dummy variables before submitting in the regression.

Outcomes –

Table 6.2 presents a summary of factors associated with vitamin D testing. The odds ratios and their *CIs* suggest that males (*OR 0.50, CI 0.58-2.25*) are half as likely as females to be tested for vitamin D. Similarly, the odds of an individual with chronic pain being tested for vitamin D are 2.3 times higher if they were from Australia (*OR 2.32, CI 1.13-4.72*), and 0.3 times less likely if they were from New Zealand (*OR 0.27, CI 0.10-0.70*), than if they were from other countries. In addition, chronic pain patients who were unemployed or on leave due to pain (*OR 1.79, CI 1.03-3.11*) and in part-time employment (*OR 1.86, CI 1.02-3.39*) were twice as likely to be tested for vitamin D. Age, education level, pain related to injury, mean pain intensity of pain and duration of pain were not associated with vitamin D testing.

Table 6.2 Summary of LASSO for factors associated with vitamin D testing.

Vitamin D Testing	**Odds ratio**	**P value**	**95% CI**	
Age (Years)				
31-40	1.12	0.68	0.64	1.93
41-50	1	1.00	0.99	1.00
51-60	1.17	0.58	0.66	2.08
60+	1.14	0.69	0.58	2.25
Gender				
Male	0.50	0.02	.278	0.92
Country of residence				
Australia	2.32	0.02	1.13	4.72
Europe	0.71	0.42	0.30	1.64
New Zealand	0.27	0.00	0.10	0.70
Employment status				
Unemployed/on leave because of pain	1.79	0.03	1.03	3.11
Part-time employment	1.86	0.04	1.02	3.39
Home duties	1.43	0.38	0.63	3.22
Student	0.79	0.52	0.38	1.63
Education level				
Tertiary	1.67	0.08	0.93	3.00
Post-graduate	1.44	0.22	0.80	2.59
Others	1.45	0.52	0.45	4.63
Pain related to injury				
Yes	1.06	0.78	0.67	1.66
Mean Pain intensity				
≥ 6	1	1.00	0.99	1.00
Duration of pain				
>1 year	1.13	0.75	0.49	2.60

Table 6.3 presents a summary of factors associated with vitamin D deficiency. The ORs and CIs suggest that for individuals with chronic pain the odds of being vitamin D deficient are approximately three times higher if they are older than 60 than if they are not (*OR 3.12 , CI 1.02-9.50*). Similarly, the individual with chronic pain who has a mean pain intensity ≥6 (*OR 2.02, CI 1.13-3.59*) on an 11 point NRS are twice as likely to be vitamin D deficient then an individual with chronic pain who has a mean pain intensity ≤5. Gender, country of residence and employment status were not associated with patient reported vitamin D deficiency.

Table 6.3 Summary of LASSO for factors associated with vitamin D deficiency.

Vitamin D deficiency	**Odds ratio**	**P value**	**95% CI**	
Age (years)				
31-40	2.62	0.03	1.06	6.45
41-50	2.28	0.07	0.93	5.59
51-60	2.94	0.02	1.15	7.51
60+	3.12	0.04	1.02	9.50
Gender				
Male	0.44	0.05	0.19	1.02
Country of residence				
Australia	1	1.00	0.98	1.01
Europe	1	1.00	0.98	1.01
New Zealand	0.64	0.49	0.18	2.26
Employment status				
Unemployed/on leave because of pain	1.24	0.51	0.63	2.42
Part-time employment	1	1.00	0.98	1.01
Home duties	1.23	0.68	0.44	3.41
Student	1.48	0.46	0.51	4.32
Mean Pain intensity				
≥ 6	2.02	0.01	1.13	3.59
Diagnosis for pain				
OA	0.76	0.50	0.35	1.67
FM	1.53	0.14	0.86	2.74
CNMP	1.96	0.07	0.92	4.15

Table 6.4 presents a summary of factors associated with taking vitamin D supplements. The ORs and CIs suggest that individuals with chronic pain aged between 51-60 years (*OR 2.59, CI 1.00-6.71*) are three times more likely to be taking vitamin D supplements than those aged

50 years or younger, and those older than 60 (*OR 6.08, CI 2.10-17.60*) are six times more likely. Not surprisingly, those who had been vitamin D deficient (*OR 6.63, CI 3.41-12.89*) were six times more likely to take vitamin D supplements than those who were not. Gender, country of residence, education level, mean pain intensity, characteristics of pain, duration of pain, pain related to injury and tested for vitamin D were not associated with vitamin D supplement intake.

Table 6.4 Summary of LASSO for factors associated with intake of vitamin D supplement.

Vitamin D intake	**Odds ratio**	**P value**	**95% CI**	
Age (years)				
31-40	0.93	0.89	0.36	2.40
41-50	2.18	0.11	0.82	5.75
51-60	2.59	0.04	1.00	6.71
60+	6.08	0.00	2.10	17.60
Gender				
Male	0.62	0.32	0.24	1.58
Vitamin D testing				
Yes	1.07	0.93	0.19	5.78
Vitamin D deficiency				
Yes	6.63	0.00	3.41	12.89
Country of residence				
Australia	0.65	0.45	0.21	2.01
Europe	1.03	0.96	0.25	4.21
New Zealand	0.98	0.98	0.18	5.12
Education level				
Tertiary	1.63	0.23	0.72	3.68
Post-graduate	1.53	0.30	0.67	3.46
Others	0.76	0.73	0.15	3.76
Pain related to injury				
Yes	0.67	0.20	0.36	1.24
Mean Pain Intensity				
≥ 6	1.32	0.36	0.72	2.41
Characteristics of pain				
1- 4	1.45	0.32	0.68	3.08
5-8	1.16	0.64	0.59	2.27
Duration of pain				
>1 year	1.02	0.96	0.33	3.17

Table 6.5 presents a summary of factors associated with doctor advised vitamin D supplementation. Individuals with chronic pain who were unemployed or on leave due to pain (*OR 3.71, CI 1.25-11.00*) and in part-time employment (*OR 2.69, CI 0.86-8.38*) were 4 times more likely than full-time employed participants to be prescribed vitamin D supplements by their doctor. Not surprisingly, being vitamin D deficient (*OR 6.67, CI 2.75-16.19*) had the largest influence on whether doctors would prescribe vitamin D. Age, gender, country of residence, education level, mean pain intensity, duration of pain and whether pain related to injury were not associated with being prescribed vitamin D supplement. Finally, and surprisingly, whether or not someone had been tested for vitamin D levels (*OR 1.49, CI 0.13-17.24*) was not associated with being prescribed vitamin D supplement.

Table 6.5 Summary of LASSO for factors associated with doctor advised vitamin D supplement

Doctor advised VD supplement	Odds ratio	P value	95% CI	
Age (years)				
31-40	0.95	0.95	0.24	3.76
41-50	2.08	0.31	0.49	8.78
51-60	1.17	0.82	0.29	4.69
60+	3.12	0.18	0.59	16.48
Gender				
Male	1	1.00	0.97	1.02
Country of residence				
Australia	1	1.00	0.98	1.01
Europe	0.45	0.19	0.13	1.51
New Zealand	1.13	0.91	0.10	11.80
Employment Status				
Unemployed/on leave because of pain	3.71	0.01	1.25	11.00
Part time employment	2.69	0.08	0.86	8.38
Home duties	3.68	0.12	0.69	19.56
Student	3.96	0.14	0.63	24.85
Education level				
Tertiary	0.61	0.43	0.18	2.08
Post-graduate	0.94	0.92	0.27	3.23
Others	0.48	0.59	0.03	7.10
Vitamin D Deficiency				
Yes	6.67	0.00	2.75	16.19
Vitamin D tested				
Yes	1.49	0.74	0.13	17.24
Pain related to injury				
Yes	0.93	0.88	0.40	2.20
Mean Pain Intensity				
≥ 6	1.33	0.49	0.57	3.07
Duration of pain				
>1 year	0.98	0.98	0.22	4.25

6.6 Discussion

Data from this cross-sectional survey suggests that gender, country of residence and employment status were associated with being tested for vitamin D. Our study findings suggest that Australians were much more likely to be tested for vitamin D than other nationalities. However, this finding could be influenced by the fact that majority of our study participants were from Australia. These findings resonate with reports that demonstrate a remarkable

3587% rise in vitamin D testing in Australia over last 10 years (282) and in the United States (378).

Older people and individuals who reported a mean pain intensity score ≥ 6 on an 11 point NRS were more likely to report vitamin D deficiency. To our knowledge, this is the first time that intensity of self-reported pain has been identified as being associated with vitamin D deficiency. That older people were more likely to report vitamin D deficiency is in line with the association between age and risk of developing vitamin D deficiency (379, 380), which has been attributed to insufficient sun exposure time (381) and decline in the capacity to synthesize vitamin D (263). Not surprisingly then, along with diagnosis of vitamin D deficiency, age was associated with taking vitamin D supplements. Supplement usage in general is reported to increase with age (382-384) but not to the levels observed here for vitamin D. Not surprisingly, doctors advised vitamin D supplementation to individuals who were vitamin D deficient, unemployed or on leave due to chronic pain and in part time employment. Although, doctor advised vitamin D supplementation was not associated with being tested for vitamin D.

To the best of our knowledge, most previous studies have investigated vitamin D deficiency and insufficiency among healthy populations in Australia (385) Europe (386) and America (387). These are findings are important as it highlights factors associated with deficiency, testing, intake and doctor advised supplementation of vitamin D in patients with chronic pain.

That vitamin D deficiency has been proposed as a cause of nonspecific muscular and bone pain (258) would predict that pain characteristics, intensity and duration would relate to testing, prescribing or taking vitamin D supplementation. We found only a relationship between pain intensity and vitamin D deficiency. Our design does not allow causal attribution, but it is notable that there are biological pathways that could lead from vitamin D deficiency to pain. For example, it is thought that vitamin D deficiency reduces calcium phosphate, which then

makes the collagen matrix surrounding the bone rubbery. This can cause pressure on the periosteal covering, which is innervated by sensory fibers (258). Even slight pressure on the bone can produce pain. In view of this mechanistic plausibility of vitamin D deficiency to modulate pain levels in patients experiencing chronic pain, it is plausible that it could be one of the reasons for higher mean pain intensity being reported by patients who were vitamin D deficient. Clearly, longitudinal data are required to investigate this possibility.

Our results may have practical implications, as identifying factors associated with a risk of vitamin D deficiency could assist to minimize the concern of over diagnosis and over treatment of vitamin D deficiency (370). It may assist doctors to identify early on chronic pain patients who would more likely benefit from vitamin D supplementation for their chronic pain problem. About 25% of adults worldwide have persistent pain – to test everyone would be expensive and perhaps of limited return. There is clearly merit in identifying pre-test risk factors in those with chronic pain, so as to minimize unnecessary testing.

Study Limitations

Our adherence to CHERRIES recommendations (356) gives us confidence in minimizing bias and our online approach allowed us to reach the *a priori* sample size and diversity that was required to fulfil our aims. However, this approach also has clear limitations. We relied on word of mouth, social media networks and promotion through consumer advocates to recruit our sample, a process that might introduce a bias towards sampling within established social media networks and diagnostic groups. That the survey was online clearly limits our sample to those with internet connectivity and engagement, and computer skills. We were also bound by considerations of participant burden (388), which meant that we decided *a priori* on the basis of pilot testing, to not collect information on participants' pain medicines, their outdoor

activities, sun exposure time and safe sun practices and the type and dosage of vitamin D supplement preferred by the participants. These data might have offered important insights. Finally, any survey is dependent on self-report and little is known about the validity of questions such as those asked here when compared to non-self-report assessment approaches.

6.7 Conclusion

Among the 465 participants, 57% reported that they had been tested for vitamin D and about 40% were aware that they had been diagnosed with vitamin D deficiency. Of those who had been tested for vitamin D, 60% were in fact taking vitamin D supplementation. The findings show that older age and higher mean pain intensity score increased an individual's chance of being vitamin D deficient. Unemployment or on leave due to pain, part-time employment, and being resident of Australia increased chances of being tested for vitamin D. While, diagnosed vitamin D deficiency and unemployment or on leave due to pain and in part-time employment were associated with doctor advised vitamin D supplementation.

In summary, the results from the present study examine the associations between vitamin D testing, deficiency, intake and doctor advised vitamin D supplementation in individuals with chronic pain. The simple demographic and pain-related factors, could be used as a guide to identify who may be at risk of vitamin D deficiency, whom to test and when to treat.

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Declaration of Interest:

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CHAPTER 7

Effect of pain education and patient-provider relationship on patient-reported pain intensity and recovery.

7.1 Preface

This chapter address the fourth objective of the thesis- What perspectives do patients with chronic pain have about the patient-provider relationship, pain education and does it affect their pain intensity and perceived time to recovery?

This chapter presents the results from the analysis conducted on the data collected from the cross-sectional survey (Chapter 5). It investigates the association between pain education and patient-provider relationship on patient-reported pain intensity and recovery.

The findings of study 1, outlined in Chapter 3 (Theme 3: Developing the right strategy) show that, for diagnosis, GPs emphasize spending more time during consultation with patients which was regarded important for taking detailed medical history but was also considered as an opportunity for building good patient-provider relationship. Further, in Chapter 3 (Theme 4: Patient centered care) educating patients with CNMP for setting realistic goals was regarded as an important part of the framework for management. However, little is known about how pain education and patient-provider relationship affects patient-reported pain intensity and perception of recovery in individuals experiencing chronic pain. Hence the current study aimed at exploring patients' views on the patient-provider relationship and pain education, and their associations with; the patient-reported pain intensity, and perception of recovery.

7.2 Abstract

Background:

Chronic pain is a global health problem. Its management perplexes patients and doctors alike. Various factors influence management of chronic pain. Two factors which have been recognized to significantly influence patient satisfaction and pain management are pain education and patient-provider relationship. But little is known about the association between patient-reported pain intensity and perception of recovery, especially among chronic pain patients who receive pain education and patient-provider relationship.

Aim:

To explore patients' views on the patient-provider relationship and pain education and their association with self-reported pain intensity and perception of recovery.

Design and Methods:

Data was collected from a cross-sectional survey of 465 individuals, with chronic pain after excluding "not applicable" cases from all covariates, the sample size obtained was 448. Univariate and multiple logistic regression was used to assess the effect of pain education and patient-provider relation on self-reported pain intensity and recovery.

Results:

Self-reported pain intensity was reported higher by individuals aged 40 years and above and by females. Positive self-reported recovery was higher in individuals aged between 18-40 years and by males. However, pain education and patient-provider relationship did not show associations with self-reported pain intensity and recovery. Interestingly, changes in pain cognition and management of pain following pain education showed significant associations

with self-reported pain intensity and positive perception of recovery. A separate regression analysis showed that changes in pain cognition and management of pain were strongly associated with pain education and patient-provider relationship. These findings suggest that pain education and self-reported pain intensity and recovery have an indirect relation, which is induced through changes in pain cognition and management of pain following pain education.

Conclusion:

Pain education and patient-provider relationship may not be effective in isolation but should be considered jointly with education prompted changes in pain cognition and management of pain.

7.3 Introduction

Pain has emerged as a major social, economic, clinical, and global health problem (389). It can affect anyone regardless of age, gender, ethnicity, income or geography. Pain that exists beyond what is regarded as the healing time (>3 months) is defined as chronic pain (337). Chronic pain causes not only physical suffering, but also affects individual's ability to work, their social life, sleep disturbances, depression, suicidal thoughts, and poor quality of life (390). An estimated 1 in 10 adults is diagnosed with chronic pain globally every year (391).

Due to a lack of training in pain management, doctors report that they feel inadequate in providing care to patients with non-malignant chronic pain (25, 26). However, their role in management is not limited to only providing treatment (392). It is reported that patients who share a good relationship with their doctor often have better treatment compliance (393) and outcomes (394, 395). Not surprisingly, patients who have a good patient-provider relationship report high levels of satisfaction, even when receiving less than optimal management and experiencing pain. This is famously known as the "*paradox of patient satisfaction"* (392). Although, the association between patient-provider relationship is known for general ailments, we still do not know if the patient-provider relationship shows any association with the patient-reported pain intensity and their time to recovery.

Management of any long term condition such as chronic pain, requires active participation from the patient. To promote self-management, research suggests empowering patients by providing education about their pain (396). Pain education has been rated higher than physical and medical therapy for chronic pain management (397). Moreover, it shows a positive effect on catastrophizing (398, 399), disability (398), pain inhibitory mechanisms (400), physical performance (398, 401, 402) and pain itself (398, 399, 401). To the author's knowledge no previous studies have focused on testing the association between patient-reported pain intensity

and their time to recovery, especially among patients receiving pain education and patient-provider relationship, in real-world conditions. By real-world conditions we mean environments uninfluenced by the researchers or the experiment.

Keeping this in view we conducted a cross-sectional study using an online survey design that explored patients' perceptions, views and beliefs about their chronic pain management and recovery. Patients' perspectives and views on their management and outcome are central to identifying areas which require improvement (403). Findings from this study may help to improve the process of care which in turn may improve treatment outcomes.

7.4 Aim and Objectives

The aim of this chapter is to explore patients' views on the patient-provider relationship and pain education and their associations with; self-reported pain intensity and perception of recovery. The key three objectives of this study are: i) To examine if self-reported pain education affects self-reported pain intensity and perception of recovery; ii) To examine if the patient-provider relationship affects self-reported pain intensity and perception of recovery; and iii) To determine the type of education material most referred to by health care professionals and if the same was perceived helpful by the patients.

7.5 Methods

Study design

The data used in this study was collected as part of a cross-sectional study conducted to understand patients' perspectives on their chronic pain management. The study protocol and questionnaire for this study has been published in the *Journal of Pain Research*. This study was approved by Human Research Ethics Committee of University of Adelaide (approval no- HREC-2016-0712) and University of South Australia (application id- 0000035791). Electronic consent was collected from all individuals participating in the survey. The survey questionnaire was developed according to a review of the literature and was built in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (356).

Study Sample

The study sample consisted of individuals aged 18 years and above with no limitation on gender, ethnicity or country of residence, who had experienced pain for more than 3 months.

Sample size

The sample size was estimated using the expected population proportion (P), the precision of the estimate δ and the type-I error. As the value of P was unknown we set it to 0.5 and δ, was

set as 0.05 for the probability of type-I error = α=0.05. Using these parameters the estimated the sample size was 384.

Outcome measures

The outcomes used in this study were; self-reported pain intensity and perceived recovery. Information on pain intensity was collected from the participants using the question: i) what is the average severity of your pain in the last 2 days? Participants were asked to complete a numerical rating scale (NRS). Starting with "0" on left side defined as no pain and "10" on the right side defined as severe or worst pain; and (23) how long do you think it will take you to recover from the current pain problem? The choices provided were "3-6 months", "6-12 months", "up to 1 year", "more than 1 year" and "never".

Due to fewer number of cases in each individual category the pain intensity reporting in the last 2 days; was dichotomised at the median as ≤ 5 and ≥ 6. Similarly, patient perceived recovery was dichotomised as "recovery" and "never". All those individuals who selected a defined time frame, described above, were grouped as those who perceived recovery and those who marked never were left as those as who perceived no recovery.

Independent variables

The independent variables used in this study were pain education and patient-provider relationship along with demographic characteristics.

Pain education

Participants were asked if they had received any form of education about their pain. The responses were coded as "1" if yes and "0" if no. The following information was also collected: i) did the pain education received change how you think about your pain? ii) Did the education received change your management? Response to both these questions was collected using simple "yes", "no" dichotomization. Information regarding who had provided them the education on pain was also collected. The choices given were general practitioner, pain physician, nurse practitioner, physiotherapist, chiropractor, massage therapist, pharmacist, self-education and other. Information collected also included the type of education material individuals were most referred to and which of them did they consider to be most helpful?

Patient-provider relationship

Patient-provider relationship was not a direct question but it is a manifest variable. This was created using information from six different questions which were; frequency of their consultation; the duration of their consultation; how they felt at their most recent consultation; were they informed about the treatment options; how helpful was this information and how satisfied they were with their involvement in the decisions about their pain management. Responses to these questions were simply summed together. The score was then re-categorised into binary variable- "good" patient-provider relationship (if the score was above the median value) and "not good" patient-provider relationship (if the score was below the median value). This was dichotomised for the reason that there were fewer cases in each of the categories.

Demographic factors

These include age, gender, education level, employment status, marital status and country of residence.

Statistical Analysis

This included basic univariate descriptive statistics such as percentages to describe the simple distributions of patients receiving pain education, patient-provider relationship, pain intensity and recovery status. Cross-tabulation was used to describe self-reported pain intensity and recovery in groups defined by age, gender, education level, employment status, marital status, patient-provider relationship, pain education, pain cognition and management of pain. As the prevalence of chronic pain was reported higher among older age groups we performed cross-tabulation on two separate age groups: 18-40 years and 41+ years. This was done to assess the impact of age on self-reported recovery and pain intensity. Individuals with self-reported pain intensity ≤ 5 were compared with individuals reporting pain intensity ≥ 6. Univariate and multiple logistic regression were used to study the effect of pain education and patient provider relation on pain intensity and patient perceived recovery before and after controlling for the potential confounders. Odds ratio (OR) and likelihood ratio test were used to test the model. In order to compare the regression models and maintain uniformity of sample size, "not applicable" cases from all the covariates were removed. This reduced the sample size from 465 to 448. Even though our estimated sample size was 384 we received responses from 573 individuals, within the allocated time period for which the survey was open, of which 465

complete sample information was used in this study. All analysis was performed in STATA.14.1. (325).

