# Effects of obesity and diet induced weight loss on cardiovascular risk factors, vascular and ventricular structure and function, prostate symptoms and sexual function in obese men.

A thesis submitted to the University of Adelaide by

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# TABLE OF CONTENTS

## ABSTRACT

Obesity is a major epidemic and is increasing in prevalence worldwide. [1,2] The health problems and consequences of obesity include cardiovascular disease (CVD) risk factors, such as hypertension, hyperlipidemia, glucose intolerance and diabetes mellitus. [3, 4] Each of these abnormalities directly promotes atherosclerosis. More recently, visceral obesity has been shown to be independently associated with abnormalities of both the ventricular and vascular structure and function. The mechanisms by which they occur remain incompletely defined.

Cardiovascular magnetic resonance imaging (CMR) offers several advantages for evaluation of cardiac structure and function in the obese. The high accuracy and reproducibility of the technique allows for detection of very small changes in ventricular volumes, mass, ejection fraction, and cardiac output with a relatively small sample size, as compared with echocardiography. In this thesis we investigated whether cardiovascular magnetic resonance imaging can better characterize possible cardiac abnormalities associated with obesity, in the absence of other confounding comorbidities.

Obesity is associated with myocardial and vascular function, the extent of reversibility of these abnormalities with rapid acute weight loss remains uncertain. Therefore the first aim of the study was to (i) determine the relationship between obesity and left ventricular structure and function using magnetic resonance imaging, and (ii) the acute effects of rapid diet-induced weight loss on cardiac and vascular function in normal obese and obese diabetic men.

Erectile dysfunction is related to cardiovascular risk factors such as obesity by an impairment of endothelial function. Therefore, symptoms of erectile dysfunction are probably to precede cardiovascular disease and events. The second aim of this study was to (i) determine the relationship between obesity and erectile function (EF), sexual desire (SD), lower urinary tract symptoms (LUTS) and quality of life (QOL) measures in obese males, and (ii) determine the effects of rapid diet-induced weight loss on EF, SD, LUTS and QOL measures in normal obese and obese diabetic men. In this group of men, obesity was associated with mild/moderate erectile dysfunction, and significant LUTS, which together with sexual desire improved following rapid diet induced weight loss, but was not directly related to the amount of weight loss or changes in measured metabolic state.

Pericardial adipose tissue (PAT) covers 80% of the heart and constitutes 20% of its weight. PAT mass is related to the amount of abdominal fat and the risk of coronary atherosclerosis. Epicardial fat mass may be a sensitive indicator of cardiovascular risk. The third aim of this study was to (i) determine the relationship between obesity and PAT volume and (ii) effectively evaluate the impact of caloric restriction and associated weight reduction on epicardical fat volume via cardiac magnetic resonance imaging (CMR). This is the first study to show a reduction in PAT volume is associated with caloric restriction.

## DECLARATION OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Date:……

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AHA | American Heart Association |
| AF | Atrial fibrillation |
| BMI | Body mass index |
| BP | SF-36 domain: Bodily pain-intensity of bodily pain or discomfort |
| cFT | Calculated free testosterone |
| CHD | Coronary heart disease |
| CMR | Cardiac magnetic resonance |
| CRP | C-reactive protein |
| CT | Computed tomography |
| CV | Coefficient of variation |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| ECHO | Echocardiography |
| ED | Erectile dysfunction |
| EF | Ejection fraction |
| Em | Mitral annular early relaxation velocities |
| FAI | Free androgen index |
| FMD | Flow mediated dilatation |
| FOV | Field of View |
| fT | Free testosterone |
| GE | Gradient-echo |
| GH | SF-36 domain: General health-general health perceptions |

| | |
|---|---|
| HDL | High density lipoprotein |
| IIEF | International index of erectile function |
| IMVS | Institute of Medical and Veterinary Science |
| IMT | intimal–medial thickness |
| IPSS | International prostate symptom scale |
| IVRT | Isovolumic relaxation |
| LAP | Left atrial pressure |
| LCD | Low calorie diet |
| LDL | Low density lipoprotein |
| LUTS | Lower urinary tract symptoms |
| LV | Left ventricular |
| LVEDV | LV end diastolic volume |
| LVESV | LV end systolic volume |
| MH | SF-36 domain: Mental health-psychological distress and wellbeing |
| MRI | Magnetic resonance imaging |
| NTG | Nitroglycerin |
| OSA | Obstructive sleep apnoea |
| PAT | Pericardial adipose tissue |
| PC | phase contrast |
| PF | SF-36 domain: Physical function-limitations in physical activities because of health problems |
| PSLAX ED | Parasternal long view, end diastole |
| PSLAX ES | Parasternal long view, end systole |
| PSSAX ED | Parasternal short axis view, end diastole |

| | |
|---|---|
| PSSAX ES | Parasternal short axis view, end systole |
| QOL | Quality of life |
| RAH | Royal Adelaide Hospital |
| RDI | Recommended daily allowance |
| RE | SF-36 domain: Role emotional-limitations in usual role activities because of emotional problems |
| RP | SF-36 domain: Role physical-limitations in usual role activities because of physical health problems |
| RT3DE | Real time 3-dimensional echocardiography |
| RV | Right ventricular |
| SBP | Systolic blood pressure |
| SD | Sexual desire |
| SDI-2 | Sexual Desire Inventory 2 |
| SE | Spin echo |
| SEM | Standard error mean |
| SF | SF-36 domain: Social functioning-limitations in social activities due to physical or emotional problems |
| SF-36 | 36-item Short form health survey |
| SHBG | Sexual hormone binding globulin |
| SWT | Systolic wall thickening |
| T | Testosterone |
| TC | Total cholesterol |
| TDE | Tissue Doppler Echocardiography |

| | |
|---|---|
| TE | Echo time |
| TR | Repetition time |
| TrueFISP | Fast imaging with steady state free precession |
| TT | Total testosterone |
| TTE | Transthoracic Echocardiography |
| TVI | Tissue velocity imaging |
| VLCD | Very low calorie diet |
| VT | SF-36 domain: Vitality-energy and fatigue |
| W | Weight |
| WC | Waist circumference |
| WHO | World Health Organisation |

# CHAPTER 1

## 1. Introduction

### 1.1 Background

The World Health Organization (WHO) estimates that the prevalence of obesity has risen dramatically in the last ten years, from 200 million in 1995 to over 300 million in 2005. Approximately 1.1 billion people are overweight and it is expected that this total may rise to over 1.5 billion by 2015. [5, 6]

The prevalence of obesity has similarly reached epidemic proportions in Australia. Data from the Florey Adelaide Male Ageing Study indicates that in men over the age of 35 the prevalence of overweight and obesity as defined by body mass index is 82%. As defined by abdominal circumference the prevalence of overweight and obesity is 68%. The prevalence of metabolic syndrome is 55%. A recent nationwide survey has emphasised the burden of these conditions in the Australian men. [7]Data from the Florey Adelaide Male Ageing study also indicate that the major health consequences of obesity include: (i) an increase in the risk of cardiovascular disease directly, as well as a consequence of associated metabolic disturbances (abnormal glucose metabolism, dyslipidaemia, and inflammation), hypertension and obstructive sleep apnoea, and (ii) significant reproductive dysfunction including low testosterone levels, decreased libido, erectile dysfunction and significant lower urinary tract symptoms.

Recently the Framingham Heart study [8] determined that the risk of heart failure increased continuously with increasing body weight, with a 104% higher risk in the obese (BMI $\geq$ 30) compared to normal weight individuals (BMI 18.5-24.9).

Weight loss has been associated with improvements in metabolic status and vascular endothelial function (Wong et al 2006)[9]. However, the only convincing evidence of improvement in myocardial function has been obtained with substantial weight loss after surgical gastric bypass (Di Bello et al. 2008)[10].

Traditional weight loss programs utilize low-calorie diets that are a 600 kilocalories (kcal) energy deficit and encourage regular exercise. An alternative method which is used in selected individuals to provide rapid weight loss of approximately 10-12 % is the very low-calorie diet (VLCD). VLCDs are commercially prepared formulas of ~450 kcal that replace all usual food intake. VLCDs also contain the recommended daily requirements for vitamins, minerals, trace elements, fatty acids and protein. Very low calorie diets produce greater initial weight loss than other diets (9–26kg over 4-20 weeks). Whether this dietary approach has similar benefits for cardiovascular burden as the weight loss induced by surgery, and whether it is safe, particular when used for people with cardiovascular disease remains unclear.

## 1.2 Obesity

### 1.2.1 What causes overweight and obesity?

Overweight and obesity are caused by an energy imbalance, where energy intake exceeds energy expenditure over a considerable period of time. Hence good nutrition and adequate levels of physical activity play an important role in the prevention of further weight gain throughout the life cycle. Global increases in overweight and obesity are attributable to a number of factors. These include a global shift in diet towards increased intake of energy-dense foods that are high in fat and sugars but low in vitamins, minerals and other

micronutrients, and a trend towards decreased physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.[11]

### 1.2.2 How overweight and obesity are defined

Overweight and obesity is measured at the population level for adults using the Body Mass Index (BMI) which is calculated by dividing weight in kilograms by height in metres squared. These cut-off points are based on associations with chronic disease and mortality and have been adopted for use internationally by the World Health Organisation (Table 1.1).

**Table 1.1** Cut-off points proposed by a WHO expert committee for the Classification of overweight and obese caucasian adults. Reproduced from: Obesity: Preventing and Managing the Global Epidemic, 2000, WHO, Geneva.



Fat distribution is also an important consideration in assessing overweight or obesity and the associated risk of disease. For example, increased abdominal obesity has been consistently shown to be related to a higher risk of cardiovascular disease, type 2 diabetes and cancer.

Central (abdominal) obesity is measured using waist circumference. The following table provides sex specific waist circumferences and risk of metabolic complications associated with obesity in Caucasians (Table 1.2).

**Table 1.2** Sex-specific waist circumference and risk of metabolic complications associated with obesity in Caucasians.

| **Risk of metabolic complications** | **Waist circumference (cm)** | |
|---|---|---|
| | **Men** | **Women** |
| Increased | > or = 94 | >or = 80 |
| Substantially increased | > or = 102 | > or = 88 |

Reproduced from: Obesity: Preventing and Managing the Global Epidemic, 2000, WHO, Geneva.

These waist circumference cut-offs have significant variations between different ethnic groups. For example, cut-off points for Asians for the same level of risk would be lower than those above, and higher for Pacific Islanders.

### 1.2.3 Health consequences of overweight and obesity

The health problems and consequences of obesity are many and varied, including musculo-skeletal problems, cardiovascular disease, some cancers, sleep apnoea, type 2 diabetes, and hypertension. Many of these are often preventable through a healthy and active lifestyle. There are several large well conducted studies that have shown a clear relationship between excessive body weight and increased mortality and morbidity.[12] Mortality and morbidity are also associated with the amount of weight gained in adult life. For example, a weight gain of

10kg or more since young adulthood is associated with increased mortality, coronary heart disease, hypertension, stroke and type 2 diabetes (Table 1.3).[12]

**Table 1.3** Diseases associated with obesity

| **Relative risk** | **Associated with metabolic consequences** | **Associated with weight** |
|---|---|---|
| **Greatly increased** | Type 2 diabetes<br>Gall bladder disease<br>Hypertension<br>Dyslipidaemia<br>Insulin resistance<br>Atherosclerosis | Sleep apnoea<br>Breathlessness<br>Asthma<br>Social isolation/depression<br>Daytime sleepiness/fatigue |
| **Moderately increased** | Coronary heart disease<br>Stroke<br>Gout/hyperuricaemia | Osteoarthritis<br>Respiratory disease<br>Hernia<br>Psychological problems |
| **Slightly increased** | Cancer (breast, endometrial, colon)<br>Reproductive abnormalities<br>Impaired infertility<br>Polycystic ovaries<br>Skin complications<br>Cataract | Varicose veins<br>Musculo-skeletal problems<br>Bad back<br>Stress incontinence<br>Oedema/cellulitis |

### 1.2.4 Economic consequences of obesity

Overweight and obesity and their associated health problems have a significant economic impact on the health care system. Medical costs associated with overweight and obesity include direct and indirect costs (Wolf and Colditz, 1998[13]; Wolf 1998[14]). Direct medical costs may are those which cover preventive, diagnostic, and treatment services related to obesity. Indirect costs relate to morbidity and mortality costs. Morbidity costs are defined as the value of income lost from decreased productivity, restricted activity, absenteeism, and bed days. Mortality costs are the value of future income lost by premature death. Several studies have attempted to estimate the costs of obesity to the community. In the USA, direct costs of obesity have been estimated to be around 9% of the total health care costs and in Europe, between 1% and 5%.[15, 16] According to a study of national costs attributed to both overweight (BMI 25–29.9) and obesity (BMI greater than 30), medical expenses accounted for 9.1 percent of total U.S. medical expenditures in 1998 and may have reached as high as $78.5 billion ($92.6 billion in 2002 dollars) (Finkelstein, Fiebelkorn, and Wang, 2003)[17]. In Australia, Caterson (Caterson 2002[18], NHMRC, 1997[19]) and colleagues calculated that the direct cost of obesity in Australia is AU$830 million.

## 1.3 Obesity and Cardiovascular abnormalities

This section presents a review of the literature evaluating the association between overweight/obesity and cardiovascular disease (CVD).

### 1.3.1 Overweight and obesity and risk of CVD

The association between overweight and obesity and CVD risk has largely originated from analyses of the Framingham Heart Study. One of the earliest of these was by Hubert et al.

1983[20]. After 26 years of follow-up they concluded that obesity, measured as the ratio of actual weight to desirable weight (MRW), was a significant independent predictor of CVD, including CHD, coronary death and congestive heart failure in both men and women; and stroke in women after adjustment for other known risk factors. After 44 years of follow-up of the Framingham Heart Study, Wilson et al. (2002)[21] showed that CVD risk (including angina, myocardial infarction, CHD or stroke) was higher among overweight men (RR 1.24; 95% CI: 1.07–1.44), and obese men (RR 1.38; 95% CI: 1.12–1.69) and obese women (RR 1.38; 95% CI: 1.14–1.68) after adjustment for age, smoking, high blood pressure, high cholesterol and diabetes. The association was not significant among overweight women. In this case, overweight was defined as BMI $\geq$ 25 but < 30, and obesity as BMI $\geq$ 30.

### 1.3.2 Atherogenesis

#### 1.3.2.1 Progression and Classification of Atherosclerotic Lesions

Pathological studies have provided insights into the early changes within the artery wall that may be associated with atherosclerosis. The earliest findings noted were of eccentric intimal thickening in arterial regions opposite the flow divider of arterial bifurcations. The earliest signs of lipid retention were isolated foam cells (macrophages) found within the intima of 45% of infants. By puberty, lipid droplets accompanied such foam cell accumulations both extra-cellular and within smooth muscle cells. These early lesions are the so-called fatty streaks, and noted in 65% of children between 12 and 14 years of age. By the third decade of life, these lesions had developed a cap of smooth muscle cells and collagen, thus forming a fibroatheroma. The formation of these fibrous caps is generally slow, however may thicken

rapidly with the deposition of platelets and fibrin on its surface as a consequence of thrombus dependent fibrotic organisation (Worthley et al. 2001).[22]

Based on the above pathological data, atherosclerotic plaque progression was subdivided into 5 phases and lesions types by the American Heart Association Committee on Vascular Lesions (Figure 1.1) (Stary et al. 1994).[23]

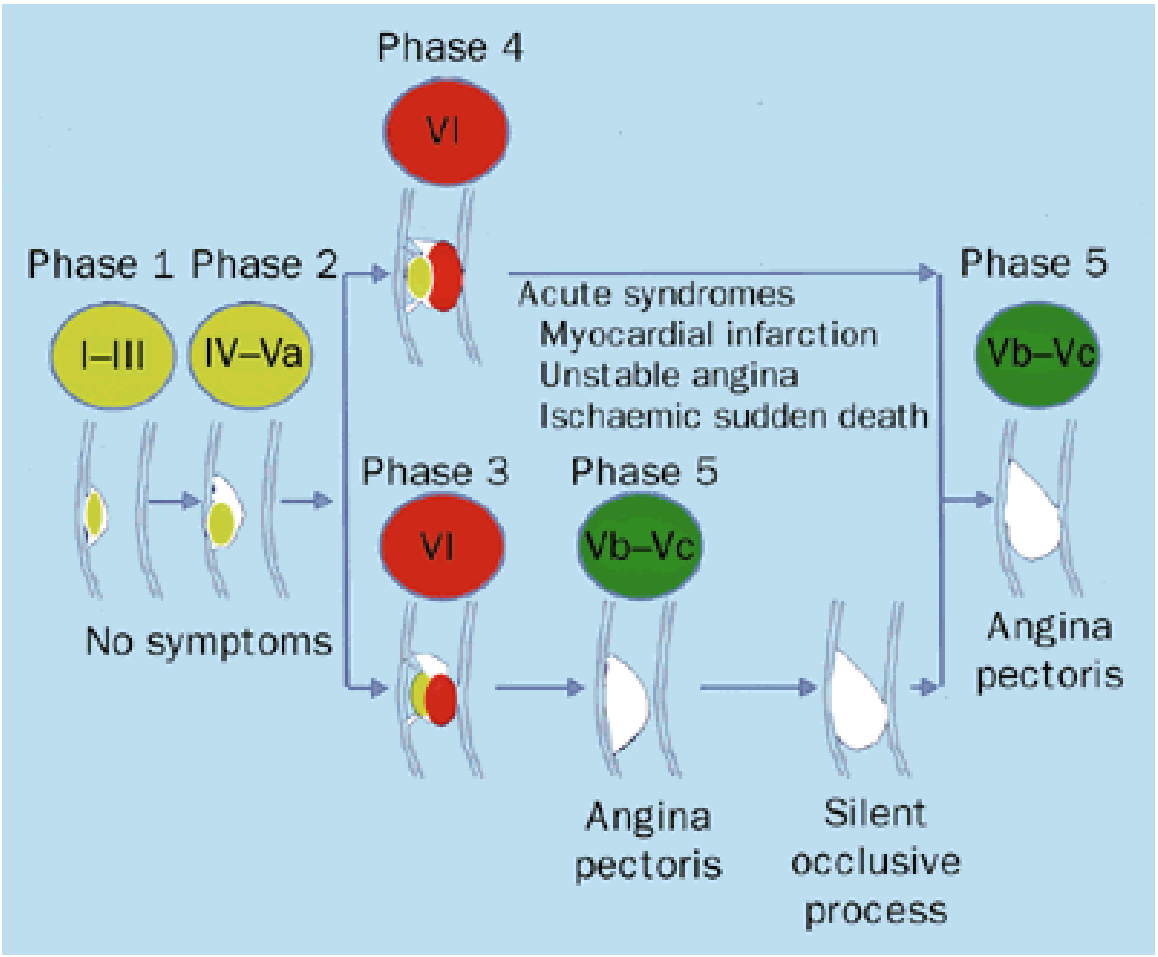



**Figure 1.1** Phase and lesion morphology of coronary atherosclerosis. Progression is based on gross pathological and clinical findings. An early lesion (phase 1) can become a fibrolipid plaque (phase 2). Phase 2 can progress into an acute phase (phase 3 or 4). Formation of thrombosis or hematoma may cause angina pectoris (phase 3) or an ACS due to occlusive thrombosis (phase 4). Phase 3 and 4 lesions can evolve into a fibrotic phase (phase 5) characterized by more stenotic plaques that may progress to occlusive lesions. Yellow indicates lipid accumulation; red, thrombosis and hemorrhage; and green, fibrous tissue. Roman numerals indicate lesion types, as follows: I to III, early lesions with isolated macrophage-foam cells (I), multiple foam-cell layers (II), and isolated extra-cellular lipids (III); IV to Va, advanced lesions (fibrolipid plaques with confluent extra-cellular lipid pools [IV] and fibromuscular tissue layers and atheroma [Va]); VI, advanced lesions (complicated plaques with surface defects, hemorrhage, or thrombus deposition); and Vb to Vc, advanced lesions with calcifications (Vb) and those with fibrous tissue (Vc).

Type IV and Va lesions are particularly important, as although not severely stenotic by coronary angiography, they are more susceptible or “vulnerable” to disruption and subsequent thrombosis. Type IV lesions have a high extracellular lipid content intermixed with fibrous

tissue beneath a fibrous cap. In contrast, type Va lesions contain a larger lipid-rich core with a thin fibrous cap. Upon disruption, these minimally stenotic coronary lesions may lead to acute occlusive thrombosis associated with the acute coronary syndromes, or a small nonocclusive thrombus may result, which may lead to a severe stenotic lesion upon fibrous organization within the underlying atherosclerotic plaque. This abrupt episodic progression of disrupted "vulnerable" plaques leads to the complicated type VI lesion, which accounts for three-quarters of patients with acute coronary syndromes.

#### 1.3.2.2 Importance of Rheology, Endothelial Dysfunction and Inflammation in Early Atherosclerosis

The arterial vessel wall and thus the endothelial cells are subject to mechanical forces including the hydrostatic force exerted by blood within the vessel, circumferential stress from motion of the vessel during the cardiac cycle and shear stress resulting from blood flow within the vessel. The biological implication of these mechanical forces is clearly demonstrated by the preferential localization of atherosclerotic lesions at certain sites within the arterial tree despite the presence of the same systemic, genetic and environmental factors. It is the last of these forces, shear stress, which appears to have the greatest impact upon events occurring at the blood-vessel wall interface because it stimulates the release of vasoactive substances, changes such cellular processes as gene expression (i.e. via shear stress responsive elements), cell metabolism and cell morphology (Worthley et al. 2000).[24] At areas of abrupt curvature in the vessel (such as at the carotid bulb) the laminar blood flow is disrupted, resulting in recirculation vortices that lead to low mean shear stress and flow reversal. There is a strong correlation between endothelial dysfunction and areas of low mean

shear stress and oscillatory flow with flow reversal (Worthley et al. 2000).[24] These sites demonstrate the appearance of cellular adhesion molecules on the endothelial cell surface, increased uptake of lipoproteins, inflammatory cell transmigration and the secretion of chemokines and cytokines leading to the proliferation of smooth muscle cells and macrophages within the vessel wall. Thus, high mean shear stress inhibits leukocyte binding and chemokine and cytokine expression, while low mean shear stress promotes inflammatory cell binding.

The endothelium plays a central role in arterial hemostasis, through the regulation of plasma lipoprotein permeability and leukocyte adhesion, and the production of prothrombotic and antithrombotic factors, growth factors and vasoactive substances (Figure 1.2).

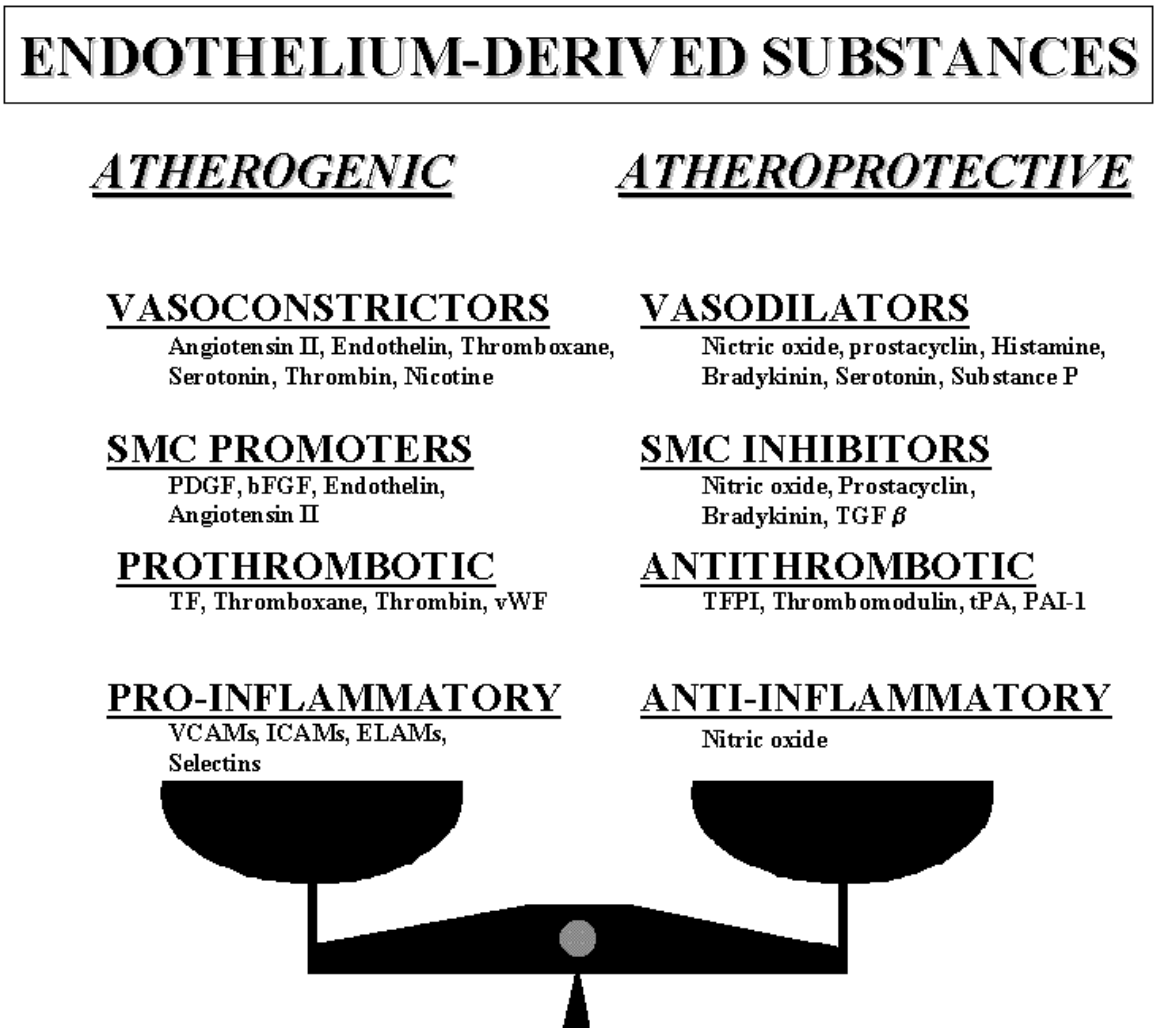



**Figure 1.2** Endothelium-derived substances. Note the list of pro- and anti-atherogenic factors that could be produced by the endothelium (see text). PDGF. -Platelet Derived Growth Factor; bFGF. -basic Fibroblast Growth Factor;VCAM. -Vascular Adhesion molecules; ICAM. – Intercellular Adhesion Molecules; ELAM. -Endothelial Leukocyte Adhesion Molecule; TGF-b. - Transforming Growth Factor Beta; TFPI. -Tissue Factor Pathway Inhibitor; tPA. – tissue type Plasminogen Activator; PAI-1. -Plasminogen Activator Inhibitor-1; vWF. -von Willebrand factor.

There is substantial data, demonstrating that shear stress is an important stimulus for the secretion of Prostacyclin (Grabowski et al. 1985[25]; Ross 1999[26]) and nitric oxide (NO)(Rubanyi et al. 1986[27]; Busse et al. 1989[28]; Vanhoutte 1992[29]), both of which are potent inhibitors of platelet aggregation. Furthermore, shear stress has been shown to regulate the production of thrombomodulin (Malek et al. 1994[30]), which (through interaction with protein C and S) inactivates specific clotting factors, stimulates the expression of tissue plasminogen

activator (Malek et al. 1994[31]; Takada et al. 1994[32]; Kawai et al. 1997[33]) and reduces the secretion of plasminogen activator inhibitor type 1 (Kawai et al. 1997[33]), thus promoting fibrinolysis as well. The genes for the production of tissue factor, one of the most potent stimuli for thrombin generation via the extrinsic pathway of the coagulation cascade, are upregulated in conditions of low mean shear stress (Lin et al. 1997[34]), leading to the existence of a prothrombotic endothelial surface. Thus, in conditions of low mean shear stress, there is not only the removal of anticoagulant mechanisms, but also the emergence of procoagulant ones.

The recruitment of monocytes into the vessel wall is an early step in the formation of an atherosclerotic lesion. The fatty streak, the precursor for atherosclerotic lesions, contains macrophages and T lymphocytes exclusively (Stary et al. 1994[23]), although the deposition of lipidic material precedes this inflammatory cellular influx in patients with hypercholesterolemia (Simionescu et al. 1986[35]; Napoli et al. 1997[36]). The subsequent migration of leukocytes across the endothelium depends on chemotactic factors such as monocyte chemoattractant protein 1 and oxidized LDL (Rajavashisth et al. 1990[37]) as well as adhesion molecules such as platelet-endothelial cell adhesion molecules (Muller et al. 1993[38]). Factors such as monocyte colony stimulating factor appear to be important for the survival and multiplication of macrophages within the growing atherosclerotic lesions (Qiao et al. 1997[39]; de Villiers et al. 1998[40]). T-cells are similarly dependent on interleukin 2 (Ross 1999[26]). Macrophages produce many growth factors (including PDGF, basic FGF, and epidermal growth factor) in addition to the inflammatory agents described above. However, it is the production of matrix degrading substances (in particular matrix metalloproteinases and heparanases), which are crucial to the perpetuation and growth of the early lesion (Celentano

et al. 1997[41]). Gelatinase A (MMP 2) degrades the collagen found in the basement membranes, and appears to be critical in facilitating smooth muscle migration through the basement membrane (Pauly et al. 1994[42]). The major control of MMP activity, once activated from the inactive zymogen, lies with the production of tissue inhibitors of MMPs (TIMPs) (Celentano et al. 1997[41]), of which three have been identified to date. It appears that the ratio of MMPs to TIMPs is crucial in determining connective tissue and basement membrane breakdown. Lymphocytes, including CD4 and CD8 positive T-cells, have been identified in significant numbers within atherosclerotic lesions, and invariably play a role in the inflammatory processes in plaque genesis and progression (Jonasson et al. 1986[43]; van der Wal et al. 1989[44]). These T-cells are activated when they bind antigens processed and presented by both macrophages and smooth muscle cells. One such antigen may be oxidized LDL (Stemme et al. 1995).[45]

Smooth muscle cell proliferation is an important feature of atherosclerotic lesions and is stimulated by endothelial factors, of which shear stress is one of the regulators (Kraiss et al. 1993[46]). Low mean shear stress (which is pro-atherogenic) has been shown to be associated with increased production of endothelial platelet derived growth factor (PDGF) (Kraiss et al. 1993[46]). High mean shear stress (which is anti-atherogenic or atheroprotective) has been associated with reduced production of endothelin 1(Sharefkin et al. 1991[47]) and angiotensin II (Rieder et al. 1997[48]) (smooth muscle mitogens), and increased production of NO (Buga et al. 1991[49]; Ohno et al. 1995[50]), transforming growth factor β (TGF-β) (inhibitors of smooth muscle cell growth). Thus, substantial evidence exists for shear stress mediated modulation of vascular smooth muscle cell proliferation.