7.6 Results

All outcome measures were adjusted for confounding factors such as age, gender, education level, employment status and marital status.

Pain intensity was reported by all 465 individuals. Of these 465 individuals 40% (185/465) reported their pain intensity to be ≤ 5 and 60% (280/465) reported their pain intensity to be ≥ 6. The age-adjusted reporting of pain intensity ≤ 5 was 43% (84/196) in younger (18-40) compared to their counterparts aged +41 (38%, 101/269). Higher pain intensity (≥6) was reported among older age groups (62.45%=168/269) compared to their younger counterparts, 57% (112/196).

Table 7.1 shows the self-reported pain intensity in different groups. The prevalence rates of pain intensity ≥ 6 increased relatively more among older individuals with chronic pain than younger participants. With the exception of individuals aged between 18- 40 years, who were students, unemployed or partnered. Women rated their pain intensity higher than men. Individuals with primary education rated their pain intensity higher compared to individuals with other education. This association was more significant in individuals aged 41 years and above. Being unemployed or on leave because of pain was associated with higher pain intensity in both the age groups (18-40, +41 years).

Compared to their younger counterparts individuals aged 41 years and above reported higher pain intensity if they did not receive pain education and did not report a good patient-provider relationship. Individuals aged 41 years and above reported higher pain intensity if their duration

of pain was greater than 1 year. The association between higher pain intensity was also stronger among individuals aged 41 years and above who received pain education but did not change their pain cognition and management of pain.

Table 7.1 Self-reported pain intensity by participants aged 18 years and above.

	Age 18-40 years					Age 41 + years				
	Pain intensity ≥6		Pain intensity ≤5			Pain intensity ≥6		Pain intensity ≤5		
Variable	**No**	**%**	**No**	**%**	**Total**	**No**	**%**	**No**	**%**	**Total**
Sex										
Female	100	59%	70	41%	170	149	64%	84	36%	233
Male	12	46%	14	54%	26	18	51%	17	49%	35
Education level										
Primary	26	60%	17	40%	43	32	64%	18	36%	50
Others	86	56%	67	44%	153	134	62%	83	38%	217
Employment status										
Full time employed	36	58%	26	42%	62	47	64%	27	36%	74
Unemployed/ on leave because of pain	37	82%	8	18%	45	58	72%	23	28%	81
Part time employment	15	39%	23	61%	38	27	49%	28	51%	55
Home duties	5	63%	3	38%	8	22	58%	16	42%	38
Student	17	43%	23	58%	40	7	54%	6	46%	13
Marital status										
Married	34	52%	31	48%	65	88	58%	63	42%	151
Single/unmarried	47	63%	28	37%	75	56	69%	25	31%	81
Partnered	31	56%	24	44%	55	21	64%	12	36%	33
Pain education										
No	9	47%	10	53%	19	24	71%	10	29%	34
Yes	103	58%	74	42%	177	144	61%	91	39%	235
Patient-provider relationship										
Not good	39	52%	36	48%	75	67	63%	40	37%	107
Good	73	60%	48	40%	121	101	62%	61	38%	162
Duration of pain										
< 1 year	7	50%	7	50%	14	8	42%	11	58%	19
> 1 year	105	58%	77	42%	182	160	64%	90	36%	250
Change in pain management										
No	41	56%	32	44%	73	84	74%	29	26%	113
Yes	71	58%	52	42%	123	84	54%	72	46%	156
Change in pain cognition										
No	46	59%	32	41%	78	72	72%	28	28%	100
Yes	66	56%	52	44%	11	96	57%	73	43%	169

Table 7.2 shows the unadjusted and adjusted ORs obtained from logistic regression analysis on reported pain intensity, with the base category being pain intensity ≤ 5. The unadjusted association between pain intensity and gender (unadjusted OR,1.69; 95% confidence interval (CI) 0.98-2.92), being unemployed or on leave because of pain (unadjusted OR, 0.50; 95% CI, 0.29-0.85), part-time employed (unadjusted OR, 1.81; 95% CI, 1.06-3.11), change in management of pain (unadjusted OR, 1.59; 95% CI, 1.07-2.36) and change in pain cognition (unadjusted OR, 1.53; 95% 95% CI, 1.03-2.27) on receiving pain education had strong unadjusted associations. In the adjusted analysis the association between pain intensity and gender increased, the adjusted OR was two times higher (adjusted OR, 2.03; 95% CI, 1.12-3.67) in male compared to female. However, the adjusted associations between pain intensity and being unemployed or on leave because of pain (adjusted OR, 0.49; 95% CI, 0.28-0.85) and part time employed (adjusted OR, 1.86; 95% CI, 1.06-3.25) did not change much. In addition, in the adjusted analysis being a student or unemployed showed an association with pain intensity, the adjusted OR was two times higher (adjusted OR, 2.03; 95% CI, 1.03-4.00) compared to full time employment status. There was collinearity between employment status and changes in management of pain and pain cognition on receiving pain education and hence they were removed from the logistic regression analysis.

Table 7.2 Unadjusted and Adjusted Odds Ratios for Pain Intensity among individuals with chronic pain aged 18 years and above

	Pain intensity			
	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
18-40 years	1		1	
+41 years	0.84 (0.57-1.23)	0.38	0.92 (0.59-1.41)	0.71
Gender				
Male	1.69 (0.98-2.92)	0.05	2.03 (1.12-3.67)	0.01
Female	1		1	
Marital status				
Married	1		1	
Single/unmarried	0.68 (0.44-1.05)	0.08	0.75 (0.46-1.20)	0.23
Partnered	0.87 (0.52-1.44)	0.59	0.85 (0.49-1.49)	0.58
Education level				
Primary	1		1	
Others	1.09 (0.67-1.76)	0.70	0.92 (0.55-1.54)	0.76
Employment status				
Full time employment	1		1	
Unemployed/on leave because of pain	0.50 (0.29-0.85)	0.01	0.49 (0.28-0.85)	0.01
Part time employment	1.81 (1.06-3.11)	0.02	1.86 (1.06-3.25)	0.02
Home duties	1.11 (0.56- 2.21)	0.75	1.21 (0.58-2.52)	0.60
Student	1.78 (0.93-3.40)	0.07	2.03 (1.03-4.00)	0.04
pain education				
Yes	0.94 (0.51-1.73)	0.85	0.79 (0.40-1.56)	0.51
Patient-provider relationship				
good	0.83 (0.56-1.22)	0.35	0.77 (0.50-1.20)	0.26
Change in pain management				
Yes	1.59 (1.07-2.36)	0.01	1.65 (0.99-2.74)	0.05
Change in pain cognition				
Yes	1.53 (1.03-2.27)	0.03	1.27 (0.76-2.12)	0.34

Table 7.3 shows self-rated recovery in different groups among individuals with chronic pain. The prevalence rates of reporting positive recovery was higher in younger individuals (37% = 72/196) compared to older individuals (30% = 80/269) with chronic pain. A higher proportion (46% and 49%) of men in both age groups perceived that they could recover compared to women. Similarly, individuals with higher education and married were more likely to report their perception of recovery as "recover". Individuals who reported receiving pain education and changes in management of pain or pain cognition on receiving education rated their recovery to be positive, this association was more significant in individuals aged 41+ years. Similarly, individuals who had reported patient-provider relationship to be "good" also reported a positive recovery. However, being unemployed or on leave because of pain and duration of pain was inversely associated with self-reported recovery.

Table 7.3 Self-reported recovery according to age among individuals with chronic pain aged 18 years and above (n=448)

	Age 18-40 years					Age 41 + years				
	Self-reported recovery (No)		Self-reported recovery (Yes)			Self-reported recovery (No)		Self-reported recovery (Yes)		
Variable	**No**	**%**	**No**	**%**	**Total**	**No**	**%**	**No**	**%**	**Total**
Sex										
Female	110	65%	60	35%	170	170	73%	63	27%	233
Male	14	54%	12	46%	26	18	51%	17	49%	35
Education										
Primary	25	58%	18	42%	43	41	82%	9	18%	50
Others	99	65%	54	35%	153	147	68%	70	32%	217
Employment status										
Full time employed	44	71%	18	29%	62	47	64%	27	36%	74
Unemployed/ on leave because of pain	25	56%	20	44%	45	60	74%	21	26%	81
Part time employment	21	55%	17	45%	38	41	75%	14	25%	54
Home duties	6	75%	2	25%	8	26	68%	12	32%	38
Student	25	63%	15	38%	40	8	62%	5	38%	13
Marital status										
Married	39	60%	26	40%	65	100	66%	51	34%	151
Single/unmarried	47	63%	28	37%	75	65	80%	16	20%	81
Partnered	37	67%	18	33%	55	22	67%	11	33%	33
Pain education										
No	14	74%	5	26%	19	22	65%	12	35%	34
Yes	110	62%	67	38%	177	167	71%	68	29%	235
Patient-provider relationship										
Not good	48	64%	27	36%	75	76	71%	31	29%	107
Good	76	63%	45	37%	121	113	65%	61	35%	174
Duration of pain										
< 1 year	4	29%	10	71%	14	2	11%	17	89%	19
> 1 year	120	66%	62	34%	182	187	75%	63	25%	250
Change in pain management										
No	54	74%	19	26%	73	86	76%	27	24%	113
Yes	70	57%	53	43%	123	103	66%	53	34%	156
Change in pain cognition										
No	58	74%	20	26%	78	78	78%	22	22%	100
Yes	66	56%	52	44%	118	111	66%	58	34%	169

Table 7.4 shows unadjusted and adjusted ORs obtained from logistic regression analysis on self-reported recovery, with the reference category being "recover". With positive perception of recovery, gender (unadjusted OR, 2.11; 95% CI, 1.21-3.66), change in pain cognition (unadjusted OR, 2.06; 95% CI, 1.34-3.16) and management of pain (unadjusted OR, 1.90; 95% CI, 1.25-2.90) had the strongest associations. The association between gender and positive recovery remained unchanged in the adjusted analysis (adjusted OR, 2.10; 95% CI 1.17-3.77). However the association between positive recovery and change in management of pain (adjusted OR, 1.58; 95% CI, 0.93-2.69) and change in pain cognition (adjusted OR, 1.73; 95% CI 1.01-2.96) reduced slightly in the adjusted analysis.

Table 7.4 Unadjusted and Adjusted Odds Ratios for Self-reported recovery among individuals with chronic pain aged 18 years and above

	Self-reported recovery ("recover") (n=448)			
	Unadjusted		**Adjusted**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age				
18-40 years	1		1	
+41 years	0.70 (0.47-1.04)	0.08	0.67 (0.43-1.04)	0.08
Gender				
Female	1		1	
Male	2.11 (1.21-3.66)	0.00	2.10 (1.17-3.77)	0.01
Marital status				
Single/unmarried	0.74 (0.47-1.16)	0.20	0.73(0.45-1.19)	0.21
Partnered	0.92 (0.54-1.56)	0.76	0.86 (0.49-1.53)	0.62
Education level				
Primary	1		1	
Others	1.22 (0.73-2.03)	0.43	1.20 (0.70-2.04)	0.49
Employment status				
Full time employed	1		1	
Unemployed/on leave because of pain	0.99 (0.59-1.67)	0.99	1.02 (0.58-1.77)	0.93
Part time employment	0.98 (0.56-1.74)	0.97	0.96 (0.53-1.74)	0.91
Home duties	0.83(0.39- 1.73)	0.62	1.00 (0.45-2.23)	0.98
Student	1.27 (0.65-2.48)	0.46	1.33 (0.66-2.68)	0.42
Pain education				
Yes	0.98 (0.52-1.85)	0.96	0.77 (0.38-1.54)	0.46
Patient-provider relationship				
good	1.06 (0.71-1.59)	0.76	0.91 (0.58-1.44)	0.70
Changes in pain management				
Yes	1.90 (1.25-2.90)	0.00	1.58 (0.93-2.69)	0.08
Changes in pain cognition				
Yes	2.06 (1.34-3.16)	0.00	1.73 (1.01-2.96)	0.04

In an analysis conducted separately, receiving pain education and having a good patient provider relationship showed an association with the change in pain cognition (Table 7.5) and change in management of pain (Table 7.6). Surprisingly, individuals who were employed part-time were also twice as likely to report changes in pain cognition as compared to full-time employees. In the adjusted analysis the association between pain cognition and management of pain with pain education and patient-provider relationship reduced slightly.

Table 7.5 Unadjusted and Adjusted Odds Ratios for Self-reported changes in pain cognition among individuals with chronic pain aged 18 years and above

	Pain education changed pain cognition (n=448)			
	Unadjusted		**Adjusted**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age				
+41 years	1.12(0.76-1.65)	0.53	1.08 (0.69-1.68)	0.71
Gender				
Male	1.15 (0.65-2.04)	0.61	1.50(0.80-2.83)	0.19
Marital status				
Single/unmarried	0.77 (0.50-1.19)	0.24	0.73 (0.45-1.17)	0.19
Partnered	0.82 (0.49-1.38)	0.46	0.75 (0.42-1.34)	0.33
Education level				
Primary	1		1	
Others	1.16 (0.72-1.87)	0.52	1.16(0.69-1.94)	0.56
Employment status				
Unemployed/on leave because of pain	1.40 (0.85-2.31)	0.18	1.29 (0.75-2.21)	0.34
Part time employment	2.42 (1.34-4.37)	0.00	2.31 (1.24-4.28)	0.00
Home duties	0.87 (0.44-1.71)	0.69	0.65 (0.31-1.37)	0.26
Student	0.82 (0.43-1.56)	0.55	0.85 (0.42-1.71)	0.65
Pain education				
Yes	3.30 (1.66-6.55)	0.00	3.33 (1.67-6.61)	0.00
Patient-provider relationship				
good	2.57 (1.68-3.94)	0.00	2.60 (1.70-3.98)	0.00

Table 7.6 Unadjusted and Adjusted Odds Ratios for Self-reported changes in management of pain among individuals with chronic pain aged 18 years and above

	Changes in pain management (n=448)			
	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
+41 years	0.84 (0.57-1.24)	0.40	0.66 (0.39-1.11)	0.12
Gender				
Male	0.66 (0.38-1.15)	0.14	0.57 (0.28-1.16)	0.12
Marital status				
Single/unmarried	0.87 (0.56-1.33)	0.52	0.88 (0.50-1.53)	0.66
Partnered	0.95 (0.57-1.59)	0.85	0.92 (0.46-1.81)	0.81
Education level				
Primary	1		1	
Others	1.12 (0.70-1.80)	0.62	1.15 (0.63-2.12)	0.63
Employment status				
Unemployed/on leave because of pain	0.97 (0.59-1.60)	0.93	0.71 (0.37-1.34)	0.29
Part time employed	1.26 (0.72-2.19)	0.40	0.67 (0.33-1.35)	0.26
Home duties	1.11 (0.55-2.22)	0.76	1.16 (0.47-2.86)	0.74
Student	0.78 (0.41-1.50)	0.46	0.66 (0.28-1.57)	0.35
Pain education				
Yes	4.83 (2.47-9.44)	0.00	2.44 (1.06-5.60)	0.03
Patient-provider relationship				
good	3.39 (2.27-5.06)	0.00	2.43 (1.48-3.98)	0.00

Figure 7.1 shows the top five most referred education material. Results from the survey show that individuals with chronic pain were more likely to be referred to the following type of education material in the order of preference; website (53%), book (47%), handouts (33%), YouTube (16%) and video (11%).

Figure 7.1 Top 5 most referred type of education material

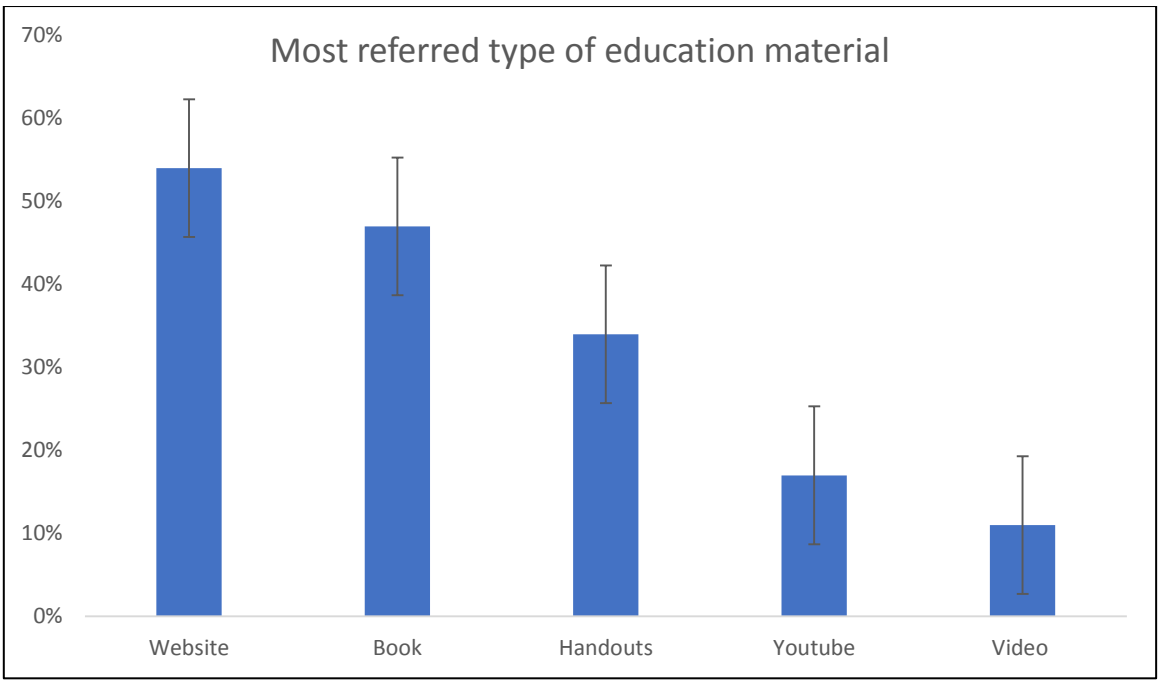
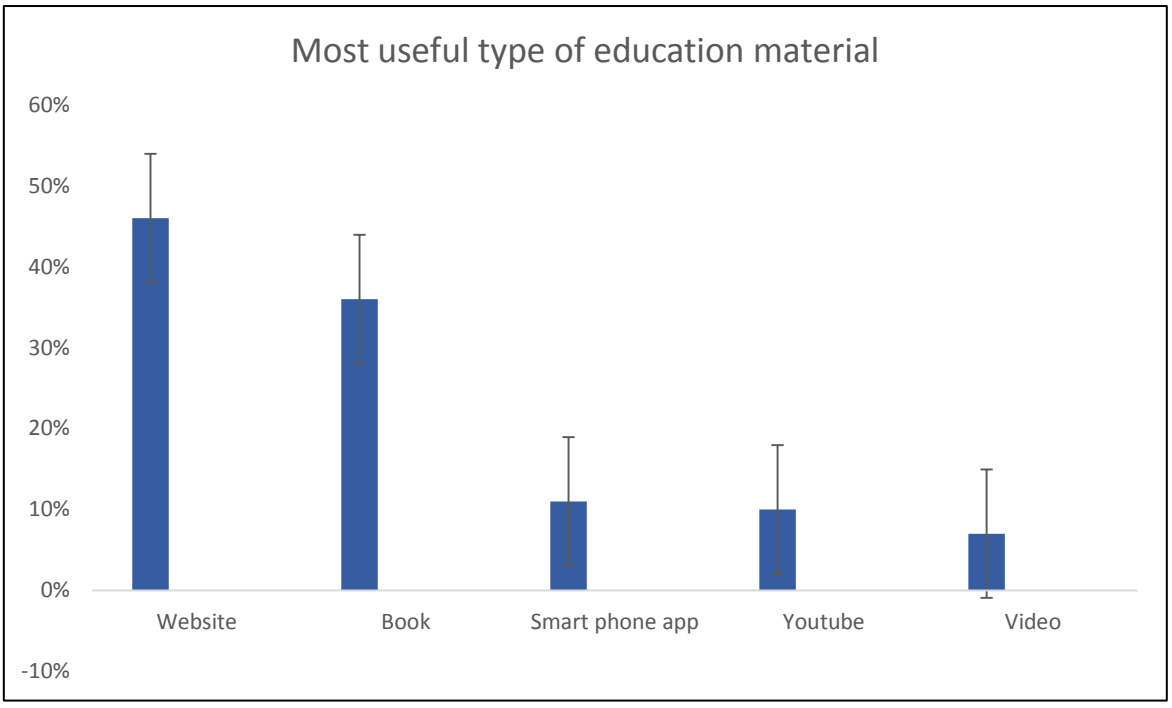


Figure 7.2 shows the type of education materials reported most helpful by the individuals experiencing chronic pain. The most useful type of education material were, in the order of preference; website (46%), book (36%), smart phone app (11%), YouTube (10%) and video (7%). Of the referred material only handouts were not preferred by participants.