### 1.3.2.3 Platelets and Thrombosis in Early Atherosclerosis and Acute Coronary Syndromes

Platelet deposition and thrombosis atop an atherosclerotic lesion leads to one of two broad events (Figure 1.3).

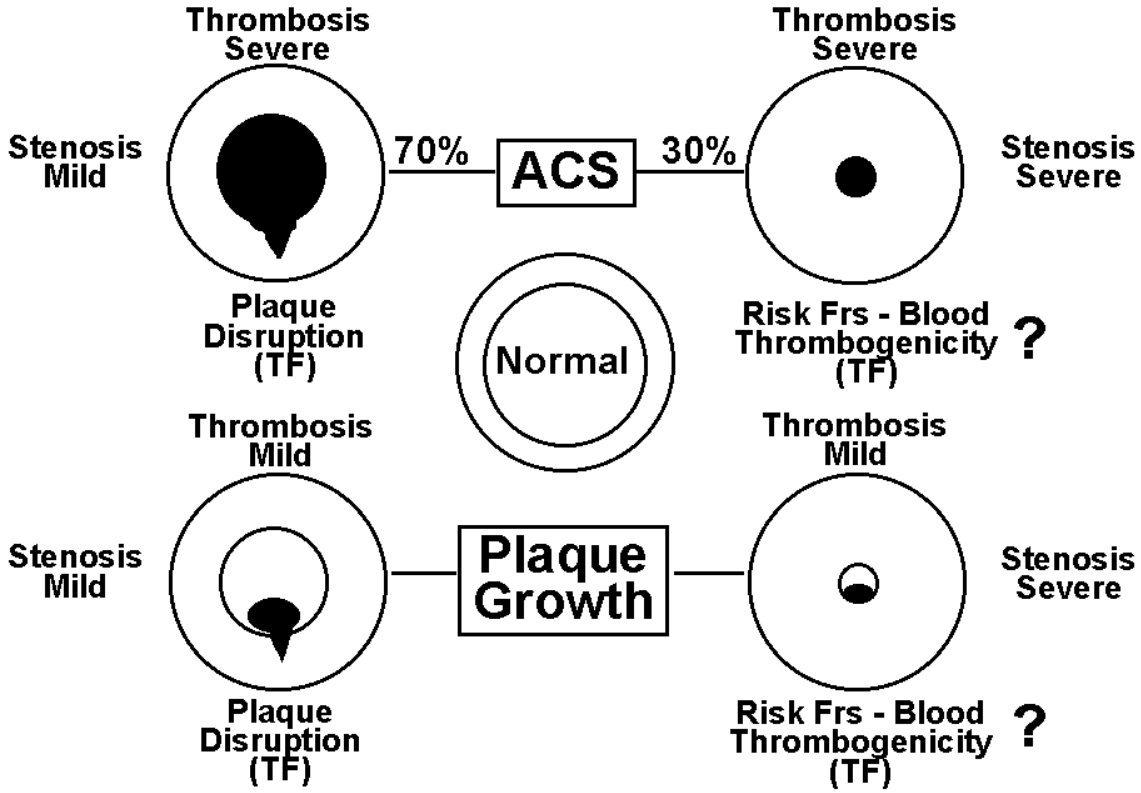



**Figure 1.3** Diagram showing the various outcomes that result from the thrombotic complications of atherosclerotic disease. Plaque disruption and subsequent thrombosis are associated with 70% of the acute coronary syndromes, while the remaining 30% seem to be caused by the existence of a severe stenosis triggering thrombosis. ACS. -Acute Coronary syndromes. The ? marks refer to the potential effect of a newly reported systemic pool of tissue factor (TF).

Firstly, non-occlusive luminal thrombosis leading to silent, rapid plaque growth. During serial angiographic studies, where the presence of a mild or moderately stenotic plaque (<50%) was the most frequent cause of acute ischemic events (Ambrose et al. 1988[51]; Little et al. 1988[52]; Nobuyoshi et al. 1991[53]; Giroud et al. 1992[54]), it was further noted that even in the absence of clinical symptoms, some minor lesions had rapidly progressed in size over a short period in

time. Post-mortem studies of patients dying from ischemic events have elucidated the cause of both the above to be intimately related to plaque-associated thrombosis (Davies et al. 1985[55]; Falk 1992[56]; Falk et al. 1995[57]; Davies 1996[58]; Mann et al. 1996[59]; Felton et al. 1997[60]). The atherosclerotic lesions that appeared susceptible or prone to such thrombotic phenomenon were noted to have common histological characteristics. These so-called "vulnerable" plaques are more prone to plaque disruption and subsequent thrombus formation.

Secondly, occlusive (transiently or permanently) luminal thrombosis associated with unstable angina pectoris, acute myocardial infarction or sudden cardiac death. Plaques containing a large atheromatous core are more prone to disruption, and indeed three-quarters of such plaques are responsible for the atherothrombotic complications leading to the acute coronary syndromes (Falk 1983[61]; Richardson et al. 1989[62]; Frink 1994[63]; van der Wal et al. 1994[64]). Most of the other cases are associated with plaque thrombosis atop macrophage-rich intimal erosion in a more fibrotic plaque, often in association with a severe arterial stenosis (Falk 1983[61]; Richardson et al. 1989[62]; van der Wal et al. 1994[64]).

### 1.3.3 The association between obesity and other major established CVD risk factors

This section examines whether there is an association between obesity and the development of CVD through its underlying pathology.

#### 1.3.3.1 Relationship between obesity and development of atherosclerotic cardiovascular disease

A cross-sectional study by Takami et al. (2001)[65] of 849 Japanese men aged 20–78 years investigated the relationship between body fatness (particularly abdominal fat) and carotid atherosclerosis. They found that general adiposity (as measured by BMI), waist circumference, WHR, abdominal subcutaneous fat and intra-abdominal fat were all correlated with carotid intimal–medial thickness (IMT) after adjustment for age and smoking habit.

A study by McGill and others (2002) [66] examined early stages of atherosclerosis from around 3,000 people aged 15–34 years who had died from injuries or poisoning. They found that obesity (BMI $\geq$ 30) and thick panniculus adiposus (central pattern of obesity) were related to accelerated coronary atherosclerosis at autopsy in adolescent and young men, but not women. When adjustment was made for standard CVD risk factors (cholesterol, smoking and high BP) the size of the effect was reduced by around 15%.

#### 1.3.3.2 Age at which weight gain occurs and cardiovascular risk

Berenson et al. 1992[67] showed that atherosclerosis of the aorta and coronary arteries were related to obesity in youth. The study revealed that obesity was associated with the early development of atherosclerotic lesions as evidenced by fatty streaks and/or fibrous plaque lesions, particularly among young men.

Hubert et al. 1983[20] concluded in their analysis of the Framingham Heart Study that an increase in relative weight after the age of 25 years independently predicted the risk of CVD, particularly in men. Kannel, D'Agostino & Cobb 1996[68] refined this risk based on their

summary of the effect of weight on CVD using the Framingham Heart Study and other studies, by concluding that the amount of weight gained after the age of 25 (or on completion of musculoskeletal growth) carries a proportionately increased risk of CVD. However, this linear association may not continue into old age. Analysis of results from the American Cancer Society's Cancer Prevention Study I (Stevens et al. 1998b)[69] involving 324,135 participants showed that excess body weight increased the risk of death from CVD in healthy white adults aged 30–74 years followed up over a period of 12 years. Above 74 years, however, the RR of death was not significantly increased for either men or women. Hubert et al. 1983[20] noted in their analysis of the Framingham Heart Study that although an increase in relative weight after the age of 25 years increased the risk of CVD, the association was stronger among men and women aged less than 50 years. Similar results were obtained by Baik et al. 2000[70] in the Health Professionals Follow-up Study. CVD mortality among obese (BMI $\geq$ 30) men aged less than 65 years was significantly greater (RR 3.92) after accounting for other risk factors compared with those with a BMI < 23 (RR $\leq$ 1). Among men 65 years or older, there was no significant relationship between BMI and risk of CVD mortality.

The distribution of fat and the effects of obesity and cardiovascular disease are discussed in section 1.3.5.

### 1.3.4 Excess body weight and other risk factors

#### 1.3.4.1 Hypertension

Although obesity and hypertension are both conditions in their own right, studies have shown that there is a strong and close relationship between the two (Frohlich 1991)[71]. Blood pressure (BP) increases as BMI increases and people who are obese have been found to have a much

higher prevalence of hypertension. (Doll et al. 2002[72]; WHO 2000[73]; Kemper et al. 1999[74]; McCarron & Reusser 1996[75]; Stamler 1991[76]; Garn et al. 1988[77]).

In the three US National Health and Nutrition Examination Surveys (NHANES), high BP defined as 140/90 mmHg or greater or was independently associated with higher BMI. In all three surveys, higher BMI was responsible for around 30% of the prevalence of high BP (Hajjar & Kotchen 2003).[78] After adjustments were made for age, sodium and potassium excretion, alcohol intake and smoking status, the NHANES II study of American adults found that high BP among those with excess body weight was three times as common as among those with normal weight (van Itallie 1985).[79] The latest NHANES phase (Hajjar & Kotchen 2003)[78], conducted in 1999–2000, observed an increase in participants with high BP when compared with the previous two phases of the NHANES survey conducted between 1988 and 1991, and 1991 and 1994. Within this same period, Flegal et al. 2002[80] also found an approximate increase of 8% in the prevalence of obesity (BMI≥30). After adjustments were made for age, sex and race/ethnicity, BMI was independently and positively associated with high BP prevalence and was found to contribute to more than half the increase (Hajjar & Kotchen 2003)[78].

The distribution of fat and the effects of obesity and cardiovascular disease are discussed in section 1.3.5.

#### 1.3.4.2 Total Cholesterol

Several studies have shown consistent positive independent associations between excess body weight and total cholesterol (TC) levels (Owen et al. 2003[81]; WHO 2000[73]; Ferrara et al. 1997[82]; Stamler et al.1997[83]; Ernst & Obarzanek 1994[84]; Denke et al. 1993[85]; Dattilo & Kris-Etherton 1992[86]; Garn et al.1988[77]). Garn et al. 1988 examined 5,507 white people aged 15–

75 to study the association of skinfold thickness and lipids and BP. They discovered that increased adiposity, measured using the sum of four skinfolds (triceps, subscapular, iliac and abdominal), was associated with an increase in plasma levels across all age groups. This study found an average 13 mg/dL increase (0.34 mmol/L) in TC from the lowest to the highest level of body fatness. This increase was found to be slightly more marked in males. Significant correlations between body weight and TC levels were also observed in other studies reviewed by Denke et al. 1993. [85]

#### 1.3.4.2.1 Low-density lipoprotein (LDL) cholesterol

Significant correlations between body weight and LDL cholesterol levels were found in the Framingham Offspring Study (reviewed by Denke et al. 1993)[85], the Cardiac Study (Denke et al. 1993)[85] and the Rancho Bernardo Study (Ferrara et al. 1997).[82] People with excess body weight are more likely to have increased levels of LDL cholesterol (Ferrara et al. 1997[82]; Stamler et al. 1997[83]; Kuller et al. 1995[87]; Ernst & Obarzanek 1994[84]; Denke et al. 1993[85]; Dattilo & Kris-Etherton 1992[86]).

#### 1.3.4.2.2 High-density lipoprotein (HDL) cholesterol

Excess body weight is associated with lower levels of HDL cholesterol (WHO 2000[73]; Ferrara et al. 1997[82]; Ernst & Obarzanek 1994[84]; Denke et al. 1993[85]; Dattilo & Kris-Etherton 1992[86]). The Lipid Research Clinics Program Prevalence Study also showed a significant negative correlation between HDL cholesterol and body weight in those aged 12–79 years (reviewed by Denke et al. 1993[85]). The NHANES II study found that HDL cholesterol levels were negatively correlated with BMI and this was significant across age groups (Denke et al. 1993)[85].

#### 1.3.4.2.3 Weight loss and Hypertension, TC, LDL and HDL

Muzio et al. 2007 [88] compared the effects of 2 diets on cardiovascular disease risk factors in obese patients with the metabolic syndrome. The study was carried out in 100 patients randomly assigned to either a diet relatively rich in carbohydrate [65% of energy as carbohydrate, 13% as protein, and 22% as fat (17% as unsaturated fat)] or a diet that was low in carbohydrate and high in protein and in monounsaturated fat [48% of energy as carbohydrate, 19% as protein, and 33% as fat (24% as unsaturated fat)]. All 100 patients completed the study. At the end of the study, all the components of the metabolic syndrome (except HDL, which did not change) decreased significantly in both groups. With the high-carbohydrate diet, a significant decrease in LDL-cholesterol concentrations was also observed. Although the extent of the resolution of the metabolic syndrome was not different between groups, the low-carbohydrate diet was associated with a greater decrease in the prevalence of hypertension ($P < 0.05$) and of hypertriglycerideaemia ($P < 0.001$).

Smith et al. 2007[89] investigated changes in hypertensive individuals participating in an exercise and weight loss intervention. This study involved 133 sedentary men and women with high blood pressure (BP; 130-180 mmHg systolic BP and/or 85-110 mmHg diastolic BP) who participated in a 6-month intervention consisting of three groups: aerobic exercise, aerobic exercise and weight loss, and a waiting list control. Participants in both treatment groups demonstrated significant improvements in aerobic capacity and lower BP compared with participants in the control group.

### 1.3.4.3 Inflammation

Raised concentrations of inflammatory mediators may reflect inflammation in the arterial wall associated with atherosclerosis but may also be causally involved in the disease process.[90, 91] Moreover, levels of obesity have been shown to be associated with low-grade inflammation.[92, 93] Cardiovascular disease (CVD) is associated with elevated markers of systemic inflammation, including C-reactive protein (CRP) and members of the coagulation cascades.[94] Elevated levels of these proteins are also associated with cardiovascular risk factors, such as obesity, diabetes mellitus, and angina pectoris.[95]

TNFα, and IL-6 are examples of cytokines that may have a role in the metabolic syndrome. Plasma TNF$\alpha$ levels are directly proportional to fat mass and has been shown to be involved in the development of insulin resistance.[96] In-vitro studies have demonstrated that TNF$\alpha$ decreases the insulin receptor tyrosine phosphorylation, and down regulates several steps in the insulin signaling pathway[97,98,99,100] while neutralizing agents for TNF$\alpha$ have been shown to improve insulin resistance.[101] Thus, TNFα is not only a classical cytokine but may be causal in the insulin resistance of the metabolic syndrome of aging.

There is increasing evidence that cytokines in general and tumour necrosis factor (TNF) in particular play an important role in cardiovascular disease. This is not surprising since TNF modulates both cardiac contractility and peripheral resistance, the two most important haemodynamic determinants of cardiac function. Thus, increased levels of TNF or of its soluble receptors have been implicated in the pathophysiology of ischaemia-reperfusion injury, myocarditis, cardiac allograft and, more recently, also in the progression of congestive heart failure.

IL-6 is another cytokine derived from adipose tissue. Its expression and circulating levels correlate directly with the degree of obesity, and weight loss lowers circulating levels. Elevation of circulating IL6 is a predictor of the development of cardiovascular disease and diabetes.[102] Infusion of IL6 results in hyperlipidemia, hyperglycemia and insulin resistance in experimental models.[103] Additionally, IL6 decreases the expression of adiponectin, an 'anti-diabetic' cytokine.[104] IL-6 plays a role in the development of insulin resistance and may directly cause induction of CRP.