Figure 7.2 Top 5 Most useful type of education material



7.7 Discussion

Self-reported Pain intensity

In this study, pain intensity was reported as being higher in individuals aged 40 years and above. The findings also show that women were twice as likely to report higher pain intensity as men. Our results show an agreement with previous studies which also reported a higher prevalence of pain in older age groups, and females (284, 345). However, the participation rate of individuals in this study, was slightly higher by individuals aged 40 years and above (58%) and considerably higher by females (87%) which may have also contributed to the age and sex differentials.

Individuals unemployed or on leave because of pain were equally (50%) likely to report lower pain intensity compared to individuals who were full time employed. Surprisingly, part-time employment showed a strong association with lower pain intensity. Though, pain education and patient-provider relationship did not show an association, the findings suggest that individuals who reported receiving pain education and good patient-provider relationship were twice as likely to report lower pain intensity. These findings are in contrast to the popular belief that pain education improves pain intensity (398, 399). However, what is new in our findings is that education induced changes in thought processes and management led to a reduction in pain intensity. Separate regression analysis results presented in Tables 7.5 and 7.6 also show the statistically significant effect of pain education on pain cognition and management of pain. Which leads to the hypothesis that the effects of pain education may not be direct but indirect, prompted by changes in management and pain cognition through pain education.

Self-reported recovery

Self-reported recovery is often tested in post-surgical cases, however to our understanding factors associated with patient-reported recovery in individuals with chronic pain have not been investigated before, especially in chronic pain sufferers. The findings suggest that self-reported positive recovery was higher in younger individuals aged between 18-40 years compared to individuals aged 40 years and above. Men were more likely to report positive perception of recovery compared to females. It is possible that as the prevalence of chronic pain is less in younger adults and males are more likely to report positive recovery. Moreover, studies show that older individuals often report more than one chronic disease including chronic pain which may also affect their perception of recovery (404). Age, marital status, education level and employment status showed no association with self-reported good recovery. Once again, similar to the results from the pain intensity study (reported in Table 7.3), pain education and patient-provider relationship showed no direct association with recovery. However, changes in pain cognition and management of pain showed an association with patient-reported recovery. Thus once again supporting the previously stated hypothesis.

To confirm our suggested new hypothesis we conducted separate regressions between changes in pain cognition and management of pain and pain education. Interestingly we found that pain education was a predictor of these two factors. The results from this analysis showed that individuals who received pain education were three times more likely to report changes in pain cognition (Table 7.5) and were four times more likely to report changes in management of pain. These findings are in line with studies which report that pain education assists patients to re-conceptualize pain (398, 400, 405).

Additionally we also conducted separate regressions between changes in pain cognition and management of pain and patient-provider relationship. Not surprisingly, the patient-provider relationship also showed a strong association with changes in pain cognition and management of pain. The results also suggest that individuals who had a good patient-provider relationship with their health care professional were more likely to report positive changes in pain cognition and pain management.

It may be that pain education and patient-reported pain intensity and recovery show an indirect relationship which is induced through pain education as follows:

Pain Education→ Changes in pain cognition→ Changes in management of pain → Patient-reported pain intensity and similar for recovery

The study results also indicate that handouts, though used widely for pain education are not rated useful by patients. Website, book, smart phone app, YouTube and videos were rated as the top 5 most useful pain education tools. This is an important finding as todays' patients increasingly have access to the internet, which opens a plethora of information sources on various diseases including chronic pain. Sadly, though some of this information comes from non-certified health experts. It is important to consider these modern options such as apps and YouTube videos for providing pain education.

7.8 Conclusion

Data from the self-report internet survey shows that pain education may have an indirect effect on patient-reported pain intensity and recovery through change in pain cognition and management of pain. Pain education and patient-provider relationship may not be effective in isolation. However they must be considered jointly with education prompted change in management and pain cognition.

These findings are important for future research and practice as they give a new direction for employing pain education towards enhancing patients' overall understanding of their pain. Additionally, strategies should include education directed towards improving individual pain management and changing their understanding of pain.

Study limitations

This was a pragmatic study where data was collected from individuals experiencing chronic pain in a real world scenario. Low or no participation from individuals who have lower education and no internet access is a limitation. We may have also missed assessing areas of importance such as the number of education session individuals received. However to avoid participation burden and fatigue, it was considered best to limit the length of the study. Finally, the accuracy of the data was dependent on participants self-reporting and subjective assessment of their experiences. No objective assessment strategies were used to verify the quality of participant responses.

CHAPTER 8

Discussion & Conclusion’s

This thesis investigated the role of vitamin D deficiency in patients with chronic nonspecific musculoskeletal pain (CNMP). This research examined two very distinct elements – CNMP and vitamin D which have previously not been studied extensively. The current research is timely as the use of opioids for non-malignant chronic pain has recently become more regulated (36). More than ever before there is now a high demand for alternative treatment options to manage chronic pain. Moreover, vitamin D deficiency has been described as a pandemic (82), which has been associated with many chronic painful conditions (37-39).

CNMP is a type of chronic pain characterized by the clear absence of anatomical or pathological source (226), with a high prevalence reported in individuals seeking medical care (217, 228). Currently there are no International Classification of Diseases (ICD) diagnostic codes (275) or guidelines for the management of CNMP, as a result it is often a diagnosis of exclusion. Moreover, as described in Chapter 2, due to the limited knowledge about its presentation and symptoms, the label of CNMP can often be used interchangeably with fibromyalgia and chronic widespread pain. But, we do not know how CNMP is currently managed in general practice, especially in the absence of guidelines and information regarding its aetiology and presentations. GPs are central to management of patients with pain in Australia (21, 22). We therefore, conducted a qualitative study, using focus groups, of GPs practicing in various medical practices in Adelaide.

Many studies report a high prevalence of vitamin D deficiency in patients with CNMP (37, 200). The discovery of non-classical effects of vitamin D such as immune modulation, anti-inflammatory, cell regulation and neuroprotection (51, 61) has led to an increase in research about the involvement of vitamin D in various chronic painful conditions. As detailed in section 2.2 (chronicles of pain) in the literature review, the evolution of pain models from the biomedical model to the relatively new biopsychosocial model allows us to understand how

and why vitamin D deficiency, its supplementation, and vitamin D associated co-morbidities such as stress, anxiety and depression can affect chronic painful conditions. This model provides a basis for how diverse aspects of an individual's life such as body weight, nutrition, supplement intake, lifestyle, attitude, belief, family support, employment, psychological factors and even interaction with their doctor can potentially influence and change their pain experience and thereby health outcomes.

8.1 Summary of the findings

A qualitative exploration of GPs' perspectives on managing chronic non-specific musculoskeletal pain in Australian general practice

The first study in this thesis investigated the clinical reasoning GPs' employ when diagnosing and managing patients with CNMP. Using a qualitative study design, data was collected from GPs practicing in Adelaide. The results showed that GPs employed an individual patient-centered approach for both the diagnosis and management of CNMP. GPs believe CNMP to be preceded by a range of factors including injuries, falls, sprains, infections, autoimmune disease; and long-term use of medications like statins, benzodiazepines and opioids. There was general consensus among GPs that more female patients are diagnosed with CNMP which was attributed to their general higher uptake of medical services. Though, management was also tailored to the individual patient, more emphasis was put on building a strong patient-provider relationship and managing the psychosocial health of the patient.

The findings also showed that GPs' were concerned about vitamin D levels in chronic pain patients and recommended vitamin D supplementation if indicated by a patient's medical history and lifestyle. Testing for vitamin D levels was widely discouraged by the participating GPs. This is consistent with current Australian guidelines for vitamin D testing which recommend testing only in people at risk of moderate to severe deficiency defined as 25(OH)D level <25nmol/L (406). Our findings are consistent with another study, investigating strategies applied by Dutch GPs for managing unexplained symptoms (296).

Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis.

Studies reporting a strong association between vitamin D and CNMP are more commonly observational studies (described in Chapter 2). Very few randomized controlled trials (RCT's) were found in the literature search, and the results from these studies varied from demonstrating a "high effect" to "no effect". To understand why these RCT's were unable to replicate the findings of the observational studies, a systematic review was performed. Further, a meta-analysis was used to investigate the association between vitamin D and CNMP. This was the first study to use the quantitative technique of meta-analysis to determine if vitamin D supplementation is a useful treatment for CNMP. Only studies using an RCT design, comparing vitamin D supplementation to placebo in patients with CNMP were included. The initial search identified 107 studies, however on systematic appraisal of these studies 104 were excluded for the following reasons; i) they did not meet our study selection criteria of an RCT design, ii) the investigators had experimentally induced pain or iii) they had included participants

experiencing more than one type of chronic pain. Finally 3 RCTs with total 492 participants were selected and included in the meta-analysis. The smaller number and size of the included studies highlights the need for more well-designed RCTs to be conducted. The findings from the meta-analysis suggested no effect of vitamin D supplementation on pain in patients with CNMP. However, it is important to interpret this results cautiously because the number of studies and total number of participants were small. Moreover, there was heterogeneity within the studies selected because of differences in the dose and dose regimes of supplementation used. In part this may be due to the absence of universal supplementation guidelines for replenishing vitamin D levels.

Factors associated with vitamin D deficiency, testing and supplementation in patients with chronic pain.

As described in Chapter 2 certain factors (such as age, gender, skin pigmentation, reduced sun exposure time) are associated with a higher risk for developing vitamin D deficiency in the general population. However, no studies have examined the factors associated with vitamin D deficiency, it's testing and intake in patients with chronic pain. As described in Chapter 3, GPs involved in our study were concerned about vitamin D levels in patients with chronic pain which was associated with reduced sun exposure and physical activity in these patients. The GPs also recommended supplementation based on a patients' medical history and lifestyle. Therefore, we performed a cross-sectional study to examine what factors, as described by patients with chronic pain, were associated with testing, deficiency and intake of vitamin D as detailed in Chapter 6. We also examined factors associated with vitamin D supplementation as

advised by doctors for patients with chronic pain. We developed a simple prediction model from data collected using the LASSO regression technique. The findings from this study showed that older age was consistently associated with testing, deficiency and intake of vitamin D. As, older age is widely recognized as a risk factor for vitamin D deficiency (379, 380) it may be the reason why elderly people have higher rates of not only deficiency but also testing and intake of vitamin D.

In addition, being unemployed or on leave due to pain or in part-time employment and being resident of Australia was associated with vitamin D testing. This result reflects the increase in testing for vitamin D reported by Medicare Australia (370). Higher mean pain intensity score ≤6 on an 11 point numerical rating scale was associated with vitamin D deficiency; and being diagnosed with vitamin D deficiency was associated with intake of vitamin D. Being vitamin D deficient and unemployed or on leave due to pain or in part-time employment were associated with doctor advised vitamin D supplementation. To our knowledge this is the first study that has successfully developed a model to predict vitamin D testing, deficiency, intake and doctor advised vitamin D supplementation in individuals with chronic pain. These findings have clinical implications and the model could be useful for identifying patients with chronic pain who are at risk of deficiency and therefore benefit from testing or supplementation. By using simple demographic and self-reported pain related factors, which are readily accessible by GPs, more rationale and cost-effective management of chronic pain could be achieved.

Effect of pain education and patient-provider relationship on patient-reported pain intensity and recovery

The focus groups with GPs (detailed in Chapter 3) stressed the importance of educating patients about their pain and helping them set realistic goals (Theme 3). In addition, building a good relationship with the patients (Theme 4) was also considered fundamental for management of patients with chronic nonspecific musculoskeletal pain. Previous studies have rated the patient-provider relationship and pain education as an important aspect of management for patients with chronic pain. However, to our knowledge no previous studies have tested the association between patients receiving pain education and patient-provider relationship and patient-reported pain intensity and their perception of recovery.

Therefore, we performed a cross-sectional survey to examine if patient-reported pain intensity and recovery were associated with receiving pain education and patient-provider relationship in patients with chronic pain as detailed in Chapter 7. We used univariate and multiple logistic regression to study the effect on pain education and patient-provider relationship on pain intensity and recovery before and after controlling for the potential confounders.

The findings from this study show that individuals aged 40 years and above, and female were more likely to report higher pain intensity and poor perception of recovery compared to young individuals and males. These findings are in line with previous studies which report higher prevalence of pain in older age groups and females (284, 345).

In addition, being in part-time employment also showed association with higher pain intensity compared to individuals who were employed full-time. However, pain education and patient-provider relationship did not show a association with pain intensity and recovery. These

findings are in contrast to other studies which report that pain education improves pain intensity (398, 399).

But, education induced changes in pain cognition and management do lead to a reduction in pain intensity and positive recovery. We therefore, hypothesized that the effects of pain education were induced by changes in pain cognition and management on pain intensity and recovery. Therefore, we tested this hypothesis by a separate regression between changes in pain cognition and management of pain and pain education. The results from this analysis showed that individuals who received pain education were more likely to report changes in pain cognition and management of pain. Thus confirming our hypothesis that pain education has an indirect relationship with patient-reported pain intensity and recovery mediated by change in pain cognition and management of pain. We also conducted a separate regression between changes in pain cognition and management of pain and patient-provider relationship. The findings showed that individuals who reported good patient-provider relationship were more likely to report positive changes in pain cognition and management of pain. The study results also show that individuals with chronic pain rate website, book, smart phone app, YouTube and videos as the most preferred material for obtaining pain education.

These findings have implications for future research and practice. It informs two key corollaries of pain education which have potential for altering pain intensity and recovery of individuals experiencing chronic pain. It also illustrates the need to integrate modern technology into pain education and management.

8.2 Synthesis of the findings

GPs in the focus group study (chapter 3) reported that it was challenging if not impossible to isolate the effect of vitamin D supplementation on CNMP. They did not believe that vitamin D supplementation alone could reduce the pain. But they still recommended vitamin D supplementation in patients if indicated by their history. Similar findings were observed in the second study of systematic review and meta-analysis (chapter 4). The meta-analysis showed that vitamin D may not directly reduce the pain, but it was theoretically plausible that it could alleviate some of the associated pain. This raises the question that though vitamin D deficiency may not be able to cause pain, it could certainly exacerbate the pain. Suggesting that it may not be enough to just evaluate vitamin D alone, but sun exposure levels, physical activity, body-mass index, diet, sun-protection used which can influence vitamin D levels should also be monitored. This is reflected from the focus group study findings were GPs' prefer a holistic approach to management tailored to individual patient needs. This finding was further supported by the results of the patient survey that highlighted the importance of educating patients to improve their understanding of pain. Also, results from the survey data analysis suggest that patients with higher mean pain intensity score (>5) or presentations of CNMP should also be considered for screening of vitamin D deficiency.

8.3 Limitations

The limitations of each study were discussed in the relevant chapters. This section discusses the limitations of this thesis in general and potential future research.

The primary limitation of the study reported in Chapter 3 was the focus group methodology used. Due to the nature of the study design, in depth information could not be collected.

However, as discussed in Chapter 3, CNMP is a poorly researched topic which required a setting that could facilitate interaction between participants and encourage sharing of encounters and experiences to allow refinement during the discussion. The second limitation of the study was moderator bias which could inject personal biases into participants' exchange of experiences and can also lead participants to certain conclusion. In order to minimize moderator bias, a loosely structured questionnaire was followed for each focus group discussion to maintain uniformity in the topics discussed.

The major limitation of Chapter 4, systematic review and meta-analysis was the paucity of high quality RCT's. However, unlike the Cochrane review (242) of chronic painful conditions, our systematic review included a meta-analysis and focused only on patients with the same clinical condition (CNMP) as combining multiple conditions, as done in the Cochrane review, that have distinct pathophysiological aetiologies, does not make clinical sense and could lead to erroneous conclusions.

The study described in Chapters 6 and 7 used data collected from a cross-sectional survey described in Chapter 5. The primary aim of this study was to investigate the views, beliefs and perceptions of individuals with chronic pain on their pain management, with a special focus on vitamin D supplement intake, pain education and the patient-provider relationship. It was the first study to explore these factors which form an integral part of pain management in individuals with chronic pain. Cross-sectional study designs are often used for this type of research because of their ability to cross geographical barriers, however it could be argued that a longitudinal design would have enabled a more thorough collection of data. Finally, the data was a subjective assessment of patients' views and beliefs, no objective assessment was used to verify or validate the participant responses.

8.4 Concluding remarks

This thesis explores the management of chronic pain, with special focus on CNMP. Although previous studies have reported an increasing prevalence of CNMP in clinical practice, research on this condition is limited and currently there are no guidelines for managing it. This thesis used qualitative and quantitative methods considered applicable to provide detailed findings.

This thesis helps to fill a significant gap in knowledge about how CNMP is identified, diagnosed and managed in by GPs and the effect of vitamin D supplementation on patients with CNMP. This thesis also provides a simple predictive model using demographic and pain-related factors for identifying patients with chronic pain who are at risk of vitamin D deficiency and who therefore may benefit from testing or supplementation. In addition, the thesis shows how pain education may have an indirect effect on patient-reported pain intensity and recovery through education induced changes in pain cognition and management. The study describes the importance of the patient-provider relationship on pain intensity and recovery as described by individuals with chronic pain. The study also indicates that individuals with chronic pain rate use of website, book, smart phone app, YouTube and videos as the most preferred material for obtaining pain education.

This thesis began with a literature review on vitamin D and its potential role in different musculoskeletal conditions. This was followed by examining the clinical reasoning GPs employ when diagnosing and managing patients with CNMP. These findings were then followed by synthesizing evidence for role of vitamin D supplementation on pain in patients with CNMP, using systematic review and meta-analysis. A cross-sectional survey study was conducted. The analysis conducted on the data collected from the survey allowed us to develop

a simple prediction model and identify factors associated with testing, deficiency, intake and doctor advised supplementation of vitamin D in individuals with chronic pain. The analysis on data collected from the survey also showed that pain education and patient-provider relationship should be considered jointly with education prompted change in management and pain cognition.

8.5 Directions for Future studies

Both the results from the GP focus group and the meta-analysis suggest that Vitamin D supplementation is unlikely on its own to improve pain in patients with CNMP, however both studies support its use and report alleviation of some of the associated pain. Future research should therefore focus not only patients confirmed with the diagnosis of vitamin D deficiency but also on patients with comorbidities associated with vitamin D deficiency and pain such as obesity, mood disorders and stress. In addition, future studies should focus on investigating holistic outcomes such as quality of life, physical activity, fatigue/vitality and mental health. Moreover vitamin D functions more like a hormone than a vitamin and therefore it is necessary that future studies measure pre and post supplementation vitamin D levels and their correlation with primary and secondary outcomes.

These results could inform future research, medical practice and policy makers, to enhance the management and care for individuals with chronic pain including CNMP.

REFERENCES

1. Australia P. National Pain Strategy. 2010.
2. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? The Journal of Pain. 2009;10(11):1113-20.
3. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: understanding the relationships between chronic pain and comorbidity in the general population. Pain. 2012;153(2):293-304.
4. Croft P. Disease-related pain: an introduction. Chronic Pain Epidemiology: From Aetiology to Public Health. 2010:203-8.
5. Siddall PJ, Cousins MJ. Persistent pain as a disease entity: implications for clinical management. Anesthesia & Analgesia. 2004;99(2):510-20.
6. Smith BH, Torrance N. Management of chronic pain in primary care. Current opinion in supportive and palliative care. 2011;5(2):137-42.
7. Henderson JV, Harrison CM, Britt HC, Bayram CF, Miller GC. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. Pain Medicine. 2013;14(9):1346-61.
8. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European Journal of Pain. 2006;10(4):287-333.
9. Van Hecke O, Torrance N, Smith B. Chronic pain epidemiology and its clinical relevance. British Journal of Anaesthesia. 2013;111(1):13-8.
10. Ng KFJ, Tsui SL, Chan WS. Prevalence of common chronic pain in Hong Kong adults. The Clinical Journal of Pain. 2002;18(5):275-81.
11. Walker BF, Muller R, Grant WD. Low back pain in Australian adults. Prevalence and associated disability. Journal of Manipulative and Physiological Therapeutics. 2004;27(4):238-44.
12. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008;136(3):380-7.
13. Boulanger A, Clark AJ, Squire P, Cui E, Horbay G. Chronic pain in Canada: have we improved our management of chronic noncancer pain? Pain Research and Management. 2007;12(1):39-47.
14. Dominick C, Blyth F, Nicholas M. Patterns of chronic pain in the New Zealand population. The New Zealand Medical Journal (Online). 2011;124(1337).