There is now an extensive amount of evidence regarding CRP and CVD. Numerous studies established that hs-CRP measurements were able to predict first-time cardiovascular events.[105, 106, 107]

CRP, a major acute-phase protein, has been associated with the presence and severity of atherosclerosis [108] and has been found to predict cardiac events in subjects with [109, 110, 111] and without [112, 113, 114] prevalent cardiovascular disease. High-sensitivity CRP was shown to be a much better predictor of risk than traditional risk markers such as the cholesterol/HDL ratio.[115]

**1.3.4.3.1 Inflammation and weight loss**

Evidence for a connection between obesity and inflammation has been found in the context of clinical weight loss studies. Whether the weight loss is attributable to decreased dietary intake[116], increased fuel use through exercise[117], liposuction[119, 120, 121], or bariatric surgery[122], loss of adipose tissue is associated with a decrease in markers of inflammation. Weight loss (~10 kg) achieved through dietary intervention alone or diet and exercise resulted in decreased circulating IL-6, CRP, PAI-1, TNF-$\alpha$, soluble TNF receptor, P-selectin, intercellular adhesion

molecule-1 (ICAM-1), VCAM-1, and IL-18 in men and women of various age groups and BMIs.[116, 117, 118]

Weight loss by liposuction in obese patients was associated with significant decreases in circulating CRP, IL-6, IL-18, and TNF and sustained (6 months postoperative) improvements in insulin resistance.[119] In contrast, Klein et al. 2004 [120] reported recently that large-volume subcutaneous abdominal liposuction did not significantly alter plasma concentrations of CRP, IL-6, TNF-$\alpha$, and adiponectin, and did not significantly affect other risk factors for coronary heart disease and insulin sensitivity.[120] Thus liposuction of subcutaneous fat pads may not have as strong an impact as removal of visceral adipose tissue.[121]

In another form of dietary weight loss, gastric bypass surgery resulted in improved insulin sensitivity, amelioration of diabetes, and significant decreases in circulating IL-6 and CRP levels 14 months after the procedure.[122] Not only do these findings strengthen the evidence for the direct contribution of adipose tissue to systemic inflammation, they also imply that many of the health benefits of weight loss are attributable to these decreases in inflammatory signals.

### 1.3.5 Distribution of fat and effects of obesity and cardiovascular disease

In addition to total body fatness, abdominal fat independently increases cardiovascular risk[123]. The specific distribution of excess fat can influence the relation between obesity and cardiac disease. Individuals with increased fat accumulation in the abdominal region often have atherogenic lipid profiles and are at increased cardiovascular risk. [124, 125] Excess abdominal adipose tissue, particularly visceral fat, and excess triglyceride content in heart tissues are

associated with impaired ventricular function and increased coronary heart disease.[126] There is some evidence that central adiposity is related to the risk of high blood cholesterol independent of total adiposity (WHO 2000[73]; Despres 1994[127]). Kuller 1999 [128] found that central adiposity compared with total adiposity was positively associated with increased triglyceride level, lower HDL cholesterol and less associated with LDL cholesterol. Total adiposity was strongly associated with LDL cholesterol.

Excess body weight, especially when located in the abdominal region, has a strong association with blood glucose levels, insulin resistance and the development of diabetes. This has been a consistent finding across a range of prospective studies (Despres et al. 2001[123]; Barrett-Connor & Pyorala 2001[129]; Boyko et al. 2000[130]; Njolstad et al. 1998[131]; Chan et al. 1994[132]; Haffner et al. 1991[133]; Charles et al. 1991[134]; Colditz et al. 1990[135]), cross-sectional studies (Janssen et al. 2002[136]; Schmidt et al. 1992[137]; Dowse et al. 1991[138]; Skarfors et al. 1991[139]) and recent reviews (WHO 2003[140]; Hodge et al. 1996[141]; WHO 2000[73]; Kuller 1999[128] ; Despres et al. 1990[142]).

Most studies support that central adiposity is the dominant risk factor for the development of Type 2 diabetes, although there are some exceptions. Perry et al. 1995[143] and Skarfors et al. 1991[139] found BMI was the dominant risk factor over other measures of central adiposity for risk of developing Type 2 diabetes. A review by Hodge et al. 2001[144] concluded that both overall adiposity and central fat distribution were important independent risk factors for Type 2 diabetes.

**Cardiovascular Impact of Increased Adipose Tissue Mass**

Adipose tissue comprises a substantial proportion of total body weight. Therefore, a large quantity of fluid is present in the interstitial space of adipose tissue, as the interstitial space is ≈10% of the tissue wet weight.[145] Excess fluid in this compartment may have important implications in obese individuals with heart failure if this extra volume is redistributed into the circulation; however, modulation of blood flow through adipose tissue typically prevents this from occurring. This is because blood flow in adipose tissue is regulated by $ß_1$-receptors that mediate vasodilation, in contrast to those of skeletal muscle, which are mainly $ß_2$.[146] As a consequence of this decrease in blood flow in adipose tissue, the fluid present in the interstitial compartment is not readily accessible. Although cardiac output increases with total fat mass, the perfusion per unit of adipose tissue actually decreases with increasing obesity, that is, from 2.36 mL/min per 100 g to 1.53 mL/min per 100 g of adipose tissue (≈35%) reduction in patients who have 15% to 26% body fat compared with those with >36% body fat.[147]

Adipose tissue is not simply a passive storehouse for fat but an endocrine organ that is capable of synthesizing and releasing into the bloodstream an important variety of peptide and nonpeptide compounds that may play a role in cardiovascular homeostasis. Adipose tissue is a significant source of tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-6 (IL-6), plasminogen activator inhibitor-1, resistin, lipoprotein lipase, acylation stimulating protein, cholesteryl-ester transfer protein, retinal binding protein, estrogens (through P450 aromatase activity), leptin, angiotensinogen, adiponectin, insulin-like growth factor-I (IGF-I), insulin-binding protein 3 (IGFBP3), and monobutyrin. [148, 149, 150, 151, 152] Of clinical consideration, circulating concentrations of plasminogen activator inhibitor-1, angiotensin II, C-reactive protein (CRP),

fibrinogen, and TNF-$\alpha$ are all related to BMI.[153, 154] It has been estimated that in vivo, ≈30% of the total circulating concentrations of IL-6 originate from adipose tissue.[155] This is of importance because IL-6 modulates CRP production in the liver, and CRP may be a marker of a chronic inflammatory state that can trigger acute coronary syndromes.[156, 157]

**Ectopic fat deposition**

Recent studies have demonstrated that organ-specific deposition of fat is a strong predictor of insulin resistance in muscle and liver. Increased intramyocellular triglyceride content, assessed by muscle biopsy [158] or magnetic resonance[159, 160, 161, 162, 163, 164] correlates closely with muscle insulin resistance and is a better predictor of impaired insulin action than visceral adiposity[165]. Conversely, a decrease in intramyocellular lipid content brought about by weight loss is a strong correlate of the improved muscle insulin sensitivity. [166, 167, 168]

### 1.3.6 Obesity and epicardial fat

Epicardial fat covers 80% of the heart and constitutes 20% of its weight. It is present along the distribution of the coronary arteries, over the right ventricle, anterior surface and at the apex.

Epicardial fat assessed using echocardiography is associated with abdominal visceral fat[169, 170, 171, 172] and cardiovascular risk factors. [173, 174] Because of its proximity to the right ventricle and absence of the fascial boundary, epicardial fat may directly affect the coronary arteries and myocardium through paracrine actions of locally secreted adipocytokines and other bioactive molecules. [175, 176, 177]

Kankaanpää et al. 2006[178] evaluated myocardial and epicardial fat, left ventricular (LV) function, and metabolic risk factors in nine (five lean, four moderately obese) men. Myocardial fat percent was quantified in the septum by proton magnetic resonance

spectroscopy. Reproducibility was assessed by triplicate systolic and diastolic measurements. LV parameters and epicardial fat were determined by magnetic resonance imaging. Waist-to-hip ratio and liver enzymes (alanine transaminase) were used as surrogate markers of visceral and liver fat contents. Myocardial fat (2.1 ± 0.5 *vs*. 0.8 ± 0.1, *P* = 0.03) and epicardial fat (120 ± 33 *vs*. 55 ± 12 g, *P* = 0.08) were higher in obese than lean subjects. Myocardial fat was correlated with free fatty acid (FFA) levels (r = 0.76; *P* = 0.017), epicardial fat (r = 0.69; *P* = 0.042), and waist-to-hip ratio (r = 0.70; *P* = 0.035). Epicardial fat was associated with peripheral vascular resistance (positively) and the cardiac index (negatively). FFA levels were significantly correlated with LV mass (r = 0.72; *P* = 0.030).

#### 1.3.6.1 Weight loss and epicardial fat

Willens et al. 2007[179] investigated the effects of weight loss after bariatric surgery on epicardial adipose tissue in patients with severe obesity. The results showed a decrease in epicardial fat thickness using echocardiography in obese patients who had substantial weight loss after bariatric surgery. The magnitude of this decrease in epicardial fat was related to initial epicardial fat thickness. However, there was no statistically significant association between amount of weight loss and change in epicardial fat thickness. However, the echocardiographic assessments used of pericardial adipose tissue (PAT) are limited in both their relationship to total PAT and their reproducibility.

### 1.4 Obesity and Cardiac Structure and Function

Obesity causes a variety of hemodynamic alterations that may lead to changes in cardiac structure and function. Although such abnormalities may occur in patients with mild-to-moderate obesity, they are most pronounced in those with morbid obesity. When these alterations produce congestive heart failure, obesity cardiomyopathy is said to be present.[180]

Obesity produces an increase in total blood volume and cardiac output because of the high metabolic activity of excessive fat. In moderate to severe cases of obesity, this may lead to left ventricular dilation, increased left ventricular wall stress, compensatory (eccentric) left ventricular hypertrophy, and left ventricular diastolic dysfunction. A reduction in diastolic function is noted in 24% of severely obese subjects, and the risk is associated with BMI.[181]

### 1.4.1 Obesity and Ventricular abnormalities

### 1.4.2 Left ventricular mass, LV/RV systolic and diastolic function

Obesity is related to several disturbances in cardiac structure.[182] Obese people have greater left ventricular mass, greater wall thickness, and larger chamber size than those who are not obese,[183, 184] and the ratio between wall thickness and chamber radius (the relative wall thickness) is larger in obese people than in lean people.[182, 185] These aberrations in left ventricular mass and structure are of great importance. Left ventricular hypertrophy is one of the strongest risk factors for cardiovascular morbidity and mortality,[186] and an increase in relative wall thickness has been shown to increase cardiovascular risk.[187, 188]

The changes in left ventricular mass and structure with increasing body weight can be partially explained by the haemodynamic changes that accompany obesity.[189, 190] As body weight increases, total blood volume and cardiac output rise. This leads to a volume overload that causes left ventricular dilatation and a parallel thickening of the ventricular wall (eccentric left ventricular hypertrophy). Obesity is also closely related to arterial hypertension,[191, 192] a form of pressure overload that is followed by increased wall thickness without chamber dilatation (concentric left ventricular hypertrophy). Metabolic and hormonal factors can also influence the heart structure of obese people.[193]

Excess adiposity has been widely related to cardiac morphological changes. However, the mechanistic link between increased adiposity and left ventricular morphology is controversial and not completely understood.[194] Epicardial fat is clinically correlated with LV mass, atrial dimensions, and diastolic function, but the effect of epicardial adipose tissue on cardiac chamber modifications remains to be demonstrated.[195]

### 1.4.3 Weight loss and Cardiac Structure and Function

In 1972 Alexander and Peterson reported that raised left ventricular filling pressure in obese subjects persisted three years after weight loss and concluded that myocardial hypertrophy did not regress after weight reduction.[196] Likewise, Alpert et al. 1995 reported that surgically induced weight loss (mean 56 kg) in a group of obese patients had no effect on septal or posterior wall thickness.[197] In contrast, MacMahon et al. 1986 found that a weight loss of only 8 kg in mildly obese patients with hypertension was associated with a significant decrease in left ventricular mass,[198] and more recently, Alpert et al. 1994 observed a reduction in left ventricular mass after weight loss in obese subjects with pre-existing left ventricular hypertrophy.[199] Karason et al. 1998 showed weight reduction, even when achieved by diet, improved left-ventricular diastolic filling and ejection fraction.[200]

Weight-loss surgery resolves type 2 diabetes in 75-85% of patients, with significant improvement in 95%[201], including normalization of lipid profiles and improvement of ventricular function in patients. Furthermore the prevalence of left-ventricular hypertrophy is decreased.[202] Data also shows improvements in hypertriglyceridemia, low levels of HDL cholesterol, hypertension and hyperuricemia, compared with individuals who have not undergone weight-loss surgery.

Surgically induced weight loss produces a decrease in resting oxygen consumption and cardiac output that is proportional to the magnitude of weight loss. [203,204] Stroke volume falls in parallel to the decrease in blood volume and heart volume. Systemic arterial pressure declines, but systemic arterial resistance changes little if at all. Left ventricular stroke work diminishes. Pulmonary capillary wedge pressure tends to decrease but may still remain higher in relation to cardiac output as compared with normal-weight subjects. Left ventricular dysfunction may persist most strikingly during exercise. At any given cardiac output, all right heart pressures tend to be higher than in normal-weight subjects, with relative increases in left ventricular end-diastolic pressure.[205]

## 1.5 Obesity and Vascular Function

### 1.5.1 Endothelial dysfunction and arterial stiffness

Although obesity is linked to impaired vascular function, the mechanisms that relate fat mass to vascular health are poorly understood. Excess fat, and particularly visceral fat, predispose to the major components of the metabolic syndrome (blood pressure, insulin resistance, abnormal serum lipids and inflammation) that influence cardiac risk.

Most studies of vascular function in obese subjects have demonstrated impaired endothelial function (Williams et al. 2002;[206] Arkin et al. 2007[207]). Obese individuals show an impaired endothelial-mediated vasodilator response to increased blood flow (Arcaro et al. 1999)[208], to insulin (Westerbacka et al. 1999)[209] and to biochemical agents (Steinberg et al. 1996)[210]. Similarly, obesity is associated with greater arterial stiffness (Wildman et al. 2003)[211] and visceral adiposity is particularly detrimental (Resnick et al. 1997)[212].

This impairment of endothelial function becomes obvious early on, long before any vascular abnormalities become clinically relevant and detectable.[213] Better understanding of the mediators of obesity-induced endothelial dysfunction may lead to the identification of new targets for interventions that may prevent or postpone the development of obesity-related cardiovascular disease.

### 1.5.2 Weight loss and Vascular Function

Some weight loss studies have shown an improvement in both endothelial function (Ziccardi et al. 2002)[214] and arterial stiffness (Yamashita et al. 1998)[215]. However, the effect of weight loss on vascular function is not consistent across studies.

A recent report has suggested that there is no benefit on brachial artery FMD of a moderate extent of weight loss over 3 months (Brook et al. 2004)[216]. This discrepancy may be a result of factors such as differences in the site or techniques used to measure endothelial function, the diet that led to weight loss or the time over which weight loss was achieved.

Raitakari et al. 2004 showed that weight loss improved the function of the arterial endothelium at the level of the resistance vasculature and decrease circulating markers of endothelial damage, [217] as well as to improve brachial artery forearm mediated dilation.[218] Saltzman et al 2005, demonstrated weight loss of around 10% of initial body weight improves endothelial function as well as inflammatory and procoagulant states.[219]

These data raise the important question of the extent to which the effects of obesity on vascular stiffness are acute and therefore reversible.