15. Gerdle B, Björk J, Cöster L, Henriksson K-G, Henriksson C, Bengtsson A. Prevalence of widespread pain and associations with work status: a population study. BMC Musculoskeletal Disorders. 2008;9(1):102.
16. Von Korff M, Dunn KM. Chronic pain reconsidered. Pain. 2008;138(2):267-76.
17. Wallace AS, Freburger JK, Darter JD, Jackman AM, Carey TS. Comfortably numb? Exploring satisfaction with chronic back pain visits. The Spine Journal. 2009;9(9):721-8.
18. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JH, Brouwer S. Factors promoting staying at work in people with chronic nonspecific musculoskeletal pain: a systematic review. Disabil Rehabil. 2012;34(6):443-58.
19. Picavet H, Schouten J. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC 3-study. Pain. 2003;102(1):167-78.
20. Pfizer. *Health report:Chronic Pain*. Australia: 2010.
21. Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. Medical Journal of Australia. 2003;179(2):84-7.
22. Britt H, Miller GC, Henderson J, Bayram C, Harrison C, Valenti L, et al. General practice activity in Australia 2014–15. 2015.
23. Mäntyselkä P, Kumpusalo E, Ahonen R, Kumpusalo A, Kauhanen J, Viinamäki H, et al. Pain as a reason to visit the doctor: a study in Finnish primary health care. Pain. 2001;89(2):175-80.
24. Hutchinson K, Moreland AM, Williams AC, Weinman J, Horne R. Exploring beliefs and practice of opioid prescribing for persistent non-cancer pain by general practitioners. European Journal of Pain. 2007;11(1):93-8.
25. O'Rorke JE, Chen I, Genao I, Panda M, Cykert S. Physicians' comfort in caring for patients with chronic nonmalignant pain. The American Journal of the Medical Sciences. 2007;333(2):93-100.
26. Wenghofer EF, Wilson L, Kahan M, Sheehan C, Srivastava A, Rubin A, et al. Survey of Ontario primary care physicians' experiences with opioid prescribing. Canadian Family Physician. 2011;57(3):324-32.
27. Saffier K, Colombo C, Brown D, Mundt MP, Fleming MF. Addiction Severity Index in a chronic pain sample receiving opioid therapy. Journal of Substance Abuse Treatment. 2007;33(3):303-11.
28. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. British Journal of Clinical Pharmacology. 2014;78(5):1159-66.

29. Leong M, Murnion B, Haber P. Examination of opioid prescribing in Australia from 1992 to 2007. Internal Medicine Journal. 2009;39(10):676-81.

30. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. Medical Journal of Australia. 2011;195(5):280.

31. Hall WD, Farrell MP. Minimising the misuse of oxycodone and other pharmaceutical opioids in Australia: Simple strategies can reduce harms from misuse of pharmaceutical opioids. Medical Journal of Australia. 2011;195(5):248-9.

32. Harrison CM, Charles J, Henderson J, Britt H. Opioid prescribing in Australian general practice. Medical Journal of Australia. 2012;196(6):380-1.

33. Hogg MN, Gibson S, Helou A, DeGabriele J, Farrell MJ. Waiting in pain: a systematic investigation into the provision of persistent pain services in Australia. Medical Journal of Australia. 2012;196(6):386-90.

34. Semple TJ, Hogg MN. Waiting in pain. The Medical Journal of Australia. 2012;196(6):372-3.

35. Physicians TRACo. Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: 2008.

36. Jammal W, Gown G. Opioid prescribing pitfalls: medicolegal and regulatory issues. Australian prescriber. 2015;38(6):198.

37. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clinic Proceedings. 2003;78(12):1463-70.

38. Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Sikaris KA, et al. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clinical Endocrinology. 2012;77(1):26-35.

39. Erkal M, Wilde J, Bilgin Y, Akinci A, Demir E, Bödeker R, et al. High prevalence of vitamin D deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: identification of risk factors. Osteoporosis International. 2006;17(8):1133-40.

40. Mouyis M, Ostor A, Crisp A, Ginawi A, Halsall D, Shenker N, et al. Hypovitaminosis D among rheumatology outpatients in clinical practice. Rheumatology. 2008;47(9):1348-51.

41. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged≥ 60 y. American Journal of Clinical Nutrition. 2004;80(3):752-8.

42. Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age and Ageing. 2004;33(6):589-95.

43. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcified Tissue Int. 2000;66(6):419-24.

44. Ward KA, Das G, Berry JL, Roberts SA, Rawer R, Adams JE, et al. Vitamin D status and muscle function in post-menarchal adolescent girls. The Journal of Clinical Endocrinology & Metabolism. 2009;94(2):559-63.

45. Gaikwad M, Vanlint S, Mittinity M, Moseley G, Stocks N. Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis. Clinical Rheumatology. 2016:1-8.

46. Mellanby E. An experimental investigation on rickets. Lancet. 1919;1:407-12.

47. McCollum EV, Simmonds N, Becker JE, Shipley PG. Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. Journal of Biological Chemistry. 1922;53(2):293-312.

48. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev. 2013;34(1):33-83.

49. Kulie T, Groff A, Redmer J, Hounshell J, Schrager S. Vitamin D: an evidence-based review. J Am Board Fam Med. 2009;22(6):698-706.

50. Brannon PM, Yetley EA, Bailey RL, Picciano MF. Overview of the conference "Vitamin D and Health in the 21st Century: an Update". Am J Clin Nutr. 2008(88(suppl)):483S-90S.

51. Lai Y-H, Te-Chao F. The pleiotropic effect of vitamin D. ISRN Nephrology. 2013.

52. Norman AW, Roth J, Orci L. The vitamin D endocrine system: steroid metabolism, hormone receptors, and biological response (calcium binding proteins). Endocr Rev. 1982;3(4):331-66.

53. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Thomsen J, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med. 2000;247(2):260-8.

54. Nowson CA, Margerison C. Vitamin D intake and vitamin D status of Australians. Med J Aust. 2002;177(3):149-52.

55. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005;289(1):F8-28.

56. Holick MF. Evolution, biologic functions, and recommended dietary allowances for vitamin D. Vitamin D: Springer; 1999. p. 1-16.
57. Reichel H, Koeffler HP, Norman AW. The role of the vitamin D endocrine system in health and disease. The New England journal of medicine. 1989;320(15):980-91.
58. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. The American Journal of Clinical Nutrition. 1990;51(6):1075-81.
59. Rigby W, Denome S, Fanger M. Regulation of lymphokine production and human T lymphocyte activation by 1, 25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. Journal of Clinical Investigation. 1987;79(6):1659.
60. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. Current Opinion in Endocrinology, Diabetes and Obesity. 2002;9(1):87-98.
61. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Brit J Nutr. 2003;89(5):552-72.
62. Ralston S. Calcium homeostasis:hypercalcemial and hypocalcemia. Annals of the Rheumatic Diseases. 1990;49(12):967.
63. Holick MF. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ, editor. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 6 ed. Washington, DC: American Society for Bone and Mineral Research; 1996. p. 129-37.
64. Mundy GR, Guise TA. Hormonal control of calcium homeostasis. Clinical chemistry. 1999;45(8 Pt 2):1347-52.
65. Narooie-Nejad M, Moossavi M, Torkamanzehi A, Moghtaderi A. Positive Association of Vitamin D Receptor Gene Variations with Multiple Sclerosis in South East Iranian Population. BioMed Research International. 2015.
66. Haussler MR, Norman AW. Chromosomal receptor for a vitamin D metabolite. Proc Natl Acad Sci U S A. 1969;62(1):155-62.
67. Issa LL, Leong GM, Eisman JA. Molecularmechanism of vitamin D receptor action. Infammation Research. 1998;47(12):451-75.
68. Malloy PJ, Eccleshall TR, Gross C, van Maldergem L, Bouillon R, Feldman D. Hereditary vitamin D resistant rickets caused by a novel mutation in the vitamin D receptor

that results in decreased affinity for hormone and cellular hyporesponsiveness. Journal of Clinical Investigation. 1997;99(2):297-304.

69. Hossein-nezhad A, Holick MF. Vitamin D for Health: A Global Perspective. Mayo Clin Proc. 2013;88(7):720-55.

70. Bouillon R, Carameliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 2008;29(6):726-76.

71. Holick MF. Resurrection of vitamin D deficiency and rickets. The Journal of Clinical Investigation. 2006;116(8):2062-72.

72. Holick MF, editor High prevalence of vitamin D inadequacy and implications for health. Mayo Clinic Proceedings; 2006: Elsevier.

73. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Annals of Epidemiology. 2009;19(2):73-8.

74. Holick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. The American Journal of Clinical Nutrition. 1994;60(4):619-30.

75. Nowson C. Vitamin D status of Australians. Nutrition and Dietetics. 2006;63(4):194-5.

76. McGrath J, Kimlin MG, Saha S, Eyles D, Parisi A. Vitamin D insufficiency in south-east Queensland. Medical Journal of Australia. 2001;174(3):150-.

77. Pasco JA, Henry MJ, Nicholson GC, Sanders KM, Kotowicz MA. Vitamin D status of women in the Geelong Osteoporosis Study: association with diet and casual exposure to sunlight. Medical Journal of Australia. 2001;175(8):401-5.

78. Jones G, Blizzard C, Riley M, Parameswaran V, Greenaway T, Dwyer T. Vitamin D levels in prepubertal children in Southern Tasmania: prevalence and determinants. European Journal of Clinical Nutrition. 1999;53(10):824-9.

79. Rockell JE, Green TJ, Skeaff CM, Whiting SJ, Taylor RW, Williams SM, et al. Season and ethnicity are determinants of serum 25-hydroxyvitamin D concentrations in New Zealand children aged 5–14 y. The Journal of Nutrition. 2005;135(11):2602-8.

80. Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Medical Journal of Australia. 2012;196(11):686-7.

81. Henry HL, Bouillon R, Norman AW, Gallagher JC, Lips P, Heaney RP, et al. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines. The Journal of Steroid Biochemistry and Molecular Biology. 2010;121(1):4-6.

82. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. Brit J Nutr. 2014;111(01):23-45.
83. Turk DC, Monarch ES. Biopsychosocial perspective on chronic pain. Psychological approaches to pain management: A practitioner's handbook. 1996:3-32.
84. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: Scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.
85. Glenton C. Chronic back pain sufferers—striving for the sick role. Social Science and Medicine. 2003;57(11):2243-52.
86. Woolf CJ. What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain? Pain. 2014;155(10):1911-2.
87. Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The Past, Present, and Future. American Pain Society. 2015;16(9):807-13.
88. Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain. 2012;153(6):1144-7.
89. Engel George L. The need for a new medical model/Engel, George L. Washington: Science. 1977;196:129-36.
90. Loeser JD. Concepts of pain. In: Stanton-Hicks JB, R., editor. Chronic low back pain New York: Raven Press; 1982. p. 109-42.
91. Milne JM. The bio psychosocial model as applied to a multidisciplinary pain management programme. Journal of the New Zealand Association of Occupational Therapists. 1983;34:19-21.
92. Foster N, Pincus T, Underwood M, Vogel S, Breen A, Harding G. Understanding the process of care for musculoskeletal conditions—why a biomedical approach is inadequate. Rheumatology. 2003;42(3):401-4.
93. Harding G, Campbell J, Parsons S, Rahman A, Underwood M. British pain clinic practitioners' recognition and use of the bio-psychosocial pain management model for patients when physical interventions are ineffective or inappropriate: results of a qualitative study. BMC Musculoskeletal Disorders. 2010;11(1):1.
94. Gatchel R. The conceptual foundations of pain management: historical overview. Clinical essentials of pain management Washington, DC: American Psychological Association. 2005:3-16.
95. Engel GL. The biopsychosocial model and the education of health professionals. General Hospital Psychiatry. 1979;1(2):156-65.

96. Bendelow G. Chronic pain patients and the biomedical model of pain. Virtual Mentor. 2013;15(5):455-9.
97. Borrell-Carrió F, Suchman AL, Epstein RM. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. The Annals of Family Medicine. 2004;2(6):576-82.
98. Engel GL. A unified concept of health and disease. Perspectives in Biology and Medicine. 1960;3(4):459-85.
99. Melzack R, Wall P. On the nature of cutaneous sensory mechanisms. Brain. 1962;85(2):331-56.
100. Wall P, McMahon S. The relationship of perceived pain to afferent nerve impulses. Trends in Neurosciences. 1986;9:254-5.
101. Deardorff W. Modern Theories of Chronic Pain 2003 [cited 2016 21 August].
102. Moseley GL. Physiological and clinical investigation of the psychophysiology of pain and motor control. Sydney: University of Sydney; 2001.
103. Gatchel RJ. Perspectives on pain: A historical overview. In: Gatche RJ, Turk DC, editors. Pyschosocial Factors in pain: Critical perspectives: New York: Guilford Press.; 1999.
104. Bonica J. The management of pain. Lea & Febiger, Philadelphia. 1953:1-6.
105. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-9.
106. Melzack R. Pain: past, present and future. Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale. 1993;47(4):615.
107. Melzack R. Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. Pain. 1975;1(4):357-73.
108. Melzack R, Katz J. Pain in the 21st century: The neuromatrix and beyond. Psychological knowledge in court: Springer; 2006. p. 129-48.
109. Melzack R, Loeser JD. Phantom body pain in paraplegics: evidence for a central" pattern generating mechanism" for pain. Pain. 1977;4:195-210.
110. Melzack R. Phantom limbs and the concept of a neuromatrix. Trends in Neurosciences. 1990;13(3):88-92.
111. Melzack R. From the gate to the neuromatrix. Pain. 1999;82:S121-S6.
112. Melzack R, editor Gate control theory: On the evolution of pain concepts. Pain forum; 1996: Elsevier.
113. Chapman C, Stillman M. Pathological pain. Pain and Touch. 1996;2:315-42.
114. Keefe FJ, Lefebvre JC, Starr KR, editors. From the gate control theory to the neuromatrix: Revolution or evolution? Pain Forum; 1996: Churchill Livingstone.

115. Melzack R. Pain and the neuromatrix in the brain. J Dent Educ. 2001;65(12):1378-82.
116. Selye H. The physiology and pathology of exposure to stress. 1950.
117. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. American Psychologist. 2004;59(8):795.
118. Butler DS, Moseley GL. Explain pain. 2nd ed. Adelaide Australia: Noigroup Publications; 2013.
119. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Annals of Internal Medicine. 2004;140(6):441-51.
120. Woolf CJ. Pain hypersensitivity The Wellcome Trust: Wellcome Trust Publication; [cited 2016 24 May].
121. Schaible HG. Peripheral and central mechanisms of pain generation. Handb Exp Pharmacol. 2007;177:3-28.
122. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature. 1983.
123. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
124. Scholz J, Broom DC, Youn DH, Mills CD, Kohno T, Suter MR, et al. Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. J Neurosci. 2005;25(32):7317-23.
125. Affaitai G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino MA. Effects of treatment of peripheral pain generators in fibromyalgia patients. Eur J Pain. 2010.
126. Nijs J, van Wilgen CP, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines. Manual Ther. 2011;16(5):413-8.
127. Liu C-N, Devor M, Waxman SG, Kocsis JD. Subthreshold oscillations induced by spinal nerve injury in dissociated muscle and cutaneous afferents of mouse DRG. Journal of Neurophysiology. 2002;87(4):2009-17.
128. Lawton J, Pimm S. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature. 1992;355:2.
129. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. The Journal of Neuroscience. 2002;22(15):6724-31.

130. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage. 2011;19(5):478-82.

131. Abhishek A, Doherty M. Disease diagnosis and clinical presentation. In: Y H, D H, H K, editors. OARSI Online Primer. OARSI2011.

132. Allen KD, Coffman CJ, Golightly YM, Stechuchak KM, Keefe FJ. Daily pain variations among patients with hand, hip, and knee osteoarthritis. Osteoarthritis Cartilage. 2009;17(10):1275-82.

133. Abhishek A, Doherty M. Diagnosis and clinical presentation of osteoarthritis. Rheum Dis Clin N Am. 2013;39:45-66.

134. Goddard NJ, Gosling PT. Intra-articular fluid pressure and pain in osteoarthritis of the hip. J Bone Joint Surg Br. 1988;70(1):52-5.

135. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis. 2011;70(1):60-7.

136. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis. 2009;68(1):8-17.

137. Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. Am Fam Physician. 2000;61(6):1795-804.

138. Cao Y, Winzenberg T, Nguo K, Lin J, Jones G, Ding C. Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review. Rheumatology. 2013;52.

139. Christodoulou S, Goula T, Ververidis A, Drosos G. Vitamin D and bone disease. Biomed Res Int. 2013;2013:396541.

140. Kim HJ, Lee JY, Kim TJ, Lee JW. Association between serum vitamin D status and health-related quality of life (HRQOL) in an older Korean population with radiographic knee osteoarthritis: data from the Korean national health and nutrition examination survey (2010-2011). Health Qual Life Outcomes. 2015;13:48.

141. Al-Jarallah K, Shehab D, Abraham M, Mojiminiyi OA, Abdella NA. Musculoskeletal pain: should physicians test for vitamin D level? Int J Rheum Dis. 2013;16(2):193-7.

142. Malas FU, Kara M, Aktekin L, Ersoz M, Ozcakar L. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. Clin Rheumatol. 2014;33:1331-4.

143. Guler T, Garip Y, Yildirim P, Terzi R. Vitamin D status in symptomatic knee osteoarthritis: Association with clinical and radiographical parameters. Medical Journal of Kocaeli. 2014;2:5-10.
144. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. Int Orthop. 2011;35(11):1627-31.
145. Jacob EA, Blum L, Bedair HS, Freiberg AA, Quraishi SA. The Association of Vitamin D Status and Pre-operative Physical Activity in Patients with Hip or Knee Osteoarthritis. Journal of Restorative Medicine. 2015;4:3-10.
146. Barker T, Henriksen VT, Rogers VE, Aguirre D, Trawick RH, Lynn Rasmussen G, et al. Vitamin D deficiency associates with gamma-tocopherol and quadriceps weakness but not inflammatory cytokines in subjects with knee osteoarthritis. Redox Biol. 2014;2:466-74.
147. Skalska A, Galas A, Grodzicki T. 25-hydroxyvitamin D and physical and cognitive performance in older people with chronic conditions. Pol Arch Med Wewn. 2012;122(4):162-9.
148. Laslett LL, Quinn S, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. Ann Rheum Dis. 2014;73:697-703.
149. Glover TL, Goodin BR, Horgas AL, Kindler LL, King CD, Sibille KT, et al. Vitamin D, race, and experimental pain sensitivity in older adults with knee osteoarthritis. Arthritis Rheum. 2012;64(12):3926-35.
150. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med. 1996;125(5):353-9.
151. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. Arthritis Rheum. 1999;42(5):854-60.
152. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis Rheum. 2007;56(1):129-36.
153. McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA. 2013;309(2):155-62.

154. Jin X, Jones G, Cicuttini F, Wluka A, Zhu Z, Han W, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthrtitis. JAMA. 2016;315(10):1005-13.
155. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. The New England journal of medicine. 2011;365(23):2205-19.
156. Lin J, Liu J, Davies ML, Chen W. Serum Vitamin D Level and Rheumatoid Arthritis Disease Activity: Review and Meta-Analysis. PloS one. 2016;11(1):e0146351.
157. Kim TH, Choi SJ, Lee YH, Song GG, Ji JD. Combined therapeutic application of mTOR inhibitor and vitamin D(3) for inflammatory bone destruction of rheumatoid arthritis. Medical hypotheses. 2012;79(6):757-60.
158. Flurey CA. Capturing daily fluctuations, flare and self-management in rheumatoid arthritis: The patient perspective.: University of The West England; 2012.
159. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
160. Bartley J. Vitamin D: emerging roles in infection and immunity. Expert review of anti-infective therapy. 2010;8(12):1359-69.
161. Bikle DD. Vitamin D regulation of immune function. Vitamins and hormones. 2011;86:1-21.
162. Weiss ST. Bacterial components plus vitamin D: the ultimate solution to the asthma (autoimmune disease) epidemic? J Allergy Clin Immunol. 2011;127(5):1128-30.
163. Bartels LE, Hvas CL, Agnholt J, Dahlerup JF, Agger R. Human dendritic cell antigen presentation and chemotaxis are inhibited by intrinsic 25-hydroxy vitamin D activation. International immunopharmacology. 2010;10(8):922-8.
164. Jirapongsananuruk O, Melamed I, Leung DY. Additive immunosuppressive effects of 1,25-dihydroxyvitamin D3 and corticosteroids on TH1, but not TH2, responses. J Allergy Clin Immunol. 2000;106(5):981-5.
165. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol. 2007;179(3):1634-47.
166. Wen H, Baker JF. Vitamin D, immunoregulation, and rheumatoid arthritis. J Clin Rheumatol. 2011;17(2):102-7.
167. Athanassiou-Kostoglou I, Athanassiou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Ther Adv Endocrinol Metab. 2012:181-7.