### 1.6 Obesity and Arrhythmias

Atrial fibrillation (AF) is a cardiac rhythm disturbance that is responsible for increased morbidity and mortality.[220] This condition can cause palpitations, shortness of breath, fatigue and stroke. Weight-stable obese subjects have an increased risk of arrhythmias and sudden death, even in the absence of cardiac dysfunction, and the risk of sudden cardiac death (SCD) with increasing weight is seen in both genders.

The Framingham Heart Study suggests that obesity is associated with a 50% increase in the risk of atrial fibrillation.[221] The risk of developing AF increased progressively with increasing BMI, independently of age, sex and hypertension. Higher body mass index (BMI) results in a more than 2-fold increase in the recurrence of either paroxysmal or persistent atrial fibrillation.[222] It is unknown whether the association of obesity with increased risk of atrial fibrillation, differs by duration or persistence of AF.[223] Recently it was shown that the association with BMI was stronger for sustained AF than for transitory or intermittent AF. The obesity-AF association appears to be partially mediated by diabetes mellitus but minimally through other cardiovascular risk factors.[224]

Whether obesity per se is an independent risk factor for AF remains controversial. In one study, only hypertension and diabetes were the cardiovascular risk factors that were independent predictors of AF, while neither obesity nor alcohol intake was associated with AF.[225] However, more recent data has suggested an independent relationship between obesity

and AF,[226] by showing that obesity is associated with atrial enlargement and ventricular diastolic dysfunction, both known predictors of atrial fibrillation (AF).

### 1.6.1 Weight loss and Arrhythmias

Russo et al. 2007[227] determined the effect of severe obesity on spatial and transmural ventricular repolarization and to clarify the influence of bariatric surgery with a consequent substantial weight loss on arrhythmogenic substrate in the morbidly obese population. In severely obese patients, surgically-induced weight loss was associated with a significant decrease in the heterogeneity of ventricular repolarization.

Russo et al. 2007 [228] also investigated the influence of bariatric surgery with substantial weight loss on P-wave dispersion in morbidly obese population. It was shown that surgically induced weight loss reduction was associated with a significant decrease in P-wave dispersion. The reduction of the atrial refractoriness heterogeneity may be of clinical significance by reducing the risk of atrial fibrillation in morbidly obese subjects.

Increased QTc dispersion is a predictor for ventricular arrhythmias. Seyfeli et al. 2006[229] determined whether QTc dispersion decreased after weight loss intervention with diet and medical treatment. Substantial weight loss in obese subjects is accompanied by significantly decreased QTc dispersion and the degree of QTc dispersion reduction was associated with the amount of weight loss.

## 1.7 Erectile Dysfunction, Obesity and Cardiovascular Disease

### 1.7.1 Obesity and Erectile Dysfunction

Current literature offers strong evidence that endothelial dysfunction and erectile dysfunction are linked. Erectile dysfunction (ED) is the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity.[230] Worldwide, 100 million men are estimated to have some degree of ED, with around 30 million men in the United States[230] and around one million men in Australia affected. The Health Professionals Follow-Up Study revealed ED rates of 12% in men younger than 59, 22% in men 60 to 69, and 30% in men older than 70.[231] With our ageing overweight population the incidence of ED is certain to escalate. Epidemiologic evidence links well recognized risk factors for coronary artery disease, such as obesity, hypertension, and hypercholesterolemia, with ED.[232] Some even suggest that ED can predict coronary artery disease in asymptomatic men. [233, 234] As many as 70% of ED cases are caused by cardiovascular diseases such as atherosclerosis. Overweight or obese men have a 30% increased chance of impotence, and about eight out of 10 men with erectile problems are overweight or obese [233]. If neglected, excess weight gain can also lead to other conditions linked to ED like the cluster of increased risk factors for cardiovascular disease, such as the Metabolic Syndrome, and Type 2 diabetes. Between 35-50% of men with diabetes experience ED because the disease can damage nerves and arteries, making it difficult to achieve an erection.

There is a large and expensive industry dealing with erectile dysfunction in men. Esposito et al. 2004 have shown that lifestyle changes are an effective management option. Men who initiated physical activity in midlife in the Massachusetts Male Aging Study also had a 70% reduced ED rate compared with sedentary controls.[235]

### 1.7.2 Weight loss and erectile dysfunction

Erectile dysfunction is associated with modifiable risk factors. Obesity, physical inactivity, and the metabolic syndrome increase the incidence of ED and markers of low-grade inflammation, which in turn are associated with endothelial dysfunction. Intensive intervention with lifestyle advice focusing on a healthy diet, weight loss, and increased physical activity benefits men with ED, reducing the markers of inflammation and improving endothelial function.

Esposito et al. 2004, [236] conducted a study to determine if lifestyle changes designed to obtain a sustained and long-term reduction in body weight and an increase in physical activity would improve erectile function and endothelial function in obese men. The results demonstrated that lifestyle changes, including a reduced calorie diet and increased exercise, improve erectile function in obese men and resulted in about one-third of men with erectile dysfunction regaining sexual function after treatment. This improvement was associated with amelioration of both endothelial function and markers of systemic vascular inflammation. Interventions focused on modifiable health behaviors may represent a safe strategy to improve erectile function and reduce cardiovascular risk in obese patients.

### 1.7.3 Obesity and plasma androgen levels

The relationship between obesity, particularly abdominal obesity and low plasma total and free testosterone levels has been well established.[237]

In a multivariate analysis, it has been shown that in addition to being older, having a larger waist circumference, higher total serum triglycerides, and higher HbA1c predicted a lower plasma testosterone level. It has also been shown that obesity and in particular the metabolic

syndrome (associated with abdominal obesity) leads to a lower plasma testosterone level, rather than vice versa[238]. This is an important observation since it implies that weight loss is the preferenced treatment rather than exogenous testosterone.

### 1.7.4 Weight loss and plasma androgen levels

Studies of the effect of weight loss on testosterone level have had contradictory results, with some studies showing increases, [239, 240, 241, 242, 243, 244] other studies showing no change,[245, 246, 247] and one small study showing decreases in testosterone.[248]

### 1.7.5 Obesity and sexual desire

Clinical experience suggests that sexual dissatisfaction and/or sexual difficulties are not uncommon among our obese patients. Only a few research studies have examined the relationship between obesity and sexual desire. In men, obesity has been associated with loss of enjoyment of sexual activity, reduction in sexual desire and avoidance of sexual encounters.[249, 250, 251, 252, 253, 254]

### 1.7.6 Weight loss and sexual desire

Additionally, research is needed on the role of weight loss in improving sexual quality of life. Current research on this topic is limited. In one study, about one third of obese men with erectile dysfunction reported improved sexual function after weight loss and lifestyle changes.[255] In another study, obese men (not necessarily with erectile dysfunction) who lost weight showed increased serum testosterone but no significant improvement in sexual function scores.[256]

### 1.7.7 Obesity and Lower Urinary Tract Symptoms (LUTS)

Obesity has many associated comorbidities including lower urinary tract symptoms. Lower urinary tract symptoms may greatly affect the quality of life of older men;[257, 258, 259] the consequent cost of treatment to the community is high.[260] The prevalence of clinically demonstrated LUTS is 20% in men aged 40-49 years and 40%-50% in those over 65 years.[261,262]

According to the International Continence Society (ICS), LUTS can be divided into storage symptoms, voiding symptoms and symptoms experienced postmicturition (Table 1.4)[263]. As is evident from the table, storage symptoms tend to be irritative in nature, whereas voiding symptoms have a more obstructive cause. A nearly linear relationship has been demonstrated with increasing BMI and the presence of urinary incontinence (UI), as well as with other urinary tract symptoms, including urinary urgency, frequency, nocturia, hesitancy, straining, incomplete bladder emptying, and postmicturition dribble.[264]

**Table 1.4** Lower urinary tract symptoms

| Storage symptoms | Voiding symptoms | Postmicturition |
|---|---|---|
| Frequency | Slow stream | Feeling of incomplete emptying |
| Nocturia | Splitting or spraying | Postmicturition dribble |
| Urgency | Intermittent stream | |
| Urinary incontinence | Hesitancy | |
| Stress incontinence | Straining | |
| Urge incontinence | | |
| Adapted from Ref. (217). | | |

Rosenberg, M. T., Staskin, D. R., Kaplan, S. A., MacDiarmid, S. A., Newman, D. K. & Ohl, D. A. A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. International Journal of Clinical Practice 61 (9), 1535-1546.

Rohrmann et al 2004[265] examined the association between obesity and lower urinary tract symptoms (LUTS) in the Third National Health and Nutrition Examination Survey. This 1988–1994 US cross-sectional study included 2,797 men aged ≥60 years whose current weight, weight at age 25 years, highest weight ever, height, waist circumference, and body mass index (BMI) were assessed**.** Patients with LUTS had at least three of the symptoms of nocturia, incomplete emptying, weak stream, and hesitancy. Controls were men without symptoms or noncancer prostate surgery. Odds ratios adjusted for age and race and weighted for selection probability were estimated by logistic regression. The odds of LUTS were lower for men who were obese at age 25 years compared with men whose BMI was normal (odds ratio = 0.49, 95% confidence interval: 0.27, 0.91). An increase in BMI after 25 years and the highest BMI group was positively associated with LUTS (odds ratio = 1.90, 95% confidence interval: 0.89, 4.05). Men with a larger waist circumference (≥102 cm) were more likely to have LUTS compared with men with a smaller waist circumference (odds ratio = 1.48, 95% confidence interval: 0.87, 2.54). Results suggest that being overweight in young adulthood may be associated with a lower prevalence of LUTS later in life, whereas weight gain and central adiposity in adulthood are possibly associated with a higher prevalence of LUTS.

### 1.7.8 Weight loss and LUTS

There is no data to date as to the effects of rapid diet induced weight loss on LUTS in obese men.

### 1.7.9 Relationship between ED, androgen levels, sexual desire, and LUTS

An association between sexual desire and bioavailable testosterone (BT) levels in both healthy men and in men with ED has been reported in some but not all studies.[266, 267, 268] Recent large-scale epidemiological studies have documented a strong association between LUTS and ED, although the exact mechanism is poorly understood.[269]

In men, obesity (particularly when severe and visceral) has been linked to significant consequences for sexual, reproductive, and lower urinary tract function.

These include low plasma total and free testosterone levels,[270] penile vascular impairment[271] and erectile dysfunction,[272]loss of enjoyment of sexual activity, reduction in sexual desire and avoidance of sexual encounters,[273, 274] and irritative lower urinary tract symptoms (LUTS) (frequency, urgency and nocturia), particularly if weight gain and central adiposity occurs in adulthood.[275]

Studies on the effects weight loss on androgen levels have produced somewhat variable results.[276]

In response to a very low energy diet, a significant decrease in weight was accompanied by an increase in total and free plasma testosterone but no improvement in erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction, or sexual activity[276]; the treatment group had essentially normal baseline scores.

In a two year lifestyle intervention study, about one third of obese men reported improvements in erectile function.[272]

There is a well established link between erectile dysfunction and LUTS but the relationship between treatment of one and effect on the other is unclear[277]. There is no data as to the effects of rapid diet induced weight loss on LUTS in obese men.

Rapid diet-induced weight loss using a meal replacement is a weight management strategy associated with improved long term outcomes, but the effects on sexual function and LUTS remain.

### 1.8 Diet induced weight loss for the treatment of obesity related to cardiovascular disease

Presently, bariatric surgery is the only approach that is able to achieve large (>15%) and sustained (> 5 years) weight losses in the majority of obese subjects.[278] However, bariatric surgery is not suitable for all obese people (eg resources, individual risk or motivation). Very low calorie diets (VLCD) are often used in obesity treatment and results in rapid and profound initial weight loss. In order to improve maintenance, VLCD's are often incorporated in treatment programmes which also include physical activity and behaviour modification.[279]

#### 1.8.1 VLCD and Modified VLCD

In 1988, the American Medical Association's (AMA) Council on Scientific Affairs recognized the medical treatment of obesity and established appropriate treatment guidelines.[280] One of these treatments, the very-low-calorie diet (VLCD), typically provides fewer than 800 kcal per day, although the American Dietetic Association considers any diet of less than 1000 kcal per day to be a very-low-calorie regimen. These diets are attractive to patients because they

induce rapid weight loss and because they are easy to follow due to the imposed limitation on the amount and type of food that can be consumed; patients also report no hunger after several days on the program. They are attractive medically because they can improve weight-related disorders and reduce health risks. [281]

Medical supervision of VLCD programs is mandatory due to the metabolic characteristics of fatigue, weakness, and lightheadedness and related changes in vital signs (blood pressure, heart rate, and respiratory rate). These patients often have obesity-related medical complications such as hypertension or diabetes, which require physician monitoring for appropriate adjustment of medication.[282] Very-low-calorie diets are associated with only minor complications when administered to carefully selected patients by physicians trained in their use.[283, 284] The importance of careful patient selection is shown by attrition rates of 33% to 50% among patients receiving VLCDs.[285] As identified by the Council on Scientific Affairs[280], the Medical Letter on Drugs and Therapeutics,[286] and various investigators,[287] not all VLCDs have the same metabolic effects, protein-sparing ability, or safety.

At the Technology Assessment Conference, Wadden 1992 [288] reviewed the results of clinical trials that used VLCDs and noted that "approximately 90 percent of persons treated by a VLCD and behavior modification will attain a weight loss of this magnitude (9.1 kg or more) and 50 percent a weight loss of 18.2 kg or more".

#### 1.8.2.1 Are VLCD's safe?

VLCDs are generally safe when used under proper medical supervision in people with a body mass index greater than 30. Many people on a VLCD for 4-16 weeks report minor side effects such as fatigue, constipation, nausea and diarrhea, but these conditions usually improve

within a few weeks and rarely prevent people from completing the program. The most common serious side effect seen with VLCDs is gallstone formation.

### 1.8.2 Meal replacements

Meal replacements are defined as "a single food or pre-packaged selection of foods that is sold as a replacement for one or more of the daily meals, but not as a total diet replacement"[289] (Table1.5). These replacements exert their effect through reducing portion size, and consequently energy intake.[290] In patients with morbid obesity requiring large weight losses (BMI > 40 kg/$m^2$), specially formulated very low calorie diet (VLCD) forms of meal replacement may be used in place of all meals. However, more commonly, partial meal replacements are used for one or two meals a day, with at least one usual meal consumed as part of an overall low energy diet.

**Table1.5** Food Standards Australia and New Zealand requirements for commercial meal replacements [289]

Traditionally, there has been concern about the use of any meal replacements, probably based on concerns about the nutritional balance of some commercial mixes potential “bounce back” weight gain on discontinuing use when this use is unsupervised (as for any low-energy diet plan), and the fact that they may not teach users good long-term eating habits.

These concerns have now been largely overcome by advances in food technology, which allow more complete and better balanced nutrient mixes a move towards better training of clinicians about weight control, and the fact that most reputable products are now part of a broader weight loss program, with accompanying nutritional education about non-replacement meals (Table 1.6).

**Table1.6** Characteristics of some examples of commercially available meal replacement products in Australia

| | KicStart VLCD (Pharmacy Health Solutions) | Optifast VLCD (Novartis) | Dr MacLeod's (Orfam) | Ultra Slim (Associated British Foods) |
|---|---|---|---|---|
| Availability | Pharmacies | Pharmacies | Doctors, clinics | Supermarkets |
| Presentation | 24-sachet box | 21-sachet box | Single sachets | Tin of powder |
| Price per meal to patient | $2.04 | $2.33 | $2.65 | $1.00 |
| Protein per serve† (g) | 17.9 | 17.3 | 15.2 | 4 |
| Carbohydrate per serve† (g) | 9.8 | 15 | 19.2 | 20.5 |
| Fat per serve† (g) | 3.0 | 2.3 | 1.8 | 2.6 |
| Omega-3 and -6 fatty acids | Yes | Not listed | Not listed | Not listed |
| No. of vitamins and minerals | 26 | 27 | 16 | 24 |
| Fibre | Yes | Not listed | Not listed | Yes |
| Total energy of prepared drink (kJ) | 584 (water), 883 (skim milk) | 638 (water) | 640 (water) | 875 (skim milk) |
| Accompanying material on weight loss | Yes | Yes | Yes | No |
| Qualifies as VLCD | Yes | Yes | No | No |

*Characteristics apply to the chocolate variety of each product.† Protein, carbohydrate and fat levels are for the dry powder. If directions are to mix with skim milk, levels of protein increase by approximately 7 g, carbohydrate by 10 g and fat by 0.2 g. VLCD = very low calorie diet.

While different forms of meal replacements have been used for weight loss over many years, controlled research on the effectiveness of partial meal replacements is relatively recent. Several studies, reviews and meta-analyses now attest to the benefits of partial meal replacements. Their use commonly results in weight loss of around 9%–10% of total body weight in the short term (6–12 months), and 6%–8% in the long term (eg, 1–5 years), with no reported adverse effects when used as part of an overall low energy diet plan.[289, 290, 291, 292, 293] This compares favourably with a 3%–7% loss on some other types of diet plans, [289,290,291,292] although at least one study showed similar short-term weight losses from meal replacements and a prescriptive, structured low-fat diet plan.[294] The benefits of partial meal replacements are even more obvious when compared with no treatment. In a 5-year study, an average weight gain of over 1 kg per year occurred in control subjects, compared with a loss of 5.8 kg in men and 4.2 kg in women using partial meal replacements.[295] It has been suggested that replacing two meals a day, while maintaining one other main meal, is most effective for initial weight loss, while replacing one meal a day (preferably a meal which is usually high energy, such as lunch or dinner) is enough for long-term maintenance.[292] Quick effects from supervised short-term use might be expected to have the added benefit of increasing motivation for long-term lifestyle change. Several studies have also shown improvements in metabolic risk factors with use of partial meal replacement products, exceeding the changes achieved by dietary change alone (even structured low energy diets).[292, 294] Partial meal replacements have particular benefits for patients with diabetes.[296,297] The effects on glucose control occur within days, and last for as long as weight loss is maintained, enabling a reduction in diabetic medications, but there are also improvements in blood pressure, and serum cholesterol and triglyceride levels (probably more due to the weight loss than the meal

replacement per se). Partial meal replacements appear to have an effect across a range of ages and in both sexes (although men generally have better results than women).[295, 298] They can be used with minimal supervision, but are probably most effective when closely supervised with regular follow-up.[299] Most studies show greater patient satisfaction and lower drop-out rates with partial meal replacements than with other diets, possibly because use of meal replacements results in less hunger.[300] Partial meal replacements also seem effective in people from low socioeconomic backgrounds,[301] who are currently more likely to be overweight, and hence in greater need of weight loss treatments. Importantly, partial meal replacements are generally cheaper than other diet plans (Table 1.2), and certainly more so than non-diet meals. Meal replacements are not contraindicated in common weight-related diseases (eg, diabetes and heart disease), but food sensitivities, such as lactose intolerance or food allergies, need to be taken into account when choosing specific products.

### 1.9 Aims and Hypotheses

The overall aim of the project is to test the hypothesis that rapid weight loss, induced by a low calorie diet will reverse obesity related abnormalities in cardiovascular and reproductive function in men. Specifically we will determine the effects of obesity and diet-induced weight loss, and the extent to which the effects are dependent on, or interrelated with, other cardiovascular risk factors (hypertension, abnormal glucose tolerance, hyperlipidaemia, and obstructive sleep apnoea) on:

(i) Vascular and cardiac function using novel Magnetic Resonance Imaging (MRI) based methodology to evaluate left ventricular and vascular structure and function.

(ii) Erectile dysfunction (ED), sexual desire (SD), androgen levels, lower urinary tract symptoms (LUTS) and overall quality of life.

(iii) Pericardial adipose tissue assessed using echocardiography and MRI.

*The specific aims and objective are to answer the following questions:*

- To what extent does obesity per se, or associated abnormalities in cardiovascular risk factors, affect cardiovascular function (independent of overt coronary artery disease)?
- Do the early abnormalities in cardiovascular function associated with obesity improve with weight loss, and to what extent might this occur using a simple, easy to implement and inexpensive weight loss method.
- Is acute rapid weight loss safe and effective for these abnormalities in cardiac and vascular function? This is an important question because longer term outcomes are better with this approach, particularly in men.
- Although erectile function has previously been shown to improve after a 2-year lifestyle intervention program, the effect of rapid diet induced weight loss on erectile function and sexual desire is unknown, as is the extent to which improvements in erectile function correlate with changes in cardiovascular function. This is important as a simple, cheap and non-invasive clinical indicator.
- Can a simple and cost-effective weight maintenance program can be implemented that will preserve any observed benefits on cardiovascular function

# CHAPTER 2

## 2. Methodology

### 2.1 Subjects selection and exclusion criteria

Obese Caucasian men age 18-65 years, non smokers, and consuming 2 or fewer standard alcoholic drinks per day (on average over the past 5 years) were recruited. Obesity, for the purposes of this study, was defined by a BMI > 30 and a waist circumference >102cm. Caucasian men only were enrolled because the cut-off points for the definition of obesity vary significantly by race. Men were excluded if they had any previously diagnoses or symptomatic atherosclerotic disease, or are taking any cardiovascular medication. Thyroxine for primary hypothyroidism was permitted, provided the dose had been stable over the preceding 12 months. SSRI's for depression were permitted. Men with known gallstones, history of gout, or any contraindication to MRI were also excluded.

### 2.2 Ethics Approval

All protocols were approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

### 2.3 Measurements

#### 2.3.1 Plasma Biochemistry

At baseline and completion of the weight loss phase, venous blood was collected after a 12 hour overnight fast and immediately centrifuged, and the plasma separated and stored at -80$^{o}$C for the subsequent measurement of total cholesterol, triglycerides, LDL, HDL, glucose, insulin, electrolytes, renal, liver function tests, total testosterone and SHBG. These assays

were performed in the NATA certified laboratories of the Institute of Medical and Veterinary Science. In addition plasma was stored for the measurement of inflammatory markers (CRP, ICAM-1, p-selectin, and TNFα).

2.3.1.1 Plasma glucose

Plasma glucose concentration (mmol/l) was measured on the automated Olympus 5400 analyser using a glucose hexokinase enzymatic kit. The intra-assay coefficient of variation (CV) was 2.04% at 3.4 mmol/l.

2.3.1.2 Serum insulin

Serum insulin concentration (μU/ml) was measured on the Roche E170. The intra-assay CV was 3% at 62 μU/ml.

2.3.1.3 Serum total cholesterol

Serum total cholesterol concentration (mmol/l) was measured on the automated Olympus 5400 analyser. The intra-assay CV was 1.8% at 5.4 mmol/l.

2.3.1.4 Serum Triglycerides

Serum triglycerides concentration (mmol/l) was measured on the automated Olympus 5400 analyser. The intra-assay CV was 1.8% at 1.04 mmol/l.

2.3.1.5 Serum high-density lipoprotein

Serum high-density lipoprotein (HDL) cholesterol concentration (mmol/l) was measured after precipitation of the low-density and very-low-density lipoproteins with polyethylene glycol

6000 solution (Warnick G et al 1985), using the method listed in Section 2.3.1.3. The intra-assay CV was 3.2% at 1.7 mmol/l.

2.3.1.6 Serum low-density lipoprotein

Serum low-density lipoprotein (LDL) cholesterol concentration (mmol/l) was calculated using the modified Freidewald equation (Friedwald WT, 1972).

2.3.1.7 Total Testosterone and Sex Hormone-Binding Globulin (SHBG)

Total testosterone was determined by chemiluminescent immununoassay using Elecsys (ROCHE, Indianapolis, USA). The intra-assay CV was 10.4% at 12.5 nmol/l.

SHBG was determined in subject serum diluted to 1:21 by adding SHBG sample dilutant. DPC IMMULITE 2000 SHBG (Diagnostic Products Corporation, Los Angeles, CA), a solid-phase, two-site chemiluminescent, immunometric assay was used (CV 4% at 32.3 nmol/l. The free androgen index (FAI) was calculated as Total T/SHBG.

**2.3.2 Questionnaires**

**2.3.2.1 International Prostate Symptom Scale (IPSS)**

The International Prostate Symptom Scale (IPSS) - also known as the American Urological Symptom Index for benign Prostatic Hyperplasia – is a series of questions used to assess the severity of symptoms caused by prostatic enlargement. The questionnaire determines symptoms of both an obstructive nature and irritative nature. The symptom assessment consists of seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying and surgery. Internal consistency has been demonstrated

by a Cronbach's alpha of 0.86. The questionnaire has excellent test-retest reliability (R=0.92), and the presence of obstructive symptoms are strongly discriminative of benign prostatic hyperplasia from control subjects (ROC area 0.85). Irritative symptoms may be related to causes other than prostate enlargement, for example obesity, hypertension, and diabetes mellitus.

The IPSS symptom index (Table 2.1) is the sum of all points for the first 7 questions listed in Appendix A. Question 8 is excluded and used to assess quality of life.

**Table 2.1** International Prostate Symptom Scale (Minimum Score = 0 Maximum Score = 35)

| **Score** | **Symptoms** |
|---|---|
| 0-7 | Mild |
| 8-19 | Moderate |
| 20-35 | Severe |

#### 2.3.2.2 International Index of Erectile Function (IIEF)

The IIEF is used to assess erectile function. It was designed to be reliable and valid across cultures and can be used to monitor response to treatment. A high degree of internal consistency has been demonstrated for each of the five domains and for the total index (Chronbach's alpha values of 0.73 and higher, and 0.91 and higher, respectively) and each domain has a high degree of sensitivity and specificity to effects of treatment. Test-retest reliability correlation coefficients for the 5 domain scores were highly significant (EF = 0.84, SD = 0.71, IS = 0.81, OS = 0.77).

Erectile function was assessed by completing questions on the International Index of Erectile Function (IIEF), which is a multidimensional questionnaire. [302, 303] The questions are listed in Appendix A. The IIEF score represents the summation of questions, 2, 4, 5, 7 & 15 with a maximum score of 25. A score of 21 or less indicates erectile dysfunction (Table 2.2). An increase in score indicates clinical improvement.

**Table 2.2** International Index of Erectile Dysfunction Scores

| **Score** | **Interpretation** |
|---|---|
| 22-25 | No erectile dysfunction |
| 17-21 | Mild erectile dysfunction |
| 12-16 | Mild to moderate erectile dysfunction |
| 8-11 | Moderate erectile dysfunction |
| 5-7 | Severe erectile dysfunction |

#### 2.3.2.3 Sexual Desire Inventory 2 (SDI-2)

The SDI is a well-validated self-report questionnaire that specifically evaluates sexual desire in the absence of consummatory behaviour. The SDI measures two aspects of sexual desire: *dyadic*, meaning an interest in or wish to engage in sexual activity with another person, or a desire for intimacy and sharing with another; and *solitary* sexual desire, meaning an interest in engaging in sexual behaviour with oneself and may involve a wish to refrain from intimacy and sharing with others. Internal consistency of the inventory is high with Chronbach's alpha values of 0.86 for dyadic and 0.96 for solitary sexual desire.[304]

The total Sexual Desire [305] score was calculated by summing questions 1-14 as listed in Appendix A. A summary score for the dyadic scale is calculated by summing items 1-8. Question 9 is excluded as it is not measuring the quantity of sexual desire, but rather perceived sexual desire in relation to peers. A summary score for the solitary scale is calculated by summing items 10, 11 & 12. Item 13 is eliminated for the same reason as item 9.

#### 2.3.2.4 The Berlin Questionnaire for Obstructive Sleep Apnoea

Obstructive sleep apnea-hypopnea syndrome is characterized by excessive daytime sleepiness, disruptive snoring, repeated episodes of upper airway obstruction during sleep and nocturnal hypoxemia. The Berlin Questionnaire, includes a series of questions about risk factors for sleep apnea, including snoring behaviour, waketime sleepiness or fatigue, and obesity or hypertension.

The likelihood of a subject having obstructive Sleep Apnoea was determined by a structured questionnaire.[306] This has reliability (good test-retest correlation) of 0.92 and a validity (area under the ROC curve) of 0.79 ($p < 0.0001$).

#### 2.3.2.5 General Health and Well Being SF 36

The SF-36 questionnaire is a multi-purpose, short form health survey with 36 questions. The questions have been carefully chosen to measure all the aspects of health and wellbeing that, together, we call "quality of life".

Some questions ask about a person's physical functioning (walking, climbing stairs and so on). Others refer to the amount of pain experienced, or to energy levels or mood. There are also questions that try to understand how a person's health is affecting his or her ability to enjoy their social life, or to manage everyday tasks.

### 2.3.3 Cardiac Magnetic Resonance Imaging

#### 2.3.3.1 Left Ventricular Function

Magnetic resonance imaging was performed on a 1.5-T clinical magnetic resonance scanner with subjects in the supine position. Quantitative evaluation of ventricular function is achieved by obtaining a series of contiguous MRI slices that cover the ventricles in short-axis. By tracing the blood-endocardium boundary, the slice's volume is calculated as the product of its cross-sectional area and thickness. Ventricular volume was then determined by summation of the volumes of all slices. The MR images, once obtained, were transferred to a computer workstation for analysis using ImagePro Plus (Media Cybernetics). For LV volume analysis, the endocardial and epicardial contours were manually traced on both end–diastole and end-systole. From this data one can calculate left and right ventricular ejection fractions and stroke volumes.

#### 2.3.3.2 Brachial Artery Flow-Mediated Dilatation

MRI can also be used to accurately quantify peripheral endothelial dysfunction, as evaluated by brachial artery flow mediated dilatation. After 10 minutes rest, we measured brachial artery area by MRI, at baseline and 1 min after reactive hyperaemia induced by release of a forearm cuff inflated to 50 mmHg above systolic pressure for 5 minutes. MRI data acquisition was then repeated before and 3 minutes after a sublingual spray of nitroglycerin (NTG).

Cardiac-gated TrueFISP cine images of the brachial artery were acquired with the following parameters: TR/TE 56/3 ms, flip angle 66°, FOV 117x77 mm, matrix 384x252, 16 segments, 11 to 19 phases depending on heart rate.

2.3.3.3 Aortic and carotid measurements

Vascular distensibility of the aorta was assessed using TrueFISP (fast imaging with steady state free precession) cine sequence. For aortic distensibility, sagittal-oblique scout images were acquired aligned with the aortic arch. A high-resolution gradient-echo pulse sequence with a velocity encoding gradient for phase contrast MRI was applied with TE 2.8 ms, effective TR 1 RR-interval, flip angle 30°, matrix size 256x192, FOV 320x240 mm, slice thickness 5 mm.