168. Jankosky C, Deussing E, Gibson RL, Haverkos HW. Viruses and vitamin D in the etiology of type 1 diabetes mellitus and multiple sclerosis. Virus research. 2012;163(2):424-30.
169. Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev. 2010;9(7):507-10.
170. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. Clinical Rheumatology. 2012;31(12):1733-9.
171. Baker JF, Baker DG, Toedter G, Shults J, Von Feldt JM, Leonard MB. Associations between vitamin D, disease activity, and clinical response to therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2012;30(5):658-64.
172. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis - Results from the Iowa Women's Health Study. Arthritis Rheum-Us. 2004;50(1):72-7.
173. Costenbader KH, Feskanich D, Holmes M, Karlson EW, Benito-Garcia E. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Ann Rheum Dis. 2008;67(4):530-5.
174. Cutolo M, Otsa K, Laas K, Yprus M, Lehtme R, Secchi ME, et al. Circannual vitamin d serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. Clinical and experimental rheumatology. 2006;24(6):702-4.
175. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, et al. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis research & therapy. 2010;12(6):R216.
176. Haque UJ, Bartlett SJ. Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis. Clin Exp Rheumatol. 2010;28(5):745-7.
177. Kerr GS, Sabahi I, Richards JS, Caplan L, Cannon GW, Reimold A, et al. Prevalence of vitamin D insufficiency/deficiency in rheumatoid arthritis and associations with disease severity and activity. The Journal of rheumatology. 2011;38(1):53-9.
178. Welsh P, Peters MJL, McInnes IB, Lems WF, Lips PT, McKellar G, et al. Vitamin D deficiency is common in patients with RA and linked to disease activity, but circulating levels are unaffected by TNF alpha blockade: results from a prospective cohort study. Annals of the rheumatic diseases. 2011;70(6):1165-7.
179. Craig SM, Yu F, Curtis JR, Alarcon GS, Conn DL, Jonas B, et al. Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. The Journal of rheumatology. 2010;37(2):275-81.

180. Braun-Moscovici Y, Toledano K, Markovits D, Rozin A, Nahir AM, Balbir-Gurman A. Vitamin D level: is it related to disease activity in inflammatory joint disease? Rheumatology International. 2011;31(4):493-9.

181. Oelzner P, Muller A, Deschner F, Huller M, Abendroth K, Hein G, et al. Relationship between disease activity and serum levels of vitamin D metabolites and PTH in rheumatoid arthritis. Calcified Tissue Int. 1998;62(3):193-8.

182. Deal C. Bone loss in rheumatoid arthritis: systemic, periarticular, and focal. Current rheumatology reports. 2012;14(3):231-7.

183. Varenna M, Manara M, Cantatore FP, Del Puente A, Di Munno O, Malavolta N, et al. Determinants and effects of vitamin D supplementation on serum 25-hydroxy-vitamin D levels in patients with rheumatoid arthritis. Clinical and experimental rheumatology. 2012;30(5):714-9.

184. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. BMC Musculoskelet Disord. 2014;15:213.

185. Cimmino MA, Ferrone C, Cutolo M. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol. 2011;25(2):173-83.

186. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamaki H, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr. 2007;86(3):714-7.

187. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008;65(5):508-12.

188. Scragg R, Camargo CA, Jr. Frequency of leisure-time physical activity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2008;168(6):577-86; discussion 87-91.

189. Preece MA, McIntosh WB, Tomlinson S, Ford JA, Dunnigan MG, O'Riordan JL. Vitamin-D deficiency among Asian immigrants to Britain. Lancet. 1973;1(7809):907-10.

190. Solanki T, Hyatt RH, Kemm JR, Hughes EA, Cowan RA. Are elderly Asians in Britain at a high risk of vitamin D deficiency and osteomalacia? Age Ageing. 1995;24(2):103-7.

191. Shipley M. Chronic widespread pain and fibromyalgia syndrome. Medicine. 2010;38(4).

192. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. Jcr-J Clin Rheumatol. 2008;14(1):12-6.
193. Rohrbeck J, Jordan K, Croft P. The frequency and characteristics of chronic widespread pain in general practice: a case-control study. Br J Gen Pract. 2007;57(535):109-15.
194. Khan AA, Khan A, Harezlak J, Tu W, Kroenke K. Somatic symptoms in primary care: etiology and outcome. Psychosomatics. 2003;44:471-8.
195. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet. 1999;354(9182):936-9.
196. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. Arthritis Rheum. 2006;54(1):169-76.
197. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995;38(1):19-28.
198. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. Mayo Clin Proc. 2004;79(12):1585-6; author reply 6-7.
199. Mallen G, Peat G. Prognostic factors for musculoskeletal pain in primary care: a systematic review. Br J Gen Pract. 2007;57:655-61.
200. Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hypponen E. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. Ann Rheum Dis. 2009;68(6):817-22.
201. Macfarlane GJ, Palmer B, Roy D, Afzal C, Silman AJ, O'Neill T. An excess of widespread pain among South Asians: are low levels of vitamin D implicated? Ann Rheum Dis. 2005;64(8):1217-9.
202. McBeth J, Pye SR, O'Neill TW, Macfarlane GJ, Tajar A, Bartfai G, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. Ann Rheum Dis. 2010;69(8):1448-52.
203. McCabe PS, Pye SR, Mc Beth J, Lee DM, Tajar A, Bartfai G, et al. Low vitamin D and the risk of developing chronic widespread pain: results from the European male ageing study. BMC Musculoskelet Disord. 2016;17:32.
204. MacFarlane GJ, Croft PR, Schollum J, Silman AJ. Widespread pain: is an improved classification possible? The Journal of rheumatology. 1996;23(9):1628-32.

205. Hsiao MY, Hung CY, Chang KV, Han DS, Wang TG. Is Serum Hypovitaminosis D Associated with Chronic Widespread Pain Including Fibromyalgia? A Meta-analysis of Observational Studies. Pain Physician. 2015;18(5):E877-87.
206. Smythe HA, Moldofsky H. Two contributions to understanding of the "fibrositis" syndrome. Bull Rheum Dis. 1977;28(1):928-31.
207. Body JJ, Bergmann P, Boonen S, Devogelaer JP, Gielen E, Goemaere S, et al. Extraskeletal benefits and risks of calcium, vitamin D and anti-osteoporosis medications. Osteoporos Int Suppl. 2012;Suppl 1 S1-23.
208. Gerwin RD. A review of myofascial pain and fibromyalgia--factors that promote their persistence. Acupunct Med. 2005;23(3):121-34.
209. White KP, Speechley M, Harth M, Ostbye T. Fibromyalgia in rheumatology practice: a survey of Canadian rheumatologists. The Journal of rheumatology. 1995;22(4):722-6.
210. Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. The Journal of rheumatology. 1995;22(1):151-6.
211. Clauw DJ. Fibromyalgia: an overview. The American journal of medicine. 2009;122(12 Suppl):S3-S13.
212. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis care & research. 2010;62(5):600-10.
213. Abokrysha NT. Vitamin D deficiency in women with fibromyalgia in Saudi Arabia. Pain Med. 2012;13(3):452-8.
214. Aaron LA, Bradley LA, Alarcón GS, Alexander RW, Triana-Alexander M, Martin MY, et al. Psychiatric diagnoses in patients with fibromyalgia are related to health care–seeking behavior rather than to illness. Arthritis & Rheumatism. 1996;39(3):436-45.
215. Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, et al. Family study of fibromyalgia. Arthritis & Rheumatism. 2004;50(3):944-52.
216. Clauw DJ, Engel Jr CC, Aronowitz R, Jones E, Kipen HM, Kroenke K, et al. Unexplained symptoms after terrorism and war: an expert consensus statement. Journal of Occupational and Environmental Medicine. 2003;45(10):1040-8.
217. Bhatty SA, Shaikh NA, Irfan M, Kashif SM, Vaswani AS, Sumbhai A, et al. Vitamin D deficiency in fibromyalgia. J Pak Med Assoc. 2010;60(11):949-51.
218. Al-Allaf AW, Mole PA, Paterson CR, Pullar T. Bone health in patients with fibromyalgia. Rheumatology (Oxford). 2003;42(10):1202-6.

219. Okumus M, Koybasi M, Tuncay F, Ceceli E, Ayhan F, Yorgancioglu R, et al. Fibromyalgia syndrome: is it related to vitamin D deficiency in premenopausal female patients? Pain Manag Nurs. 2013;14(4):e156-63.
220. de Rezende Pena C, Grillo LP, das Chagas Medeiros MM. Evaluation of 25-hydroxyvitamin D serum levels in patients with fibromyalgia. J Clin Rheumatol. 2010;16(8):365-9.
221. Armstrong D, Meenagh G, Bickle I, Lee A, Curran E-S, Finch M. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Clinical rheumatology. 2007;26(4):551-4.
222. Badsha H, Daher M, Kong KO. Myalgias or non-specific muscle pain in Arab or Indo-Pakistani patients may indicate vitamin D deficiency. Clinical Rheumatology. 2009;28(8):971-3.
223. Heidari B, Shirvani JS, Firouzjahi A, Heidari P, Hajian-Tilaki KO. Association between nonspecific skeletal pain and vitamin D deficiency. Int J Rheum Dis. 2010;13(4):340-6.
224. Mateos F, Valero C, Olmos J, Casanueva B, Castillo J, Martínez J, et al. Bone mass and vitamin D levels in women with a diagnosis of fibromyalgia. Osteoporosis International. 2014;25(2):525-33.
225. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain. 2014;155(2):261-8.
226. O'Sullivan P, Beales D, Jensen L, Murray K, Myers T. Characteristics of chronic non-specific musculoskeletal pain in children and adolescents attending a rheumatology outpatients clinic: a cross-sectional study. Pediatric Rheumatology. 2011;9(3).
227. Carnes D, Underwood M. Chronic musculoskeletal pain. British J General Practice. 2007:604-5.
228. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol. 2007;21(3):403-25.
229. Hunfeld J, Perquin C, Bertina W, Hazeborek-kampschreur A, van Suijlekom-Smit L, Passchier J, et al. Stability of pain parameters and pain-related quality of life in adolescents with persistent pain:a three-year follow-up. Clin J Pain. 2002;18(2):99-106.
230. Perquin C, Hunfeld J, Hazeborek-Kampschreur A, van Suijlekom-Smit L, Passchier J, Koes B, et al. The natural course of chronic benign pain in childhood and adolescence:a two-year population -based follow-up study. Eur J Pain. 2003;7(6):551-9.

231. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JHB, Brouwer S. Factors promoting staying at work in people with chronic nonspecific musculoskeletal pain: a systematic review. Disabil Rehabil. 2012;34(6):443-58.
232. Hunfeld J, Perquin C, Duivenwoorden H, Hazeborek-kampschreur A, Passchier J, van Suijlekom-Smit L, et al. Chronic pain and its impact on quality of life in adolescents and their families. J Pediatr Psychol. 2001;26(3):145-53.
233. Konijnenberg AY, Uiterwaal CS, Kimpen JL, van der Hoeven J, Buitelaar JK, Graeff-Meeder ER. Children with unexplained chronic pain: substantial impairment in everyday life. Arch Dis Child. 2005;90(7):680-6.
234. Guite J, Logan D, Sherry D, Rose J. Adolescent self -perception: associations with chronic musculoskeletal pain and functional disability. Journal of Pain. 2007;8(5):379-86.
235. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JH, Brouwer S. Self-reported work ability and work performance in workers with chronic nonspecific musculoskeletal pain. J Occup Rehabil. 2013;23(1).
236. Perquin C, Hunfeld J, Hazeborek-kampschreur A, Van Suijlekom-Smit L, Passchier J, Koes B, et al. Insights in the use of health care services in chronic benign pain in childhood and adolescence. Pain. 2001;94(2):205-13.
237. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, et al. Pain in children and adolescents: a common experience. Pain. 2000;87(1):51-8.
238. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317-32.
239. Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JW, Moseley GL. Contingency learning deficits and generalization in chronic unilateral hand pain patients. The Journal of Pain. 2014;15(10):1046-56.
240. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of Pain 3rd ed. Edinburgh: Churchill Livingstone; 1995. p. 13-44.
241. Moseley GL, Vlaeyen JW. Beyond nociception: the imprecision hypothesis of chronic pain. Pain. 2015;156(1):35-8.
242. Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. The Cochrane database of systematic reviews. 2015;5:CD007771.

243. Siddiqui AM. Chronic Musculoskeletal Pain in Females as a Manifestation of Vitamin D Deficiency in Saudi Arabia. Ibnosina Journal of Medicine and Biomedical Sciences. 2010;2(5):205-9.

244. Armas LA, Hollis BW, Heaney RP. Vitamin D2 Is Much Less Effective than Vitamin D3 in Humans. The Journal of Clinical Endocrinology & Metabolism. 2004;89(11):5387-91.

245. Masood H, Narang AP, Bhat IA, Shah GN. Persistent limb pain and raised serum alkaline phosphatase the earliest markers of subclinical hypovitaminosis D in Kashmir. Indian journal of physiology and pharmacology. 1989;33(4):259-61.

246. Romagnoli E, Mascia ML, Cipriani C, Fassino V, Mazzei F, D'Erasmo E, et al. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D(2)) or cholecalciferol (vitamin D(3)) in the elderly. J Clin Endocr Metab. 2008;93(8):3015-20.

247. Gloth FM, 3rd, Lindsay JM, Zelesnick LB, Greenough WB, 3rd. Can vitamin D deficiency produce an unusual pain syndrome? Arch Intern Med. 1991;151(8):1662-4.

248. Prabhala A, Garg R, Dandona P. Severe myopathy associated with vitamin D deficiency in western New York. Arch Intern Med. 2000;160(8):1199-203.

249. Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. Rheumatol Int. 2012;32(8):2279-83.

250. Schreuder F, Bernsen RM, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in non-Western immigrants: a randomized controlled trial. Ann Fam Med. 2012;10(6):547-55.

251. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. The Histochemical journal. 2001;33(1):19-24.

252. Ceglia L. Vitamin D and skeletal muscle tissue and function. Mol Aspects Med. 2008;29(6):407-14.

253. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem. 1985;260(15):8882-91.

254. Grootjans-Geerts I. [Hypovitaminosis D: a veiled diagnosis]. Nederlands tijdschrift voor geneeskunde. 2001;145(43):2057-60.

255. Bergman S, Herrstrom P, Hogstrom K, Petersson IF, Svensson B, Jacobsson LT. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. The Journal of rheumatology. 2001;28(6):1369-77.

256. Wielders SJ, Bennaghmouch A, Reutelingsperger CP, Bevers EM, Lindhout T. Anticoagulant and antithrombotic properties of intracellular protease-activated receptor antagonists. Journal of thrombosis and haemostasis : JTH. 2007;5(3):571-6.
257. Shaunak S, Colston K, Ang L, Patel SP, Maxwell JD. Vitamin D deficiency in adult British Hindu Asians: a family disorder. Br Med J (Clin Res Ed). 1985;291(6503):1166-8.
258. Lyman D. Undiagnosed Vitamin D Deficiency in the Hospitalized Patient. Am Fam Physician. 2005;71(2):299-304.
259. Mascarenhas R, Mobarhan S. Hypovitaminosis D-induced pain. Nutr Rev. 2004;62(9):354-9.
260. Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. Nat Rev Immunol. 2014;14(4):217-31.
261. Buckley LM, Hillner BE. A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. The Journal of rheumatology. 2003;30(1):132-8.
262. Church JL, Haas MR, Goodall S. Cost effectiveness of falls and injury prevention strategies for older adults living in residential aged care facilities. PharmacoEconomics. 2015;33(12):1301-10.
263. Durvasula S, Kok C, Sambrook PN, Cumming RG, Lord SR, March LM, et al. Sunlight and health: attitudes of older people living in intermediate care facilities in southern Australia. Archives of gerontology and geriatrics. 2010;51(3):e94-e9.
264. Grover SR, Morley R. Vitamin D deficiency in veiled or dark-skinned pregnant women. Medical Journal of Australia. 2001;175(5):251-2.
265. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition. 2000;72(3):690-3.
266. Clemens T, Henderson S, Adams J, Holick M. Increased skin pigment reduces the capacity of skin to synthesise vitamin D 3. The Lancet. 1982;319(8263):74-6.
267. Wilde B, Starrin B, Larsson G, Larsson M. Quality of care from a patient perspective. Scandinavian journal of caring sciences. 1993;7(2):113-20.
268. Schoen C, Osborn R, Doty MM, Squires D, Peugh J, Applebaum S. A survey of primary care physicians in eleven countries, 2009: perspectives on care, costs, and experiences. Health Affairs. 2009;28(6):w1171-w83.
269. Brown L. The experience of care: patient perspectives. Topics in Clinical Nursing. 1986;8(2):56-62.

270. Cooke G, Valenti L, Glasziou P, Britt H. Common general practice presentations and publication frequency. Australian family physician. 2013;42(1/2):65.

271. Koleva D, Krulichova I, Bertolini G, Caimi V, Garattini L. Pain in primary care: an Italian survey. The European Journal of Public Health. 2005;15(5):475-9.

272. Statistics ABo. Characteristics of Bodily pain in Australia. In: Statistics ABo, editor. Canberra2011.

273. Economics A. The high price of pain: the economic impact of persistent pain in Australia. Sydney: MBF Foundation. 2007:9-11.

274. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JH, Brouwer S. Workers who stay at work despite chronic nonspecific musculoskeletal pain: do they differ from workers with sick leave? Journal of occupational rehabilitation. 2012;22(4):489-502.

275. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.

276. Fillingim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD, Turk DC, et al. The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. The Journal of Pain. 2014;15(3):241-9.

277. Klepstad P, Kaasa S, Cherny N, Hanks G, de Conno F, EAPC RSCot. Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network. Palliative medicine. 2005;19(6):477-84.

278. Rief W, Kaasa S, Jensen R, Perrot S, Vlaeyen JW, Treede R-D, et al. The need to revise pain diagnoses in ICD-11. Pain. 2010;149(2):169-70.

279. Mithal A, Wahl D, Bonjour J-P, Burckhardt P, Dawson-Hughes B, Eisman J, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporosis international. 2009;20(11):1807-20.

280. Prentice A. Vitamin D deficiency: a global perspective. Nutrition reviews. 2008;66(suppl 2):S153-S64.

281. Arvold DS, Odean MJ, Dornfeld MP, Regal RR, Arvold JG, Karwoski GC, et al. Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2009;15(3):203-12.

282. AustralianGovernment. MBS reviews: vitamin D testing report. 2014.

283. AustralianGovernment. Australia's medical workforce.

AustralianInstituteofHealthandWelfare, 2015.
284. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain. 2001;89(2):127-34.
285. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. Anesthesia & Analgesia. 2007;105(1):205-21.
286. Kumar A, Gopal H, Khamkar K, Prajapati P, Mendiratta N, Misrad A, et al. Vitamin D deficiency as the primary cause of musculoskeletal complaints in patients referred to rheumatology clinic: A clinical study. Indian Journal of Rheumatology. 2012;7(4):199-203.
287. Bowling A. Research methods in health: investigating health and health services: McGraw-Hill Education (UK); 2014.
288. Krueger RA, Casey MA. Focus groups: A practical guide for applied research: Sage publications; 2014.
289. Stewart DW, Shamdasani PN. Focus groups: Theory and practice: Sage publications; 2014.
290. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology. 2006;3(2):77-101.
291. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Academic Medicine. 2014;89(9):1245-51.
292. Czachowski S, Piszczek E, Sowińska A, olde Hartman TC. Challenges in the management of patients with medically unexplained symptoms in Poland: a qualitative study. Family practice. 2011;29(2):228-34.
293. Stewart M. Reflections on the doctor–patient relationship: from evidence and experience. Br J Gen Pract. 2005;55(519):793-801.
294. Stewart MA, McWhinney IR, Buck CW. The doctor/patient relationship and its effect upon outcome. JR Coll Gen Pract. 1979;29(199):77-82.
295. Brownell AKW, Atkins C, Whiteley A, Woollard RF, Kornelsen J. Clinical practitioners' views on the management of patients with medically unexplained physical symptoms (MUPS): a qualitative study. BMJ open. 2016;6(12):e012379.
296. Olde Hartman TC, Hassink-Franke LJ, Lucassen PL, van Spaendonck KP, van Weel C. Explanation and relations. How do general practitioners deal with patients with persistent medically unexplained symptoms: a focus group study. BMC Family Practice. 2009;10(1):1.