Carotid artery imaging was performed using a two element array surface coil. Carotid repletion time/echo time (TR/TE) 45.3 ms/2.4 ms, field of view FOV 200 mm, in-plane resolution 0.52 mm, and slice thickness 3mm.

**2.3.4 Cardiac echocardiography**

Resting echocardiography was performed in the left lateral decubitus position, using the Vivid 7 Dimension (Transducer M3S 1.5 – 4.0 MHz), a premier cardiovascular ultrasound system (GE Healthcare). Images were obtained in the standard tomographic views of the LV (parasternal long and short axis and apical four-chamber, two-chamber, and long-axis views). All images were saved digitally in raw-data format to a magneto optical disk (EDM-2300B, Sony Electronic Inc., Saitama, Japan) for offline analysis.

### 2.3.5 Low Calorie Diet

KicStart™ is a nutritionally complete, but lower energy formulated liquid meal (Table 2.3). Two sachets of, KicStart™ (one for breakfast and one for lunch) provides 450 cal of energy per day, 0.8 grams per kilogram ideal body weight of high quality protein, and the recommended daily allowances (RDI) of minerals, vitamins, trace elements, omega 3 and 6 essential fatty acids. The Kicstart was supplemented with some salads, carbohydrate free vegetables and a small piece of meat fish or chicken each day in order to achieve a total energy intake of approximately 850 kcals/day.

**Table 2.3** KicStart Nutritional Information

| **Nutritional Information: Quantity per serve (40 g)** | | | |
|---|---|---|---|
| **Energy** | 584 KJ | **Folate** | 100 um |
| **Protein** | 17.9 g | **Vitamin B6** | 0.8 mg |
| **Fat Total** | 3 g | **Vitamin B12** | 1 ug |
| **Saturated** | 0.8 g | **Biotin** | 5 ug |
| **Trans** | 0 g | **Pantothenin Acid** | 0.8 mg |
| **Monounsaturated** | 1.2 g | **Vitamin C** | 20 mg |
| **Polyunsaturated** | 0.7 g | **Vitamin D** | 4.1 ug |
| **Omega-6 LA** | 546 mg | **Vitamin E** | 4 mg |
| **Omega-3 ALA** | 63.5 mg | **Vitamin K** | 30 ug |
| **Omega-3 EPA** | 12.7 mg | **Calcium** | 264 mg |
| **Omega-3 DHA** | 54.4 mg | **Chromium** | 34 ug |
| **Carbohydrate** | 9.8 g | **Copper** | 0.5 mg |
| **Sugars** | 7.4 g | **iodine** | 75 ug |
| **Dietary Fibre** | 3.2 g | **Iron** | 4.8 mg |
| **Sodium** | 352 mg | **Magnesium** | 137 mg |
| **Potassium** | 965 mg | **Manganese** | 0.85 mg |
| **Vitamin A** | 300 ug | **Molybdenum** | 42.5 ug |
| **Thiamin** | 0.55 mg | **Phosphorus** | 259 mg |
| **Riboflavin** | 0.85 mg | **Selenium** | 17.5 ug |
| **Niacin** | 5 mg | **Zinc** | 4.8 mg |

## 2.4 Protocol

At a baseline screening visit informed consent was obtained, and the inclusion/exclusion criteria reviewed. At this visit subjects were asked to complete the questionnaires (*see 2.3.2*) One week later subjects visited the clinic, fasting, between 7.00 am and 10.00 am. Height, weight, waist circumference and seated blood pressure (after 5 minutes rest, manual method, mercury sphygmomanometer) was taken. Thereafter a venous blood sample (~40mls) was obtained and stored for the later biochemistry, hormone levels and inflammatory markers (*see 2.3.1*). Instruction in the use, and of a low calorie diet, aiming to provide ~850 Kcal/day was given and supplies of Kicstart provided (*see 2.3.5*). Subjects were told to use 2 sachets of KicStart$^{TM}$, one for breakfast, and one for lunch, dissolved in 200 ml of hot or cold water. In addition one small low saturated fat, carbohydrate free meal up to a total of 400 calories per day was permitted according to a meal plan which was provided. Water, tea, coffee and diet soft drinks may be consumed *ad-libitum*, but with a minimum of 2-litres of fluid each day. The diet continued for 8 weeks. A pedometer was provided and subjects were asked to aim to walk 10 000 steps each day. Subjects were asked to maintain a diet and activity diary and to record intake and activity on a daily basis. The data in the diary was reviewed and recorded at subsequent visits which occurred every two weeks. At each visit progress was evaluated, weight, waist circumference and seated blood pressure (after 5 minutes rest manual method) measured and caloric intake adjusted if necessary to ensure a weight loss of 1-2kg. At week 10 the investigations done in Week 2 were repeated.

### 2.5. Statistical considerations

Statistical analysis was performed using SPSS 15. All results are expressed as mean values ± SEM. For assessment of functional differences pre and post weight loss Student *t* test was performed. A value of $p<0.05$ was considered significant. Pearson's correlation was performed evaluating the correlation with change in weight and waist circumference with change in EF and endothelial function.

### 2.6 Cardiac Imaging

The ideal imaging modality would need to be safe, noninvasive, accurate and reproducible, thus allowing longitudinal studies in the same patient.[307] There are currently several imaging modalities under investigation for this purpose, and the strengths and limitations of each will be discussed.

Echocardiography has long been used to characterize systolic and diastolic function, as well as those structural alterations that accompany congestive heart failure. Computed tomography (CT) provides clinically relevant anatomic and functional information, is relatively noninvasive, and has very low short and long-term risks. Magnetic Resonance Imaging (MRI) provides clinically relevant anatomic and functional information noninvasively with minimal risk, and potential hazards such as attraction of metallic objects are avoided.

#### 2.6.1 Echocardiography (cardiac ultrasound)

Edler (a Swedish cardiologist) and Hertz (a physicist) were the first clinical team to successfully utilize ultrasound technology to non-invasively image the heart in Europe in 1954. [308] This signified the birth of transthoracic echocardiography (TTE). Since this time, major advances in TTE have occurred including the development of fast Fourier

transformation and Doppler colour flow mapping, resulting in TTE becoming the "Gold Standard" bedside cardiac imaging modality for the diagnosis of a variety of cardiac complaints. Standard TTE is the most widely available, and often first line, non-invasive imaging modality for diagnosing abnormalities of cardiac morphology (using 2D and time-motion mode measurements), valvular pathologies (combining abnormalities on both 2D imaging and spectral Doppler flow patterns) and cardiac contractile dysfunction (resting global systolic and diastolic impairment, regional wall motion abnormalities, and the use of dobutamine stress/viability protocols for the diagnosis of inducible ischaemia and myocardial viability).

### 2.6.2 The use of traditional echocardiography in the assessment of cardiac contractile function

#### 2.6.2.1 Global left ventricular (LV) systolic function

For many years TTE has been used to quantify LV systolic function by calculating the ejection fraction (EF) of the left ventricle (the total blood volume ejected from the LV during each cardiac cycle, expressed as a percentage of the total volume of blood present in the LV at the end of the diastolic filling period). Several methods are available for calculating LV EF echocardiographically, and each of these has advantages and limitations (see Table 2.4).

**Table 2.4**. Left ventricular quantification methods: Use, advantages, and limitations [309]

| Dimensions/volumes | Use/advantages | Limitations |
|---|---|---|
| **Linear**<br>M-Mode | Reproducible<br>High frame rates<br>Wealth of accumulated data<br>Most representative in normally shaped ventricles | Beam orientation frequently off axis<br>Single dimension may not be representative in distorted ventricles |
| **2D Guided** | assures orientation perpendicular to ventricular long axis | Lower frame rates than M-Mode<br>Single dimension only |
| **Volumetric**<br>Simpson's Biplane | corrects for shape distortion<br>minimises mathematical assumption | apex frequently foreshortened<br>endocardial dropout<br>relies on only two planes<br>few accumulated data on normal population |
| Area-length | partial correction for shape distortion | based on mathematical assumptions<br>few accumulated data |
| **Mass**<br>M-Mode or 2D guided | wealth of accumulated data | inaccurate in ventricles with regional abnormalities<br>Beam orientation (M-mode)<br>Small errors magnified<br>Overestimated LV mass |
| Area-length | allows for contribution of papillary muscles | insensitive to distortion in ventricular shape |
| Truncated ellipsoid | more sensitive to distortions in ventricular shape | based on a number of mathematic assumptions<br>minimal normal data |

2D; two dimensional.

Both the American Society of Echocardiography and the European Association of Echocardiography guidelines favour the use of the biplane method of discs (modified Simpson's rule) as the echo gold standard for calculating LV EF.[309] The principle underlying this method is that the total LV volume is calculated from a stack of elliptical discs, the calculated volume of which is derived from LV cavity measurements recorded in the apical 4-chamber and apical 2-chamber views. The EF is then calculated as follows:

EF(%) = (EDV-ESV)/EDV  where EDV is the LV end diastolic volume and ESV is the LV end systolic volume.

This technique requires both the presence of good endocardial definition and the absence of apical foreshortening during image acquisition. (Obese individuals often have poor echogenic windows, and as such, are not suitable subjects for the application of Simpson's rule.) In echogenic subjects and with the introduction of second harmonic imaging in the absence of contrast enhancement, interobserver errors are still significant. Thompson et al. 2001[310] showed that the interobserver variability in calculating the LV end diastolic volume (LVEDV), LV end systolic volume (LVESV) and LV EF are 13%, 17% and 18% respectively. Even with the use of both second harmonic imaging and contrast enhancement, interobserver variability for LVEDV, LVESV and LV EF are 8%, 15% and 6% respectively.[310] It is becoming increasingly acknowledged that the superior spatial resolution of newer imaging modalities, such as cardiac magnetic resonance imaging (CMR), are diagnostically more accurate in quantifying global LV systolic function by traditional methods. Indeed, applying Simpson's method of discs to a CMR trueFISP breath hold cine LV short axis series results in an interobserver variability for LVEDV, LVESV and LV EF of

8%, 4% and 5% respectively [311] – a significant improvement on standard TTE techniques. CMR also has the advantage that, unlike TTE, it is not dependent on the presence of good echogenic windows, which are often lacking in obese individuals.

2.6.2.2 Regional left ventricular systolic function

In addition to measurements of global systolic function, regional wall motion abnormalities are traditionally diagnosed by TTE by assessing the degree of systolic wall thickening (SWT) in the 17 standard American Heart Association (AHA) myocardial segments.[309] A regional wall motion scoring index can then be applied by visually classifying each AHA segment as either normal (normal SWT), hypokinetic (reduced SWT), akinetic (no SWT) or dyskinetic (paradoxical motion). SWT measures myocardial systolic contractile function in the radial plane. The heart however contracts in three planes – radial (SWT), longitudinal (myocardial fibre shortening) and circumferential (contractile "twisting" along the cardiac axis). To improve diagnostic assessment of regional systolic function assessment in greater than one cardiac plane is required.

2.6.2.3 Global left ventricular diastolic function

Abnormalities of cardiac relaxation can occur in the absence of detectable systolic dysfunction, especially in conditions (including obesity) favouring increased left ventricular mass. Diastole has four phases as shown below (and in Figure 2.1):

1) Isovolumic relaxation (IVRT)
2) Early passive LV filling
3) Diastasis
4) Late active LV filling associated with atrial contraction

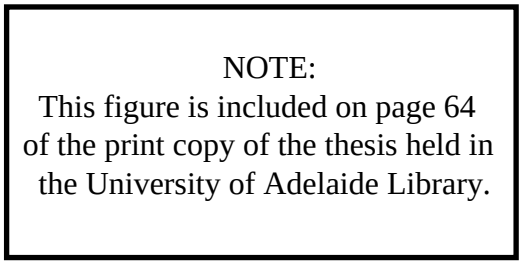



**Figure2.1**. Normal diastolic pressure/flow patterns recorded during (A) cardiac catheterisation; (B) mitral inflow Doppler trace during TTE; (C) pulmonary vein flow during TTE.[312]

Diastole is a complex process and therefore traditionally, diagnosis of diastolic dysfunction is based upon a combination of diastolic measurements including mitral inflow patterns, mitral E and A wave deceleration times, abnormal E:A ratios, abnormal pulmonary vein flow patterns and prolonged isovolumic relaxation times (Figure 2.1). Normal diastolic parameters

are shown in Table 2.5.[313] The major drawback of these methods is that the results are dependant on the haemodynamic loading conditions of the heart.

**Table 2.5.** Normal ranges for diastolic function indices in adults (95% confidence interval) [313]

| Diastolic Parameter | Normal Range |
|---|---|
| MV peak E wave (m/sec) | 0.4-1.0 |
| MV peak A wave (m/sec) | 0.2-0.6 |
| E:A ratio | 0.7-3.1 |
| MV E deceleration time (msec) | 139-219 |
| Isovolumic relaxation time (IVRT) (msec) | 54-98 |

2.6.2.4 Regional left ventricular diastolic function

Traditionally, there has been no means of assessing regional diastolic function.

### 2.6.3 New echocardiographic techniques

As alternative non-invasive imaging modalities continue to improve in diagnostic accuracy, for TTE to retain it's clinical utility, alternative methods for the accurate quantification of LV systolic function must be found. The introduction of real time 3-dimensional echocardiography (RT3DE) and tissue Doppler echocardiography (TDE) both show great promise.

### 2.6.4 Tissue Doppler Echocardiography (TDE): Tissue velocity imaging, Strain and Strain Rate Imaging

Myocardial tissue movement occurs at an amplitude of forty decibels higher and a velocity ten times slower than myocardial blood flow.[314] By applying standard autocorrelation processing but reversing low amplitude and high velocity filters it is possible to obtain images

of tissue Doppler motions of high temporal resolution without significant artefact originating from the blood pool. [314, 315] This is the basis underlying new TDE techniques. By employing the above gain/filter settings regional myocardial tissue velocities, strain and strain rates can be recorded throughout the whole of the cardiac cycle with excellent temporal resolutions.

2.6.4.1 Tissue velocity imaging

Using either pulsed-wave tissue velocity imaging (TVI) or colour TVI with post processing, myocardial velocity profiles can be generated throughout the whole of the cardiac cycle for the basal and mid segments of all LV walls. Ensuring a Doppler angle error of <20 degrees in the apical views, the resultant velocity profiles equate to the velocity profiles of myocardial contraction and relaxation in the longitudinal plane of the heart (Figure 2.2).