297. Ivetić V, Kersnik J, Klemenc-Ketiš Z, Švab I, Kolšek M, Poplas-Susič T. Opinions of Slovenian family physicians on medically unexplained symptoms: a qualitative study. Journal of international medical research. 2013;41(3):705-15.
298. Le Goaziou MF, Kellou N, Flori M, Perdrix C, Dupraz C, Bodier E, et al. Vitamin D supplementation for diffuse musculoskeletal pain: Results of a before-and-after study. The European journal of general practice. 2014;20(1):3-9.
299. Shipton EE, Shipton EA. Vitamin D deficiency and pain: clinical evidence of low levels of vitamin D and supplementation in chronic pain states. Pain and therapy. 2015;4(1):67-87.
300. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Lippincott Williams & Wilkins; 2008.
301. Khan KS, Ball E, Fox CE, Meads C. Systematic reviews to evaluate causation: an overview of methods and application. Evidence Based Medicine. 2012;17(5):137-41.
302. Abbasi M, Hashemipour S, Hajmanuchehri F, Kazemifar AM. Is Vitamin D deficiency associated with Non specific Musculoskeletal Pain? Global Journal of Health Science. 2013;5(1).
303. Chaudhary WA, Arshad SH, Waqas S, Jatoi FK, Khyyam U, Dar MT, et al. Vitamin D supplement as an adjuvant in the management of chronic musculoskeletal pain. Anaesth Pain & Intensive Care 2013;17(3):296-300.
304. Knutsen KV, Brekke M, Gjelstad S, Lagerløv P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: A cross-sectional descriptive study in a multi-ethnic general practice in Norway. Scandinavian Journal of Primary Health Care. 2010;28(3):166-71.
305. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Archives of pediatrics & adolescent medicine. 2004;158(6):531-7.
306. Holick MF. Vitamin D deficiency. New England Journal of Medicine. 2007;357(3):266-81.
307. Lips P. Worldwide status of vitamin D nutrition. The Journal of steroid biochemistry and molecular biology. 2010;121(1):297-300.
308. Bilinski K, Boyages S. Evidence of overtesting for vitamin D in Australia: an analysis of 4.5 years of Medicare Benefits Schedule (MBS) data. BMJ open. 2013;3(6):e002955.
309. Council N. National Health Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines Canberra. 2009.

310. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PloS Med. 2009;6(7):e1000097.

311. Moore RA, McQuay HJ. Bandolier's little book of making sense of the medical evidence: Oxford University Press, USA; 2006.

312. Straube S, Derry S, Moore RA, McQuay HJ. Vitamin D for the treatment of chronic painful conditions in adults. The Cochrane Library. 2010.

313. Al-Ali H, Fuleihan GE-H. Nutritional osteomalacia: substantial clinical improvement and gain in bone density posttherapy. Journal of Clinical Densitometry. 2000;3(1):97-101.

314. Malabanan AO, Turner AK, Holick MF. Severe generalized bone pain and osteoporosis in a premenopausal black female: effect of vitamin D replacement. Journal of Clinical Densitometry. 1998;1(2):201-4.

315. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. Journal of chemical neuroanatomy. 2005;29(1):21-30.

316. Féron F, Burne THJ, Brown J, Smith E, McGrath JJ, Mackay-Sim A, et al. Developmental Vitamin D 3 deficiency alters the adult rat brain. Brain research bulletin. 2005;65(2):141-8.

317. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Prognosis of non-specific musculoskeletal pain in preadolescents: A prospective 4-year follow-up study till adolescence. Pain. 2004;110(3):550-9.

318. Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG. Vitamin D Deficiency Promotes Skeletal Muscle Hypersensitivity and Sensory Hyperinnervation. J Neurosci. 2011;31(39):13728-38.

319. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. CHEST Journal. 2006;129(1):174-81.

320. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds JM, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Controll Clin Trials. 1996;17:1-12.

321. Cohen J. Statistical power analysis for the behavior science. Lawrance Eribaum Association. 1988.

322. Glass GV. Primary, secondary, and meta-analysis of research. Educational researcher. 1976;5(10):3-8.

323. Hedges LV, Olkin I. Statistical methods for meta-analysis: Academic press; 2014.
324. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library; 2008.
325. StataCorp. Stata Statitistical Software: Release 12. TX: StataCorp LP2011.
326. Bailey KR. Inter-Study Differences -How Should They Influence the Interpretation and Analysis of Results. Stat Med. 1987;6(3):351-60.
327. Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. Lupus. 2015;24:483-9.
328. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008.
329. Ryan PJ. Vitamin D therapy in clinical practice.One dose does not fit all. Int J Clin Pract. 2007;61(11):1894-9.
330. Moseley GL. Do training diaries affect and reflect adherence to home programs? Arthritis Rheum. 2006;55(4):662-4.
331. O'Connell NE, Moseley GL, McAuley JH, Wand BM, Herbert RD. Interpreting effectiveness evidence in pain: short tour of contemporary issues. Phys Ther. 2015;95(8):1087-94.
332. Pop LC, Shapses SA, Chang B, Sun W, Wang X. Vitamin D-Binding Protein in Healthy Pre- and Postmenopausal Women: Relationship with Estradiol Concentrations. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2015;21(8):936-42.
333. Kanwar G, Sharma N, Shekhawat M, Sharma P, Hada R, Chandel CS. Comparison of Vitamin D Levels in Pre And Post Menopausal Type 2 Diabetic Females. IOSR J Dental and Medical Sciences. 2015;14(8):70-3.
334. Kendall J. Designing a research project: randomised controlled trials and their principles. Emergency medicine journal: EMJ. 2003;20(2):164.
335. Sim J, Reid N. Statistical inference by confidence intervals: Issues of interpretation and utilization. Phys Ther. 1999;79(2):186-95.
336. Gaikwad M, Vanlint S, Moseley GL, Mittinty MN, Stocks N. Understanding patient perspectives on management of their chronic pain–online survey protocol. Journal of pain research. 2017;10:31.

337. Merskey H, Bogduk N. Classification of chronic pain, IASP Task Force on Taxonomy. Seattle, WA: International Association for the Study of Pain Press (Also available online at www iasp-painorg). 1994.
338. Green CR, Wheeler JR, Marchant B, LaPorte F, Guerrero E. Analysis of the physician variable in pain management. Pain Medicine. 2001;2(4):317-27.
339. Potter M, SCHAFER S, GONZALEZ-MENDEZ E, GJELTEMA K, LOPEZ A, WU J, et al. Opioids for chronic nonmalignant pain. Journal of Family Practice. 2001;50(2):145-.
340. Upshur CC, Luckmann RS, Savageau JA. Primary care provider concerns about management of chronic pain in community clinic populations. Journal of general internal medicine. 2006;21(6):652-5.
341. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. The Lancet. 2011;377(9784):2226-35.
342. Astin JA. Why patients use alternative medicine: results of a national study. Jama. 1998;279(19):1548-53.
343. Barnes PM, Powell-Griner E, McFann K, Nahin RL, editors. Complementary and alternative medicine use among adults: United States, 2002. Seminars in Integrative Medicine; 2004: Elsevier.
344. O'Dea JA. Consumption of nutritional supplements among adolescents: usage and perceived benefits. Health education research. 2003;18(1):98-107.
345. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. The lancet. 1999;354(9186):1248-52.
346. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. The Journal of Pain. 2006;7(4):281-9.
347. Organization WH. The world health report-Health systems: improving performance (Electronic edition). Geneva: World Health Organization; 2001 (consulted on 26-1-2003).
348. Oliver RL. Cognitive, affective, and attribute bases of the satisfaction response. Journal of consumer research. 1993;20(3):418-30.
349. Williams B. Patient satisfaction: a valid concept? Social science & medicine. 1994;38(4):509-16.
350. Clarke M, Oxman A. Cochrane reviewers' handbook 4.1 [updated June 2000]. Review Manager (RevMan)[Computer program] Version. 2000;4(1):208-15.
351. Ohtake PJ, Childs JD. Why publish study protocols? Phys Ther. 2014;94(9):1208-9.
352. West R. Trial protocols. Addiction. 2012;107(9):1544-.

353. Wyse SE. Advantages and Disadvantages of Surveys 2012 [cited 2016 5th October].
354. Szolnoki G, Hoffmann D. Online, face-to-face and telephone surveys—Comparing different sampling methods in wine consumer research. Wine Economics and Policy. 2013;2(2):57-66.
355. Heen MS, Lieberman JD, Miethe TD. A comparison of different online sampling approaches for generating national samples. Center for Crime and Justice Policy, CCJP. 2014;1.
356. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). Journal of medical Internet research. 2004;6(3):e34.
357. Cochran WG. Sampling techniques: John Wiley & Sons; 2007.
358. https://www.surveymonkey.com/r/3C9FXKW. 2016.
359. Nardi PM. Doing survey research: Routledge; 2015.
360. Lips P. Vitamin D physiology. Progress in biophysics and molecular biology. 2006;92(1):4-8.
361. Norman AW, Nemere I, Zhou L-X, Bishop JE, Lowe KE, Maiyar AC, et al. 1, 25 (OH) 2-vitamin D 3, a steroid hormone that produces biologic effects via both genomic and nongenomic pathways. The Journal of steroid biochemistry and molecular biology. 1992;41(3):231-40.
362. I Trochoutsou A, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the immune system: genomic and non-genomic actions. Mini reviews in medicinal chemistry. 2015;15(11):953-63.
363. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. Kidney international. 2010;78(2):140-5.
364. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. The American journal of clinical nutrition. 2004;79(3):362-71.
365. Welsh P, Sattar N. Vitamin D and chronic disease prevention. BMJ. 2014;348:g2280.
366. Huang W, Shah S, Long Q, Crankshaw AK, Tangpricha V. Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation. The Clinical journal of pain. 2013;29(4):341-7.
367. Turner MK, Hooten WM, Schmidt JE, Kerkvliet JL, Townsend CO, Bruce BK. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. Pain Medicine. 2008;9(8):979-84.

368. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. The American journal of clinical nutrition. 2008;87(4):1080S-6S.

369. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? The Journal of steroid biochemistry and molecular biology. 2014;144:138-45.

370. Bilinski KL, Boyages SC. The rising cost of vitamin D testing in Australia: time to establish guidelines for testing. The Medical journal of Australia. 2012;197(2):90.

371. Mittelstaedt M. Ontario considers curbing vitamin D testing. The Globe and Mail. 2010:2.

372. Sattar N, Welsh P, Panarelli M, Forouhi NG. Increasing requests for vitamin D measurement: costly, confusing, and without credibility. The Lancet. 2012;379(9811):95-6.

373. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2013;380(9859):2163-96.

374. Initiative NPS. National pain strategy: pain management for all Australians. Melbourne: Faculty of Pain Medicine. 2010.

375. Lemeshow S, Sturdivant RX, Hosmer DW. Applied Logistic Regression (Wiley Series in Probability and Statistics): Wiley; 2013.

376. Tibshirani R. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society Series B (Methodological). 1996:267-88.

377. Harrell F. Model uncertainty, penalization, and parsimony. ISCB Presentation on UVa Web page. 1998.

378. Epling JW, Mader EM, Roseamelia CA, Morley CP. Emerging Practice Concerning Vitamin D in Primary Care. Qualitative health research. 2014:1049732314554100.

379. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2011;96(7):1911-30.

380. van Schoor NM, Lips P. Worldwide vitamin D status. Best practice & research Clinical endocrinology & metabolism. 2011;25(4):671-80.

381. Brock K, Wilkinson M, Cook R, Lee S, Bermingham M. Associations with vitamin D deficiency in "at risk" Australians. The Journal of steroid biochemistry and molecular biology. 2004;89:581-8.

382. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA internal medicine. 2013;173(5):355-61.

383. Dickinson A, MacKay D. Health habits and other characteristics of dietary supplement users: a review. Nutrition journal. 2014;13(1):1.

384. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. American journal of epidemiology. 2004;160(4):339-49.

385. Tran B, Armstrong BK, McGeechan K, Ebeling PR, English DR, Kimlin MG, et al. Predicting vitamin D deficiency in older Australian adults. Clinical endocrinology. 2013;79(5):631-40.

386. Sohl E, Heymans MW, de Jongh RT, den Heijer M, Visser M, Merlijn T, et al. Prediction of vitamin D deficiency by simple patient characteristics. The American journal of clinical nutrition. 2014;99(5):1089-95.

387. Mitchell D, Henao M, Finkelstein J, Burnett-Bowie S-A. Prevalence and predictors of vitamin D deficiency in healthy adults. Endocrine Practice. 2012;18(6):914-23.

388. Groves RM, Fowler Jr FJ, Couper MP, Lepkowski JM, Singer E, Tourangeau R. Survey methodology: John Wiley & Sons; 2009.

389. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC public health. 2011;11(1):1.

390. Phillips CJ. The cost and burden of chronic pain. Reviews in pain. 2009;3(1):2.

391. IASP E. Factsheet 4A: Unrelieved pain is a major global healthcare problem. Retrieved on May. 2005;15:2009.

392. Dawson R, Spross JA, Jablonski ES, Hoyer DR, Sellers DE, Solomon MZ. Probing the paradox of patients' satisfaction with inadequate pain management. Journal of pain and symptom management. 2002;23(3):211-20.

393. Hall JA, Milburn MA, Roter DL, Daltroy LH. Why are sicker patients less satisfied with their medical care? Tests of two explanatory models. Health Psychology. 1998;17(1):70.

394. Arnsten JH, Gelfand JM, Singer DE. Determinants of compliance with anticoagulation: a case-control study. The American journal of medicine. 1997;103(1):11-7.

395. Williams B, Coyle J, Healy D. The meaning of patient satisfaction: an explanation of high reported levels. Social science & medicine. 1998;47(9):1351-9.

396. Geneen LJ, Martin DJ, Adams N, Clarke C, Dunbar M, Jones D, et al. Effects of education to facilitate knowledge about chronic pain for adults: a systematic review with meta-analysis. Systematic reviews. 2015;4(1):1.

397. Chapman SL, Jamison RN, Sanders SH, Lyman DR, Lynch NT. Perceived treatment helpfulness and cost in chronic pain rehabilitation. The Clinical journal of pain. 2000;16(2):169-77.
398. Gallagher L, McAuley J, Moseley GL. A randomized-controlled trial of using a book of metaphors to reconceptualize pain and decrease catastrophizing in people with chronic pain. The Clinical journal of pain. 2013;29(1):20-5.
399. Ruehlman LS, Karoly P, Enders C. A randomized controlled evaluation of an online chronic pain self management program. Pain. 2012;153(2):319-30.
400. Van Oosterwijck J, Meeus M, Paul L, De Schryver M, Pascal A, Lambrecht L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. The Clinical journal of pain. 2013;29(10):873-82.
401. Morrison GE, Chase W, Young V, Roberts WL. Back pain: treatment and prevention in a community hospital. Archives of physical medicine and rehabilitation. 1988;69(8):605-9.
402. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. The Clinical journal of pain. 2004;20(5):324-30.
403. Jenkinson C, Coulter A, Gyll R, Lindström P, Avner L, Höglund E. Measuring the experiences of health care for patients with musculoskeletal disorders (MSD): development of the Picker MSD questionnaire. Scandinavian journal of caring sciences. 2002;16(3):329-33.
404. Strong K, Mathers C, Leeder S, Beaglehole R. Preventing chronic diseases: how many lives can we save? The Lancet. 2005;366(9496):1578-82.
405. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. European Journal of Pain. 2004;8(1):39-45.
406. Vitamin D tests. [online] [Internet]. NPS MedicineWise 2013 [cited 11 November 2016]. Available from: http://www.nps.org.au/medical-tests/pathology-tests/for-individuals/blood-tests/for-individuals/vitamin-d-tests/for-health-professionals/when-is-vitamin-d-testing-appropriate.

APPENDIX

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LETTER TO THE EDITOR

Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis

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Abstract Chronic nonspecific musculoskeletal pain (CNMP) is an idiopathic condition often seen in general practice and rheumatology clinics, the aetiology of which may include vitamin D deficiency. The objective of the present study is to evaluate the effectiveness of vitamin D supplementation in the management of CNMP through a systematic review and meta-analysis. According to PRISMA guidelines, PubMed, Embase, Web of Science, Cochrane and Scopus electronic databases were searched for randomised controlled trials comparing vitamin D supplementation to a control or placebo in CNMP patients; the search was not limited by language or date. Meta-analysis was performed using the mean and standardised mean difference which was computed with 95 % confidence intervals, and overall effect size was calculated. Both fixed and random effects models were used in meta-analysis to account for heterogeneity in the studies. The initial search identified 107 studies, of which 10 were potentially relevant, with 7 studies excluded because they did not meet selection criteria. Three studies were included in the meta-analysis. We found no effect of vitamin D supplementation (standardised mean difference (SMD) 0.004; 95 % confidence interval (CI) −0.248 to 0.256) on pain in CNMP patients. Forest plot is used to present the results from meta-analysis. Contrary to a widespread clinical view, there is a moderate level of evidence that vitamin D supplementation is not helpful for treating CNMP patients.

Keywords Chronic nonspecific musculoskeletal pain · Meta-analysis · Systematic review · Vitamin D · Vitamin D supplementation

Introduction

Chronic nonspecific musculoskeletal pain (CNMP) is an idiopathic condition which is a common presentation to rheumatology clinics [1, 2]. CNMP is associated with decreased physical health, mental well-being, social life [3, 4], work ability [5] and disability [6]. Many sufferers become stuck on a descending spiral of economic, social, emotional and physical disadvantage [7, 8]. CNMP is a significant burden to the economy [9]. The aetiology of CNMP is not well understood, and although many potential contributors have been identified [10], a clear nociceptive source has not, and empirical data concerning other contributors are lacking. As a result, CNMP is difficult to diagnose, prevent or treat. One potential contributor that receives substantial attention clinically and has been investigated in a range of clinical studies is vitamin D deficiency [11, 12].

Vitamin D is involved in many regulatory biological processes. In addition to calcium homeostasis, vitamin D is thought to have anti-inflammatory, anti-apoptotic and anti-fibrotic effects; it is thought to play a role in regulating blood pressure and in innate and adaptive immune system function [13, 14]. This range of biological effects highlights the potential role of vitamin D deficiency in the development of symptoms associated with acute

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and chronic rheumatic diseases, and it is biologically plausible that vitamin D deficiency contributes to the development and maintenance of CNMP. That people with vitamin D deficiency can present with nonspecific muscular pain and bone pain has been reported [15], and several studies have suggested a causative role [16–18]. However, a recent Cochrane review [19] investigated vitamin D supplementation for the treatment of a range of chronic painful conditions and concluded no substantial effect. Given the different pathophysiological origins of the condition included, such as osteoarthritis, rheumatoid arthritis and fibromyalgia, such a finding was perhaps not surprising. The authors of that review suggested that specific conditions should be investigated individually. We contend that another aspect of that review may have contributed to its null findings: there was no attempt to confine source literature to direct comparisons between vitamin D and a control or placebo. This is important in this field because it is arguably very difficult to isolate the treatment effect attributable to vitamin D supplementation when it is instigated as a part of multimodal intervention.

Despite the clinically topical nature of the issue and the substantial literature, no attempt has been made to conduct meta-analyses. Meta-analyses provide the obvious advantage of increasing power and estimating effect sizes, which can then be re-tested in subsequent studies [20]. We aimed to fill these substantial gaps in the literature by using gold standard systematic review and meta-analysis methodology to evaluate the evidence concerning the effect of vitamin D supplementation, when compared in a randomised controlled trial to a placebo, on pain in people with CNMP.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [21] was followed for this review.

Inclusion criteria

Only randomised controlled trial (RCT) or randomised double-blind control study designs were eligible. For inclusion, RCTs had to compare vitamin D supplementation to a control or placebo and measure the pain outcome using Visual Analogue Scale (VAS). No restrictions were applied for language but restricted the studies to those conducted on "humans".

Exclusion criteria

Studies including patients previously diagnosed with an inflammatory joint disease, postsurgical patients or patients with experimentally induced pain were excluded.

Table 1 Electronic search strategy tailored to each database

PubMed				
Chronic [ALL] OR Persistent [ALL]	Nonspecific [ALL] OR Non-specific [ALL]	Musculoskeletal [ALL] OR Musculoskeletal pain* [ALL]	Pain [MH] OR Pain* [ALL]	vitamin D*[ALL] OR Cholecalciferol [ALL] OR Hydroxycholecalciferol* [ALL] OR Hydroxyvitamin D* [ALL] OR Ergocalciferol* [ALL]
Embase				
Chronic OR Persistent	Nonspecific OR "Non specific"	Musculoskeletal NEAR/4 pain*	"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR Ergocalciferol*	
Web of Science:				
Chronic OR Persistent	Nonspecific OR "Non specific"	Musculoskeletal NEAR/4 pain*	"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Ergocalciferol* OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3"	
Cochrane Library:				
Chronic OR Persistent	Nonspecific OR "Non specific"	Musculoskeletal AND pain*	"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR Ergocalciferol*	
Scopus:				
Chronic OR Persistent	Nonspecific OR "Non specific"	Musculoskeletal W/3 pain*	"vitamin D" OR "vitamin d2" OR "vitamin d3" OR Cholecalciferol OR Hydroxycholecalciferol* OR Ergocalciferol* OR "Hydroxyvitamin D" OR "hydroxyvitamin d2" OR "Hydroxyvitamin D3" OR	

Table 2 Characteristics of included studies

Author/ year	Design	Sample size	Participants	Main complaints	Intervention	Follow-up period (weeks)	Outcome
Sakalli et al. (2012)	Randomised placebo-controlled double-blind trial	Randomised group $n = 120$	- Elderly patients aged >65 years - Attended rheumatology outpatient clinic.	Nonspecific msk pain	Oral and intramuscular vitamin D	4	A single mega dose vitamin D decrease nonspecific msk pain. Improved QoL and improved functional mobility in elderly.
Schreuder et al. (2012)	Semi-crossover randomised controlled trial	Randomised Group $n = 88$	Age 18 to 60 years. - Patients from ten general practices in Delft, The Netherlands, nonwestern immigrants and their offsprings	Frequent, recurrent msk pain or pain lasting >3 months without obvious cause (trauma, arthritis, sciatica).	Oral vitamin D 150,000 IU in 7.5 ml oil OR placebo in 7.5 ml oil having same appearance and taste	6	A small positive effect on pain 6 weeks after high-dose vitamin D supplementation
Warner et al. (2008)	Randomised controlled trial	Randomised group $n = 50$ Control group $n = 104$	- Age group not specified. - Rheumatology practice, Kansas City, Missouri.	Diffuse musculoskeletal pain	50,000 IU ergocalciferol.	12	Vit D deficiency correction did not improve msk pain.

Search strategy

An electronic search was performed on five databases—PubMed, Embase, Web of Science, Cochrane and Scopus. The search period was set from the time of commencement of these databases up to 3 November 2015. The search strategies for each database are listed in Table 1. MG and SV independently searched for potentially eligible studies based on the study title and then read the abstracts and selected potentially relevant studies, from which studies not matching the selection criteria were excluded. Full articles of the remaining studies were reviewed for inclusion. The reference lists of selected studies were manually searched to find additional potential papers.

Data extraction

The final selection of the studies was collectively made by the group. Data extraction was performed by MG and MM using a standardised data extraction form similar to Table 2 highlighting the characteristics of selected studies. Data was extracted on sample size, characteristics of participants, intervention type and control group, main outcome and adverse events. The review team was never blinded to authors' names or institutions, journal of publication and study results. MM provided the statistical support and help in performing the analysis. The manuscript was collectively written by the team, and all authors approved the final draft.

Quality assessment of selected studies

The five-point Jadad score was used to assess the methodological quality of studies. Following, questionnaire formed the basis of scoring [22]

1. Was the study described as randomised?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Each question is answered either yes or no; with each yes, the study is scored 1 point and no scored 0 points. For well-described method of randomisation and blinding, additional

Table 3 Jadad scores of included studies

Study	Randomization (max points 2)		Blinding (max points 2)		Account of all patients in the trial (max 1 point)	Total points
Author/year	Randomization mentioned	Method of randomization appropriate	Blinding mentioned	Method of blinding appropriate		
Schreuder et al. (2012)	1	1	1	1	1	5
Sakalli et al. (2012)	1	1	1	1	0	4
Warner et al. (2008)	1	1	1	1	1	5

points are given respectively. However, 1 point each was deducted if the described method of randomisation and blinding was incorrect. Clinical trials scoring more than 3 are considered as high quality (refer Table 3).

Data analysis

Meta-analysis of the standardised mean differences (SMDs), and their standard errors, in VAS scores was performed between vitamin D-treated and placebo-treated groups. SMD has several versions such as Cohen's *d* [23], Glass's Δ [24] and Hedges' *g* [25]; however, we have used the simple SMD which is the ratio of the mean difference and the standard deviations. The value SMD less than 0.5 is considered to be small effect, from 0.5 to 0.8 medium effect and greater than 0.8 large effect [26]. Summary effect estimates were calculated with the fixed effects models. Analysis was performed in Stata, version 12.1, software (StataCorp LP, College Station, TX) using the metan commands [27]. The heterogeneity between studies was assessed by computing the I2 statistics. A value of 0 inferred no heterogeneity, and value above 50 % is recognised as substantial heterogeneity [26]. Following Bailey [28], we used fixed effects model, as the objective of this study is to test whether the intervention has produced an effect in a set of homogenous studies. In the fixed effects model, we weighted the data by the amount of information (inverse of the variance of the study) that is captured by the study.

Results

The initial search located 101 studies from the databases (PubMed 14, Embase 20, Web of Science 19, Cochrane Library 45 and Scopus 9). After reviewing the title, the abstract and removal of the duplicates, ten studies were identified for potential inclusion (Fig. 1). Full text of these articles was reviewed and assessed. Of these ten articles, seven were excluded because they did not meet our selection criteria of study design, thus leaving us with only three studies, for conducting the systematic review [29–31]. These three studies used a RCT study design to investigate the effect of vitamin D supplementation (treatment group) compared to a placebo (control group) in CNMP patients.

The characteristics of the selected studies are described in Table 2. The three studies included in the meta-analysis evaluated 492 participants in total. The participants were generally adults with their mean ages ranging from 41 to 76 years. The majority of participants in all studies were females. All studies measured pain, and one study also measured functional mobility and quality of life. Study sample sizes ranged from 84 to 288 subjects. All three studies used VAS to measure changes in pain (outcome); in addition, studies also used the timed up and go test (TUG) [29], functional pain scores (FPS) [31] and Likert scales [30]. All studies used oral route for administering vitamin D except Sakalli et al. study which, in addition. also used intramuscular route for administering vitamin D. This is reflected in the Fig. 2 which shows four studies namely study A, Schreuder et al. study; study B_1, Sakalli et al. oral vitamin D supplementation group; study B_2, Sakalli et al. intramuscular vitamin D supplementation group; and study C, Warner

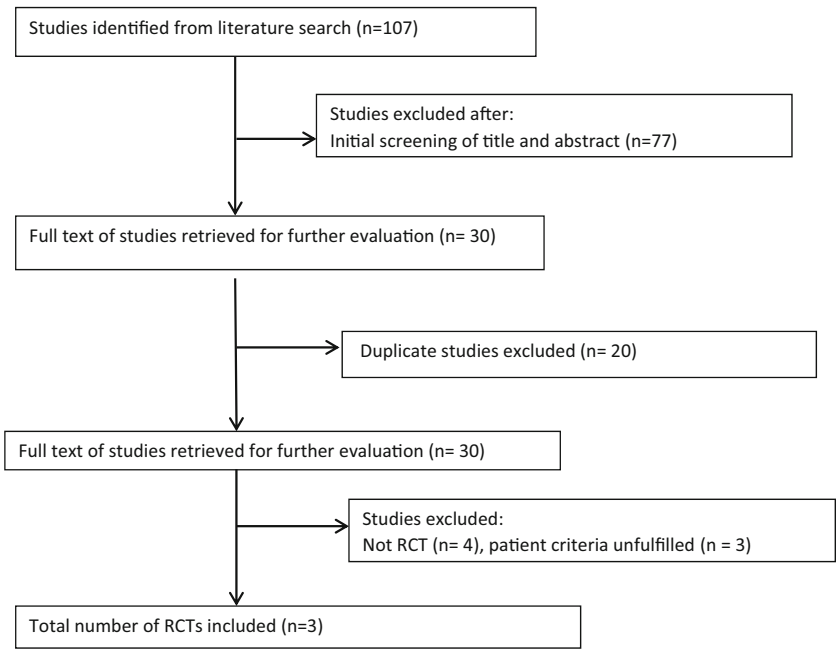

Fig. 1 Flow chart diagram of study selection

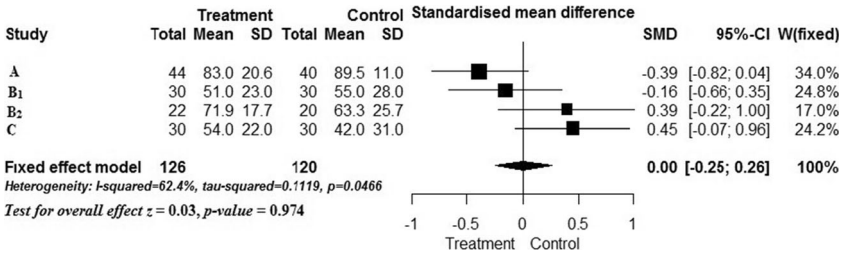

Fig. 2 Forest plot using fixed effects model

et al. study. We did this to test if the mode of administration influenced the strength of the clinical effect. The trial period of selected studies was 4 weeks [29] and 12 weeks [32, 33]. Of the three included studies, only one study reported that none of the participants experienced adverse events during the trial or in the follow-up period [30]. In general, all studies scored highly on methodological quality with two studies scoring 5 and one study scoring 4 (Table 3).

Out of the three selected studies, two showed reduction in pain, following treatment with single mega-dose vitamin D supplementation [29, 30], and one showed no effect on pain following vitamin D supplementation [31].

Meta-analysis result

The results from meta-analysis are presented in the forest plot (Fig. 2). The horizontal lines, depicting the length of confidence intervals, for study A and study B_1 are on treatment side indicating a modest effect of the intervention on pain in CNMP patients, while for study B_2 and study C, the lines are on control side representing no effect of intervention. The overall effect (represented by black diamond in Fig. 2) lies on the line of no effect, indicating that the average effect size of the pooled analysis is 0. The I2 statistic is 62.4 %, indicating a moderate level of heterogeneity in the pooled analysis, which confirms that the variation is not due to chance. The overall pooled SMD was 0 with confidence interval (CI) ranging between −0.25 and 0.26, p value = 0.97, indicating that the intervention has no clinical effect on the CNMP (Fig. 2). The test for overall effect is not statistically significant.

To split the variance as within- and between-study variance, we also analysed data using random effects model (Fig. 3). The overall pooled SMD was 0.05 with CI ranging from −0.37 to 0.46, I2 = 61.4 and p value = 0.05 reiterating no statistical significance.

Discussion

We aimed to evaluate the evidence concerning the effect of vitamin D supplementation, when compared in a RCT to a placebo, on pain in people with CNMP. Our results are in contrast to the prevailing clinical opinion [1, 17, 32] insofar as they suggest that vitamin D supplementation does not decrease pain in CNMP, when compared to a placebo. Our results also show, however, that robust RCT data are perhaps more limited than would be assumed: despite a comprehensive search strategy, only three RCTs, with total of 492 participants, satisfied our a priori criteria. The included trials composed of participants aged between 41 and 76 years with vitamin D levels of 20 nmol/L or less. A range of doses of vitamin D were administered in each included trial, but there was no evidence of a dose-response relationship.

The current study raises new questions for the investigation of CNMP. Our results clearly suggest that vitamin D supplementation is not helpful for CNMP. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [33], we suggest that there is low to moderate evidence (one high-quality study or several studies with some limitations but consistent results) [33] that vitamin D supplementation is not helpful for people with CNMP.

It is notable that the proposed mechanisms by which vitamin D deficiency might contribute to CNMP—disruption of calcium homeostasis and a loss of anti-inflammatory, anti-apoptotic or anti-fibrotic effects [13, 14]—imply that the primary cause of CNMP lies within the tissues of the body. Although such mechanisms seem intuitive, they are not necessarily consistent with

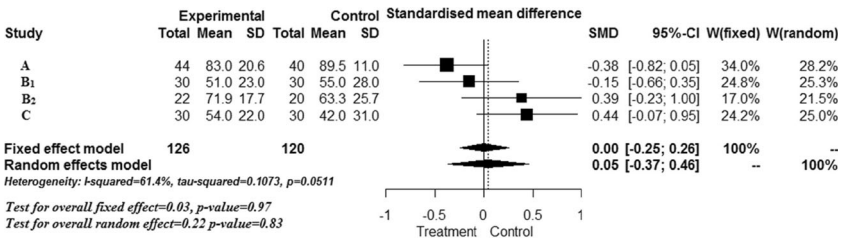

Fig. 3 Forest plot using random effects model

modern models of CNMP and other chronic pain conditions. Although vitamin D deficiency, through disruption of immune regulation [13, 14], could disrupt the neuroimmunological processes that subserve pain [34], the assumption that this would increase pain rather than decrease it remains to be properly tested. The prevailing theories with regard to chronic pain place greater emphasis on enhanced sensitivity within the nociceptive system [35], increased contribution of non-nociceptive sensory inputs and associative learning [36], and cognitive mechanisms that emphasise perceived threat to body tissue and behavioural processes linking fear of pain, activity avoidance and catastrophising [37] and de-emphasise ongoing tissue pathology or damage (with some exceptions, for example, seronegative arthropathies) [38]. Indeed, CNMP is widely considered to be influenced by a wide range of biological, physical, psychological and social factors [7] and management approaches reflect this biopsychosocial framework [39, 40]. Perhaps, vitamin D supplementation might play a more important role in painful conditions that more obviously relate to tissue inflammation, for example, rheumatoid arthritis, although this remains to be determined.

The biological complexity of vitamin D effects leaves open the possibility that supplementation could offer benefit for people with CNMP and that the current research base is not sufficient to detect it. That is, protocols of the RCTs may have led to inadequate rise in serum vitamin D levels postsupplementation [41] due to noncompliance, although one might argue that such interventions are really "advice to take a particular action" rather than the action itself [42]. Different effects may also relate to heterogeneity of body mass index (BMI) between participants. Alternatively, standard doses of vitamin D supplementation may not always produce predictable increases in the vitamin D levels [41] or predictable rates at which vitamin D level changes [43], potentially masking positive effects. That other study designs, for example, clinical studies [1], observational [18], cross-sectional and case report studies [17], have demonstrated moderate benefit following supplementation may reflect an advantage of tailored supplementation regimes (although considering the findings of such studies, one should remember that these study designs are highly vulnerable and may overestimate true effects) [44].

The relative paucity of RCTs comparing vitamin D supplementation to placebo is surprising, considering the widespread clinical endorsement of the idea. The available data are also not very generalisable to all ages because most studies have investigated primarily postmenopausal women and compared nonstandard doses for which there is little justification. Estradiol is recognised as a physiological predictor of vitamin D binding protein [45], and postmenopausal women show a higher natural decline in vitamin D levels than premenopausal women [46], suggesting that it would be important to investigate the variance in vitamin D levels in premenopausal women with depleting estradiol levels as well as in younger women with normal estradiol levels. Furthermore, CNMP is highly prevalent in children and adolescents, but this group has not been investigated with regard to vitamin D.

There are several considerations, strengths and limitations of the current study. We included the Warner et al. study [31] even though they diagnosed participants with primary fibromyalgia, not CNMP. On closer appraisal, the participants in their study did not satisfy the ACR criteria for fibromyalgia but did satisfy criteria for CNMP. The strengths of this study are its focus on CNMP and inclusion of meta-analysis, as was recommended in a recent Cochrane review [19]; the absence of language or publication restrictions, giving confidence that we did not miss important studies; and the confinement of included studies to those that used a RCT design, because they provide the most rigorous method of verifying if a cause-effect relationship exists between the intervention and outcome [47]. We used SMD score to evaluate the clinical relevance and CI for inference because it focuses on the probability and significance of the intervention and helps to establish the clinical and statistical significance of the findings [48]. There are also limitations: the forest plot shows variability between the studies, and broad 95 % CIs show the imprecision of the results, a common problem with small sample sizes [48]. The most significant limitation is indeed the lack of source literature, which is particularly pertinent to the field because it contrasts with popular clinical belief.

This study shows that there is no proven effect of vitamin D supplementation on pain in people with CNMP, when compared to a placebo. We conclude that there is GRADE C (low) to level B (moderate) evidence that vitamin D supplementation is not helpful for people with CNMP. Clearly, more robust and nuanced RCTs might have an important impact on our confidence in the estimate of effect [33].

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Compliance with ethical standards

Conflict of interest MG, SV, MM and NS declare that they have no conflict of interest. GLM—Noigroup Publications royalties, speaker's fees and Pfizer consultancy. This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Kumar A, Gopal H, Khamkar K et al (2012) Vitamin D deficiency as the primary cause of musculoskeletal complaints in patients referred to rheumatology clinic: a clinical study. Indian J Rheumatol 7:199–203
2. O'Sullivan P, Beales D, Jensen L, Murray K, Myers T (2011) Characteristics of chronic non-specific

musculoskeletal pain in children and adolescents attending a rheumatology outpatients clinic: a cross-sectional study. Pediatr Rheumatol Online J 9:3
3. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JHB, Brouwer S (2012) Factors promoting staying at work in people with chronic nonspecific musculoskeletal pain: a systematic review. Disabil Rehabil 34:443–58
4. Konijnenberg AY, Uiterwaal CS, Kimpen JL, van der Hoeven J, Buitelaar JK, Graeff-Meeder ER (2005) Children with unexplained chronic pain: substantial impairment in everyday life. Arch Dis Child 90:680–6
5. Guite J, Logan D, Sherry D, Rose J (2007) Adolescent self-perception: associations with chronic musculoskeletal pain and functional disability. J Pain 8:379–86
6. de Vries HJ, Reneman MF, Groothoff JW, Geertzen JH, Brouwer S (2013) Self-reported work ability and work performance in workers with chronic nonspecific musculoskeletal pain. J Occup Rehabil 23: 1–10
7. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC (2007) The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 133:581–624
8. Perquin C, Hunfeld J, Hazeborek-Kampschreur A et al (2003) The natural course of chronic benign pain in childhood and adolescence: a two-year population-based follow-up study. Eur J Pain 7:551–9
9. Perquin C, Hunfeld J, Hazeborek-kampschreur A et al (2001) Insights in the use of health care services in chronic benign pain in childhood and adolescence. Pain 94:205–13
10. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M (2004) Prognosis of non-specific musculoskeletal pain in preadolescents: a prospective 4-year follow-up study till adolescence. Pain 110:550–9
11. Plotnikoff GA, Quigley JM (2003) Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 73:1463–70
12. Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG (2011) Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. J Neurosci 31: 13728–38
13. Lai Y-H, Fang T-C (2013) The pleiotropic effect of vitamin D. ISRN Nephrol Article ID 898125
14. Zittermann A (2003) Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 89:552–72
15. Lyman D (2005) Undiagnosed vitamin D deficiency in the hospitalized patient. Am Fam Physician 71:299–304
16. Body JJ, Bergmann P, Boonen S et al (2012) Extraskeletal benefits and risks of calcium, vitamin D and anti-osteoporosis medications. Osteoporos Int 23(Suppl 1):S1–23
17. Chaudhary WA, Arshad SH, Waqas S et al (2013) Vitamin D supplement as an adjuvant in the management of chronic musculoskeletal pain. Anaesth Pain Intensive Care 17:296–300
18. Knutsen KV, Brekke M, Gjelstad S, Lagerløv P (2010) Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. Scand J Prim Health Care 28:166–71
19. Straube S, Derry S, Straube C, Moore RA (2015) Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev
20. Guyatt G, Gutterman D, Baumann MH et al (2006) Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest 129:174–81
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PloS 6
22. Jadad AR, Moore A, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
23. Cohen J (2013) Statistical power analysis for the behavioral sciences. Academic Press
24. Glass GV (1976) Primary, secondary, and meta-analysis of research. Educ Res 5:3–8
25. Hedges LV, Olkin I (2014) Statistical method for meta-analysis. Academic press
26. Higgins PT, Green S (2008) Cochrane handbook for systematic reviews of interventions. Wiley-Blackwell, Chichester, England
27. StataCorp (2011) Stata Statistical Software: Release 12. StataCorp LP, TX
28. Bailey KR (1987) Inter-study differences: how should they influence the interpretation and analysis of results. Stat Med 6:351–60
29. Sakalli H, Arslan D, Yucel AE (2012) The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. Rheumatol Int 32:2279–83
30. Schreuder F, Bernsen RM, van der Wouden JC (2012) Vitamin D supplementation for nonspecific musculoskeletal pain in non-western immigrants: a randomized controlled trial. Ann Fam Med 10:547–55
31. Warner AE, Arnspiger SA (2008) Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. J Clin Rheumatol 14
32. Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H (2015) A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. Lupus 24:483–9
33. Guyatt G, Oxman AD, Vist GE et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J 336:924
34. Grace PM, Hutchinson MR, Maier SF, Watkins LR (2014) Pathological pain and the neuroimmune interface. Nat Rev Immunol 14:217–31
35. Woolf CJ (2014) What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain? Pain 155:1911–2
36. Moseley GL, Vlaeyen JWS (2015) Beyond nociception: the imprecision hypothesis of chronic pain. Pain 156:35–8
37. Vlaeyen JWS, Linton SJ (2012) Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain 153:1144–7
38. Moseley GL, Butler DS (2015) Fifteen years of explaining pain: the past, present, and future. J Pain 16:807–13
39. Butler DS, Moseley GL (2013) Explain pain, 2nd edn. Noigroup Publications, Adelaide
40. Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JW, Moseley GL (2014) Contingency learning deficits and generalization in chronic unilateral hand pain patients. J Pain 15:1046–56
41. Ryan PJ (2007) Vitamin D therapy in clinical practice. One dose does not fit all. Int J Clin Pract 61:1894–9
42. Moseley GL (2006) Do training diaries affect and reflect adherence to home programs? Arthritis Rheum 55:662–4
43. Abbasi M, Hashemipour S, Hajmanuchehri F, Kazemifar AM (2013) Is vitamin D deficiency associated with non specific musculoskeletal pain? Glob J Health Sci 5
44. O'Connell NE, Moseley GL, McAuley JH, Wand BM, Herbert RD (2015) Interpreting effectiveness evidence in pain: short tour of contemporary issues. Phys Ther 95:1087–94
45. Pop LC, Shapses SA, Chang B, Sun W, Wang X (2015) Vitamin D-binding protein in healthy pre- and postmenopausal women: relationship with estradiol concentrations. Endocr Pract 21:936–42

46. Kanwar G, Sharma N, Shekhawat M, Sharma P, Hada R, Chandel CS (2015) Comparison of vitamin D levels in pre and post menopausal type 2 diabetic females. IOSR-JDMS 14:70–3
47. Kendall JM (2003) Designing a research project: randomised controlled trials and their principles. Emerg Med J 20:164–8
48. Sim J, Reid N (1999) Statistical inference by confidence intervals: issues of interpretation and utilization. Phys Ther 79:186–95

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STUDY PROTOCOL

Understanding patient perspectives on management of their chronic pain – online survey protocol

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Background: It is widely recognized that both doctors and patients report discontent regarding pain management provided and received. The impact of chronic pain on an individual's life resonates beyond physical and mental suffering; equal or at times even greater impact is observed on an individual's personal relationships, ability to work, and social interactions. The degree of these effects in each individual varies, mainly because of differences in biological factors, social environment, past experiences, support, and belief systems. Therefore, it is equally possible that these individual patient characteristics could influence their treatment outcome. Research shows that meeting patient expectations is a major challenge for health care systems attempting to provide optimal treatment strategies. However, patient perspectives and expectations in chronic pain management have not been studied extensively. The aim of this study is to investigate the views, perceptions, beliefs, and expectations of individuals who experience chronic pain on a daily basis, and the strategies used by them in managing chronic pain. This paper describes the study protocol to be used in a cross sectional survey of chronic pain patients.

Methods and analysis: The study population will comprise of individuals aged ≥18 years, who have experienced pain for ≥3 months with no restrictions of sex, ethnicity, or region of residence. Ethics approval for our study was obtained from Humans research ethics committees, University of Adelaide and University of South Australia. Multinomial logistic regression will be used to estimate the effect of duration and character of pain, on patient's perception of time to recovery and supplement intake. Logistic regression will also be used for estimating the effect of patient-provider relationship and pain education on patient-reported recovery and pain intensity.

Discussion: Knowledge about the perceptions and beliefs of patients with chronic pain could inform future policies, research, health care professional education, and development of individualized treatment strategies.

Keywords: chronic pain, pain management, patient perspectives, survey, time to recovery

Introduction

The International Association for the Study of Pain (IASP) defines chronic pain as "pain that persists beyond the normal tissue healing time, usually ≥3 months", in the absence of an obvious underlying biological cause.[1] With nearly 20% of the population affected worldwide, chronic pain has become a disease in its own right, rather than just being considered a symptom.[2–5] Furthermore, chronic pain is often associated with numerous physical and psychological complications such as disability, sleep disturbances, fatigue, depression, and social isolation. The traditional approach for managing an injury or other illness of diagnosis and treatment offers little hope to individuals experiencing

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chronic pain by trapping patients with chronic pain in a vicious cycle of trial and error treatments. Both patients and their doctors struggle with pain management with studies reporting a feeling of inadequacy about providing optimal treatment among physicians[6–8] and dissatisfaction among patients concerning the treatments provided.[9]

Studies show that between 40% and 60% of the general population use dietary supplements to promote health and manage conditions.[10–12] Approximately 33% of those who use supplements quote pain as the primary reason.[11] However little is known about their benefits as perceived by patients with chronic pain. Moreover, pain is a subjective sensory emotional experience,[13] which may be influenced by an individual's biological, environmental, social, and psychological factors. Together with belief systems and expectations, these factors may also guide individual experiences, and influence treatment outcome(s). Even though studies report factors which predict chronic pain,[14,15] their association with patients' perspectives of chronic pain and its management has not been studied extensively. In addition, meeting patients' expectations is an important objective for health care systems[16] as it appears to improve treatment satisfaction between 8% and 25%.[17,18] Aligning patient expectations with a management plan can enhance treatment outcome and benefits.

Best practice insight recommends publishing a protocol prior to undertaking the study as it facilitates awareness of the research in progress.[19] It also helps to maintain the transparency in reporting of the study.[20,21] This paper describes the protocol and the questionnaire used in a cross-sectional survey of individuals who experienced pain for ≥3 months.

Aim and objectives

The aim of this study protocol is to investigate the views, perceptions, beliefs, and expectations of individuals who experience chronic pain on a daily basis, and the strategies used by them in managing this pain. The objectives of this study protocol are to investigate if pain-related factors (such as duration and characteristics) and pain education, affects chronic pain patients' intake of supplements and perception of recovery. This study will also examine if health professionals support, and pain education to family and employer is related to pain intensity and perception of time for recovery in patients with chronic pain.

Methods

Design

An online survey method was selected for this study as it is cost-effective and easy to administer; unlike face-to-face interviewing, a survey provides a standardized approach allowing uniformity of questions asked to all participants. It also provides access to individuals without geographical dependency thus allowing the collection of rich data.[22] Although online surveys may limit participation from individuals without access to the internet[23] the advantages of this method have been shown to outweigh the disadvantages in terms of external validity.[24]

A questionnaire was designed specifically for this study following the checklist for reporting results of internet e-surveys (CHERRIES) protocol[25] for the ethical reporting of surveys and was administered online using Survey Monkey. Ethics approval for this study was obtained from the Human Research Ethics Committee of the University of Adelaide (approval no: HREC-2016-0712) and the University of South Australia (application id: 0000035791).

Recruitment

The survey was advertised on multiple educational, basic, and clinical science websites and on social media in different countries, including Australia, Ireland, India, New Zealand and the US. Individuals accessing these websites were invited to participate in the study if they met the inclusion criteria. The survey was open for participants from all ethnicities and regions of residence. Data collection ceased by the end of October 2016. All participants activated an electronic consent prior to beginning the survey.

Inclusion criteria

Individuals for inclusion in the survey should be: 1) currently aged 18 years and above and 2) must have experienced pain ≥3 months duration.

Exclusion criteria

Individuals are not eligible to participate in the survey if: 1) their current age is below 18 years; 2) they suffer from acute pain of <3 months duration; and 3) they do not consent to be a part of the survey study.

Consent and confidentiality

Individuals who click the link to participate in the study are first taken to an information page. The information page describes the proposed study, its relevance and also outlines what type of information will be asked from the participants and the time required to complete the survey. The information page notifies the participants that the survey is voluntary and their choice of participating or not participating will have no effect on their own pain management in any way. It also

provides the participants with information regarding whom to contact in case of distress or if they have a complaint. The information page also explains that the survey is completely anonymous – information that could disclose the participant's identity is never asked at any stage during the survey.

Data storage and handling

The data was stored on a secure computer owned by University of Adelaide, with password-controlled access. Only the research team (all authors listed) had access to the data.

Sample size

Sample size calculations for estimation are based on three parameters, the variance or spread of the observations, the precision and the level of significance, or probability of type-1 error.

$$n = \left(\frac{1.96^2 P(1-P)}{\delta^2} \right)$$

where n=sample size, P=estimated population proportion, δ= precision of the estimate.

For this sample size estimation, the values chosen were P=0.5 and δ=0.05. Thus, it gives a sample size of 384 with 95% confidence interval and 80% power. This is the simple random sampling approach.[26]

Questionnaire development

Currently, there are very few studies examining the perspectives and the expectations of individuals who experience chronic pain regarding their pain management. Due to the unavailability of validated scales of chronic pain patients' perspectives, this questionnaire was developed by the team of authors through discussions and literature search. The questionnaire (Supplementary material) comprises of 5 sections and 39 items in total. A pilot study to verify the face and content validity of the questionnaire was conducted prior to finalizing it.[27]

Analysis

Statistical analysis plan

All analyses will be performed using STATA 14.1 Statistical software Release 12.

Multinomial logistic regression will be performed to estimate the effect of duration and character of pain; education about pain and variation in supplement intake on chronic pain patients' perception of time to recovery. Univariate logistic regression will be used to examine the effect of support received from health professionals, family, and employers on chronic pain patients pain levels, quality of life, and physical goals. The analysis will be adjusted for confounding factors such as age, sex, education, employment, and marital status.

Simple descriptive statistics such as mean, proportions, and variances will be described for the entire sample. Participants will be described in terms of pain duration, average length of their consulting time and frequency of visits, and satisfaction about their education and involvement in pain management.

Measures

Dependent variables/outcomes

1. Patients' perception of time to recovery. Information regarding participants' perceived time to recovery from their current pain problem will be collected.
2. Supplement intake. Information regarding each participant's intake of complementary medicines or dietary supplements (eg, calcium, magnesium, fish oil) and alternative medicines (eg, Chinese, herbal, Ayurvedic) will be collected, in addition to information regarding testing of vitamin D, vitamin D deficiency, and vitamin D supplementation.

Independent variables/confounders

1. Demographic data. Information regarding each participants' age, sex, area of residence, education, employment, and marital status will be collected.
2. Pain history. Information pertaining to each participants' history of current pain problem such as diagnosis received, duration, character, and intensity of pain will be collected.
3. Pain education. Information regarding method of education received, provider of education and influence of education on understanding, and management of pain will be collected.
4. Goals from pain management. The goals from pain management are classified into pain related outcomes; quality of life and physical functioning. Information pertaining to each classification will be collected.
5. Other variables. Information regarding each participant's most recent health care consultation, as well as information regarding provision of pain education to their family and employers, and its perceived impact on their recovery time will be collected.

Dissemination

The results from this survey analysis will be included as a chapter in MG's thesis and published in peer-reviewed

scientific journals as well as used for conference presentations. The results of the study will be made available via the institutional websites.

Discussion

We aim to better understand whether patients' perspectives, views, and beliefs about their chronic pain management are associated, with perception of time to recovery and particularly with reference to testing and prescription of supplements. Moreover, the study has been promoted internationally and it is anticipated that the analysis will capture the variability of patients' perceptions and beliefs across countries (if the distribution of the sample obtained allows subgroup analysis). It is also expected that the results from the survey study will provide insight about what patients with chronic pain expect from their pain management and how these expectations are challenged by the duration of pain, the character of the pain, the quality of pain education, and support of health professionals. A deeper understanding of patients' perceptions with regards to their pain management will enable researchers, policy makers, and health professionals to design policies, interventions and prevention strategies which are tailored to individual patient needs and are intended to improve the treatment outcome.

This study will also provide information on intake of complementary and alternative medicines, dietary supplements, nonpharmacological therapies, and educational sources most frequently used by the chronic pain patients for managing their pain. It is also anticipated that this evidence-based knowledge will describe the self-management strategies most frequently implemented by chronic pain patients.

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References

1. Merskey H, Bogduk N. *Classification of Chronic Pain*. Seattle: IASP Press 1994.
2. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain.* 2006;10(4):287–287.
3. Henderson JV, Harrison CM, Britt HC, Bayram CF, Miller GC. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. *Pain Med.* 2013;14(9):1346–1361.
4. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anesth*. 2013;111(1):13–18.
5. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. *Pain.* 2001;89(2):127–134.
6. Green CR, Wheeler JR, Marchant B, LaPorte F, Guerrero E. Analysis of the physician variable in pain management. *Pain Med*. 2001;2(4):317–327.
7. Potter M, Schafer S, Gonzalez-Mendez E, et al. Opioids for chronic nonmalignant pain. *J Fam Pract*. 2001;50(2):145–145.
8. Upshur CC, Luckmann RS, Savageau JA. Primary care provider concerns about management of chronic pain in community clinic populations. *J Gen Intern Med.* 2006;21(6):652–655.
9. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *The Lancet.* 2011;377(9784):2226–2235.
10. Astin JA. Why patients use alternative medicine: results of a national study. *JAMA.* 1998;279:1548–1553.
11. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Semin Integr Med.* 2004;2(2):1–19.
12. O'Dea JA. Consumption of nutritional supplements among adolescents: usage and perceived benefits. *Health Educ Res.* 2003;18(1):98–107.
13. International Association for the Study of Pain. [webpage on the Internet]. Pain, IASP Pain Terminology. Available from: http://www.iasp-pain.org/Taxonomy?navItemNumber=576#Pain. Accessed October 6, 2016.
14. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet.* 1999;354(9186):1248–1252.
15. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain*. 2006;7(4):281–289.
16. World Health Organization. The World Health Report–Health Systems: Improving Performance (Electronic edition). Geneva. 2001. Available from: http://www.who.int/entity/whr/2000/en/whr00_en.pdf?ua=1. Accessed March 10, 2016.
17. Oliver RL. Cognitive, affective, and attribute bases of the satisfaction response. *J Consum Res*. 1993;20(3):418–430.
18. Williams B. Patient satisfaction: a valid concept? *Soc Sci Med*. 1994;38(4):509–516.
19. Ohtake PJ, Childs JD. Why publish study protocols? *Phys Ther*. 2014;94(9):1208–12099.
20. West R. Trial protocols. *Addiction*. 2012 Sep 1;107(9):1544. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2012.03989.x/full. Accessed March 10, 2016.
21. Ohtake PJ, Childs JD. Why publish study protocols? *Physical Therapy.* 2014;94(9):1208–1209.
22. Wyse SE. Advantages and Disadvantages of Surveys. *Retrieved February* 20 (2012): 2014. Available from: http://www.snapsurveys.com/blog/advantages-disadvantages-surveys/. Accessed October 5, 2016.

23. Szolnoki G, Hoffmann D. Online, face-to-face and telephone surveys – comparing different sampling methods in wine consumer research. *Wine Econ Policy.* 2013;2(2):57–66.
24. Heen MS, Lieberman JD, Miethe TD. A comparison of different online sampling approaches for generating national samples. UNLV, Center for Crime and Justice Policy. 2014. University of Nevada, Las Vegas.
25. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res*. 2004;6(3):e34
26. Cochran WG. *Sampling Techniques*. Hoboken: John Wiley & Sons, 2007.
27. Nardi PM. *Doing Survey Research*. Oxford: Routledge, 2015.

Survey Questionnaire

1 Demographic Information

1.1 Age (years)

☐ 18-30 ☐ 31-40 ☐ 41-50 ☐ 51-60 ☐ 61-70 ☐ 71-80 ☐ 81-90 ☐ 90+

1.2 Sex

☐ Female ☐ Male ☐ Prefer not to say

1.3 Region of residence

☐ Australia ☐ North America ☐ South America ☐ Europe

☐ Asia ☐ Africa ☐ New Zealand

☐ Other (please specify)

1.4 Level of education

☐ Primary ☐ Secondary ☐ Tertiary

☐ Post graduate ☐ Other education

1.5 Are you currently employed?

☐ Yes ☐ No ☐ Prefer not to say

1.6 What best describes your current work status?

☐ Full time paid employment ☐ Part time paid employment ☐ Retired

☐ Unemployed due to pain ☐ Unemployed (not pain related) ☐ Home duties

☐ On leave from work due to pain ☐ Studying ☐ Other

1.7 What is your marital status?

☐ Married ☐Partnered ☐ Unmarried ☐ Single ☐ Prefer not to say

2 Medical History

2.1 Have you received any of the following diagnosis for your current pain problem (tick all that apply)?

☐ Osteoarthritis ☐ Rheumatoid arthritis ☐ Fibromyalgia

☐ Chronic Fatigue ☐ Chronic widespread pain ☐ Lower back pain

☐ Neck pain ☐ Migraines ☐ Headaches

☐ Pelvic pain ☐ No specific diagnosis but experience pain

2.2 Do you take any of the following supplements *for your current pain problem*?

☐ Calcium ☐ Vitamin D ☐ Fish oil ☐ Magnesium ☐ Ayurveda medicines

☐ Chinese medicine ☐ Herbal medicines ☐ other

2.3 Do you take any of the following supplements *for any other reason*?

☐ Calcium ☐ Vitamin D ☐ Fish oil ☐ Magnesium ☐ Ayurveda medicines

☐ Chinese medicine ☐ Herbal medicines ☐ other

2.4 Do you take any of the following supplements *because you were advised by a health care professional to do so?*

☐ Calcium ☐ Vitamin D ☐ Fish oil ☐ Magnesium ☐ Ayurveda medicines

☐ Chinese medicine ☐ Herbal medicines ☐ other

2.5 Have you ever been tested for Vitamin D levels?

☐ Yes ☐ No

2.6 If yes, have your test results for Vitamin D ever been deficient?

☐ Yes ☐ No ☐ not applicable

2.7 If yes, have you ever been told that it may contribute to your current pain problem?

☐ Yes ☐ No ☐ not applicable

3 The Pain Questionnaire

3.1 Was your current pain problem triggered by an injury?

☐ Yes ☐ No

3.2 How long has the pain been present?

☐ Less than 6 months ☐ 6- 12 months ☐ >12 months

3.3 What best describes the character of your pain? (tick all that apply)

☐ Aching ☐ Burning ☐ Cold ☐ Electric shocks ☐ Dull ☐ Hot

☐ Flushed ☐ Lightning-like ☐ Tingling ☐ Numb ☐ Pins & Needle ☐ Sharp

☐ Stabbing ☐ Throbbing ☐ Ants crawling ☐ Other

3.4 Over the past 2 days what's the average severity of your pain on a scale of 1-10

(0= no pain, 10 = severe/ worst pain)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

4. Pain experience

4.1 How well do you understand the cause of your pain?

(0 = I do not understand at all, 10 = I understand very well)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

4.2 Have you received any education about your pain?

☐ Yes ☐ No

4.3 If yes, was this education provided in person by any of the following professional?

☐ General Practitioner ☐ Nurse Practitioner ☐ Pain Physician ☐ Physiotherapist

☐ Chiropractor ☐ Massage therapist ☐ Pharmacist ☐other (please specify)

☐ Not applicable

4.4 Have you been referred to any of the following types of education material about pain?

☐ Book ☐ Website ☐ video ☐ YouTube ☐ Audio book ☐ Smart phone App

☐ Pamphlets/Brochure ☐Not applicable

4.5 What was the most helpful type of education?

☐ Book ☐ Website ☐ video ☐ YouTube ☐ Audio book ☐ Smart phone App

☐ Pamphlets/Brochure ☐ Not applicable

4.6 How helpful was this education? (0= not helpful; 5= very helpful)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

4.7 Did the education change the way you think about your pain?

☐ Yes ☐ No

4.8 Did the education change the way you manage your pain?

☐ Yes ☐ No

4.9 Did you receive any information about your pain treatment options?

☐ Yes ☐ No

4.10 How helpful was this information? (0= not at all helpful; 5 = extremely helpful)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

4.11 How satisfied you were about your involvement in the decision about your pain treatment strategy? (0= not satisfied all, 10 = very satisfied)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

4.12 Regarding the most recent health care consultation for your current pain problem, was the appointment duration?

☐ Too long ☐ Just right ☐ Not long enough ☐ Not applicable

4.13 How frequent are your consultations with medical health professional?

☐Too frequent ☐Just right ☐Not frequent ☐ Not applicable

4.14 Do you use any non-medicine methods to relieve your pain?

☐ Yes ☐No

4.15 If yes, which of the following methods have you used?

☐Cold pack ☐ Heat ☐ Deep breathing ☐ Meditation ☐ Listen to music

☐ Distraction (TV/reading) ☐ Prayer ☐ Relaxation ☐Imagery ☐ Visualization

☐ Massage ☐Walking ☐Movement ☐ Other ☐ Not applicable

4.16 If yes, which have you found helpful?

☐Cold pack ☐ Heat ☐ Deep breathing ☐ Meditation ☐ Listen to music

☐ Distraction (TV/reading) ☐ Prayer ☐ Relaxation ☐Imagery ☐ Visualization

☐ Massage ☐Walking ☐Movement ☐ Other option not applicable

4.17 At your last consultation where any of the above non-medication methods recommended as a way to relieve pain?

☐ Yes ☐No

4.18 At your last health care consultation, how did you feel? (tick all that apply)

☐ Understood ☐ Believed ☐ Not taken seriously ☐ Dismissed ☐ Ignored

5. Outcome expectation

5.1 How long do you think it will take you to recover from your current pain problem?

☐ >3 months ☐ <6 months ☐ >6 months

☐ upto 1 year ☐ >1 year ☐ Never

5.2 What do you believe will help you achieve better treatment outcome?

☐ More frequent doctor visits ☐ Longer duration of doctor visits

☐ More education about pain ☐ Practical strategies for managing pain

☐ Learning how to set realistic goals ☐ More support from health care professionals

☐ Having a team approach to management ☐ Training in self-management of pain

☐ Education about your pain for your family member's

☐ Education about your pain for your employer

5.3 Choose the three top goals you want to achieve from your pain treatment?

☐ Less Pain ☐ No pain ☐ Improved quality of life

☐ Increase movement ☐ Improved activity levels ☐ Improved sleep

☐ Improved mood ☐ Less stress ☐ Going back to work

☐ Increase in social activities ☐ other

Table 1 NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question (including explanatory notes)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series