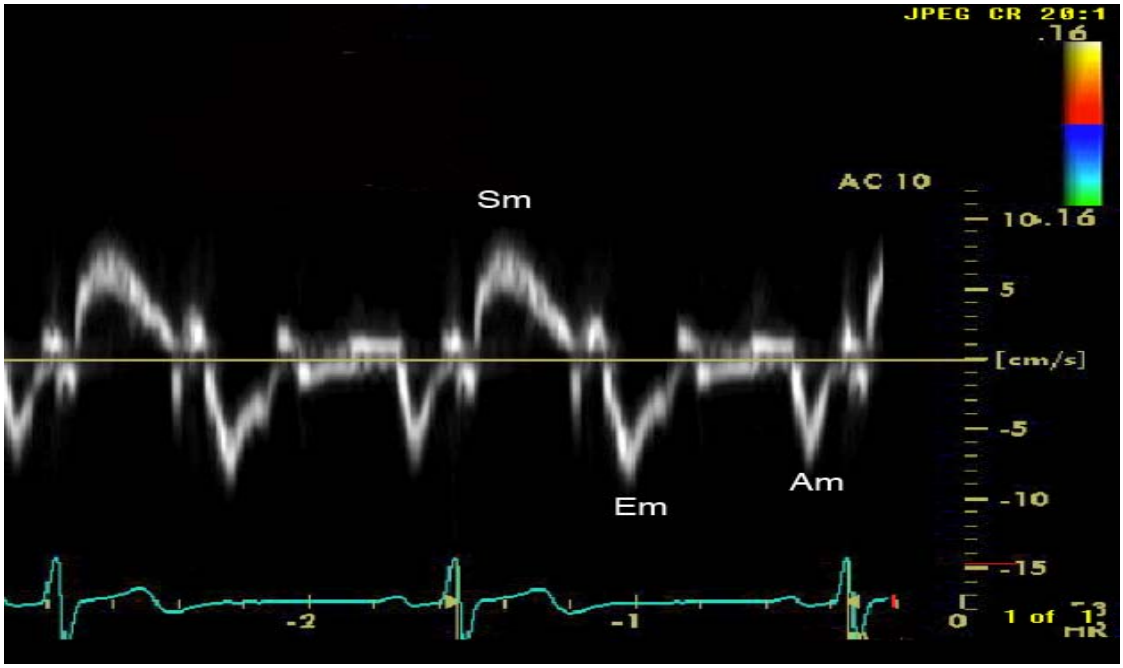



**Figure 2.2.** A normal pulsed-wave tissue Doppler trace acquired at mitral valve annulus; Sm, peak systolic mitral annular velocity; Em, peak early diastolic mitral annular velocity; Am, peak mitral annular velocity associated with atrial contraction.

2.6.4.2 Regional systolic function

The peak systolic velocities of the basal walls of the LV in a normal heart are as shown in Table 2.6.

**Table 2.6.** Pulsed-wave Tissue Doppler Systolic Myocardial Velocities of the Normal Left Ventricle[316]

| PW sample position | Peak systolic myocardial tissue velocity (cm/sec) |
|---|---|
| Basal septum | 7.5 ± 1.3 |
| Basal lateral wall | 10.3 ± 1.9 |
| Basal anterior wall | 10.3 ± 1.6 |
| Basal inferior wall | 9.6 ± 0.9 |
| Basal posterior wall | 9.9 ± 1.3 |

2.6.4.3 Regional diastolic function

The peak velocities of early diastolic relaxation in the normal heart are as shown in Table 2.7. Unlike traditional indices of diastolic function, Em velocities are an index of LV relaxation that are relatively independent of cardiac preload.[317, 318, 319]

**Table 2.7**. Pulsed-wave Tissue Doppler Diastolic Myocardial Velocities of the Normal Left Ventricle[320]

| Mitral Annular Position | Peak mitral annular diastolic relaxation velocity, Em (cm/sec) |
|---|---|
| Basal septum | 12.3 ± 2.8 |
| Basal lateral wall | 15.8 ± 3.8 |
| Basal anterior wall | 13.7 ± 4.0 |
| Basal inferior wall | 13.6 ± 3.6 |

#### 2.6.4.4 Global diastolic function

Elevated left ventricular filling pressures occur when diastolic dysfunction is present. Traditionally left ventricular filling pressures are measured invasively at the time of cardiac catheterisation. Recently it has been demonstrated that the ratio of peak mitral E wave velocity to early peak mitral annular velocity correlates well with pulmonary capillary wedge pressure and hence calculated mean left atrial pressure (LAP).[321]

#### 2.6.4.5 Strain and strain rate imaging

Langrangian strain is the degree of myocardial deformation, at a given time point within the cardiac cycle, in relation to end-diastole as the reference point. Strain analysis enables calculation of the instantaneous velocity gradient between two sample points at a pre-defined distance. This velocity gradient is then divided by the sample distance to yield the temporal changes of deformation known as myocardial strain rate. The potential advantages of myocardial strain and strain rate over current assessments of LV systolic function are four fold: 1) they allow sensitive assessment of regional myocardial function at high temporal resolutions, far excelling those of the naked eye; 2) the resultant strain graphs are both objective and quantifiable; 3) Strain assesses myocardial *deformation* not myocardial *velocity* and so distinguishes between active contraction and passive inward motion of akinetic myocardium being "dragged" inwards by pulling forces from adjacent contracting myocardium, 4) strain enables assessment of systolic contraction in two cardiac contractile planes; radial (positive strain) and longitudinal (negative strain), compared to standard methods which assess contraction in the radial plane only. Changes in systolic strain can be documented over time, and is a more sensitive measure of changes in systolic contractile function than calculated ejection fraction. Strain is most commonly assessed in the

longitudinal plane from the apical views (Figure 2.3). Normal longitudinal and radial systolic strain values are shown in Table 2.8.

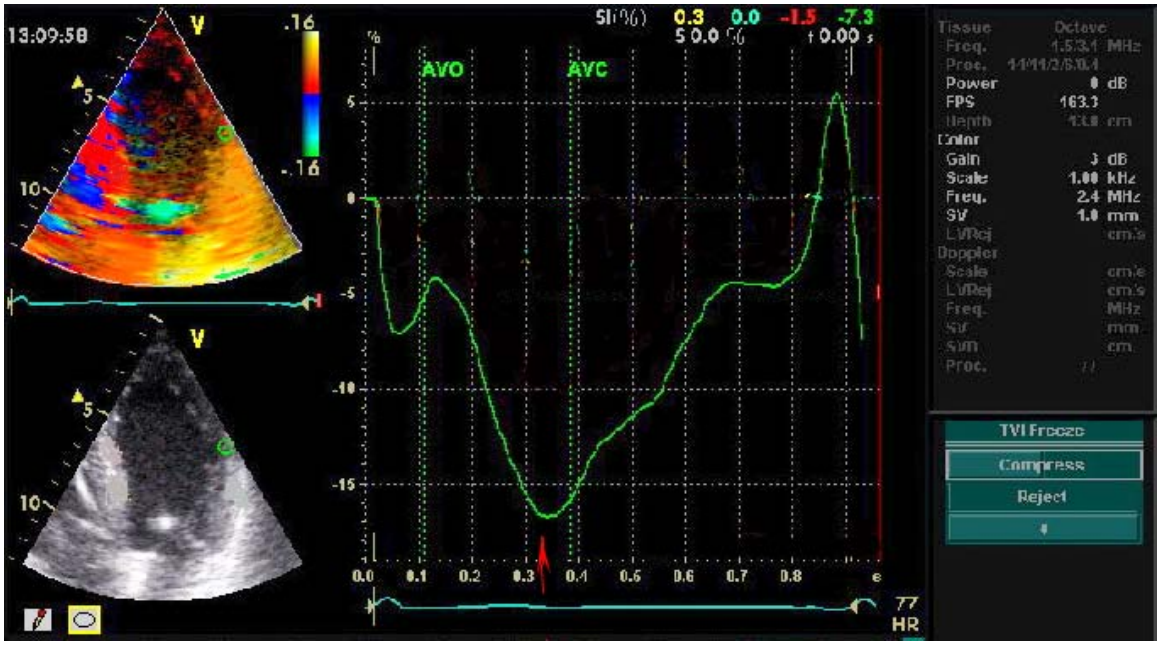



**Figure 2.3**. Longitudinal strain profile. The arrow indicates peak systolic strain

**Table 2.8.** Peak systolic strain in the normal left ventricle

| **Strain Imaging Plane** | **Normal Peak Systolic Strain values** |
|---|---|
| Radial strain[322] | + 41.0 ± 17.0% |
| Longitudinal strain[323] | - 18.7 ± 3.7% |

While undoubtedly CMR has superior spatial resolution to echocardiography, TDE has the advantage over CMR, by virtue of the fact that it is a real time technique, and unlike CMR is not dependant on frame (phase) averaging. High frame rates with TDE (≥ 150fr/sec) are readily achievable and so although the spatial resolution is not as good as CMR, the temporal resolution is far superior.

### 2.6.5 Real time three dimensional echocardiography (RT3DE)

While strain and tissue velocity imaging improve assessment of LV contractile function by providing sensitive 2D measures of regional systolic and diastolic tissue contractile indices with excellent temporal resolution, the development of RT3DE has improved the echocardiographic assessment of left ventricular volumes and accuracy of volumetric calculations.

RT3DE largely overcomes the geometrical limitations of standard 2D TTE. A 3D acquisition of the LV is performed from the apical window, from data gathered over 4-5 cardiac cycles. Using semi-automated endocardial border detection, the LVEDV and LVESV are measured from the resulting three-dimensional left ventricular volume. The LV EF is then calculated from the LV volumes as described previously. The changes in regional volumes between end-diastole and end-systole are also displayed by the software (Figure 2.4). Jacobs et al[324] have shown RT3DE to have significantly better reproducibility than standard 2D TTE, with RT3DE interobserver variability's of 10%, 11%, 5% for LVEDV, LVESV and LVEF respectively. Volumetric calculations using RT3DE correlate well with cardiac MRI derived measurements.[325]

**Figure 2.4**. Change in AHA 17 segment regional LV volumes over time with RT3DE [326]

### 2.6.6 LV morphological, haemodynamic and contractile changes in Obesity

Obesity is associated with altered cardiac morphology including increased LV mass, left ventricular hypertrophy and increased LV volumes diagnosed echocardiographically. These findings have been indexed against height/BMI in otherwise healthy obese individuals and are independent of hypertension, diabetes, hyperlipidaemia and smoking.[327]

Controversy exists over the effect obesity per se has on LV systolic function. Previous studies, employing standard 2D TTE techniques have shown preserved,[327] increased [328] and reduced [329] LVEF in obese individuals compared to non-obese controls. Haemodynamic measures of LV systolic function suggest preserved or increased cardiac output, due to increase in stroke volume.[330] LV filling pressures are high in obesity, and increased SV has

therefore been attributed to increased preload. Alpert et al. 1993 [331] has demonstrated an inverse correlation between increasing LV volumes and LV fractional shortening and also determined that duration of obesity is the strongest predictor congestive heart failure. These findings suggest that the presence of chronically elevated pre-load results in LV remodelling, with an initial increase in SV and cardiac contractile function in response to increased LV volumes and diastolic wall stretch, with further adverse remodelling and gradual decompensation over time. Recent work using more sensitive tissue Doppler assessments of LV systolic function, have suggested the presence of subclinical systolic dysfunction in obese individuals with preserved LVEF.[327, 332] This further supports the hypothesis of an obesity related cardiomyopathy.

Diastolic abnormalities are well documented in obesity.[327, 332, 333, 334, 335, 336, 337] Doppler derived IVRT and mitral inflow patterns suggest diastolic dysfunction due to either abnormalities predominantly due to abnormal LV relaxation (prolonged IVRT, reduced peak mitral E wave velocity, reduced E/A ratio, prolonged mitral deceleration time) or predominantly due to reduced LV compliance (short IVRT, increased peak mitral E wave velocity, increased E/A ratio, short mitral deceleration time). These indices however are dependant on haemodynamic loading conditions, which are altered in obese individuals. More recently load-independent tissue Doppler indices have been used to assess diastolic function and mitral annular early relaxation velocities (Em) are consistently lower in obese individuals compared to non-obese individuals.[327,332] Doppler E/Em ratios are high,[328] which is consistent with catheter derived measures confirming elevated left ventricular end-diastolic pressure, pulmonary capillary wedge pressure and mean left atrial pressure.[330] The finding of

high mean left atrial pressures in conjunction with increased left atrial size [328, 329, 338] may explain the increased incidence of atrial arrhythmias associated with the obese population.

The development of new, more sensitive echocardiographic techniques now enables us to image the heart in ways that were not previously possible. RT3DE employs more sensitive and accurate measures of changes in cardiac volumes, while new tissue Doppler techniques enable sensitive quantitative load independent assessments of both left ventricular systolic and diastolic contractile function. These methods allow us to diagnose subclinical abnormalities of cardiac contractile function associated with obesity and other clinical conditions, and enable us to sensitively track changes in cardiac contractility before and after dietary and other interventions.

### 2.6.7 Magnetic Resonance Imaging (MRI)

Cardiovascular magnetic resonance (CMR) is an accepted gold standard for non-invasive, accurate and reproducible assessment of cardiac mass and function.[339, 340, 341, 342. 343, 344, 345] The assessment of function by CMR has some advantages over other techniques such as echocardiography, namely the ability to provide accurate and reproducible tomographic static and dynamic images of high spatial and temporal resolution in any desired plane without exposure to ionizing radiation. Recent MRI image acquisition protocols are faster and provide assessment of cardiovascular anatomy, global and regional ventricular function, myocardial perfusion and viability, quantitative flow analysis and tissue imaging.

Complexity of cardiac anatomy

The cardiac anatomy is complex, and cardiac structures have different appearances depending on the imaging plane. The most useful imaging planes are those parallel and perpendicular to the cardiac axes. Obtaining images in these double-oblique planes requires the use of multiple localizing sequences and knowledge of the target anatomy. The more accurate localization, the more accurate pathologies or functional interferences will be displayed in the images. Localization involves four steps: orthogonal multi-slice localizer, 2-chamber localizer, 4-chamber localizer and short axis localizer.

2.6.7.1 Orthogonal multi-slice localizers

An orthogonal multi-slice localizer provides several transverse, sagittal, and coronary slices of the heart (Figure 2.5).

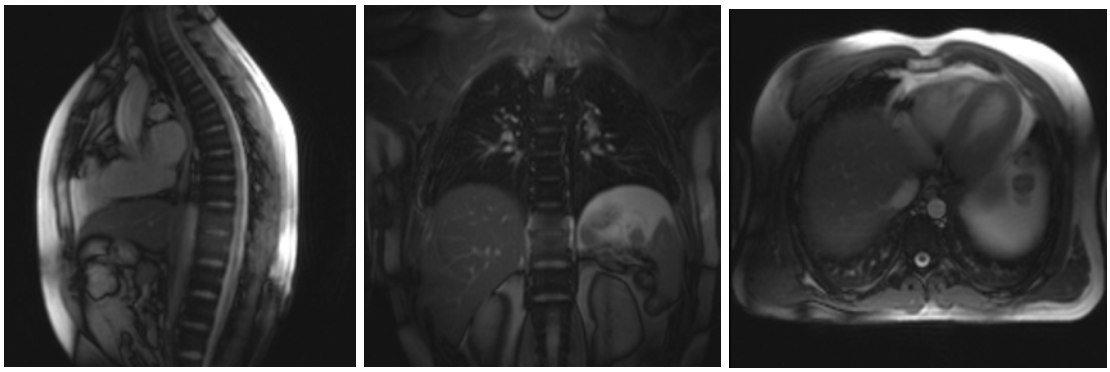


**Figure 2.5** Orthogonal localizers

2.6.7.2 Two chamber view/vertical long axis view

A two chamber view is a long axis view perpendicular to the four chamber view covering the anterior and inferior wall of the LV (Figure 2.6a).

2.6.7.3 Three Chamber view/vertical long axis

The 3 chamber view (left ventricular inflow and outflow tract) shows the left ventricle, left atrium, anterior septum, back side wall of the left ventricle and the aortic and mitral valve (Figure 2.6b).

2.6.7.4 Four chamber view /horizontal long axis view

A four chamber view or horizontal long-axis view transects the LV through the apex and the midpoint of the mitral valve. It also covers the left atrium, right ventricle and right atrium at their maximal diameters (Figure 2.6c).

2.6.7.5 Short Axis View

Short axis views transect the left ventricle (LV) perpendicular to its long axis (which is defined by the LV apex and the midpoint of the mitral valve) (Figure 2.6d).

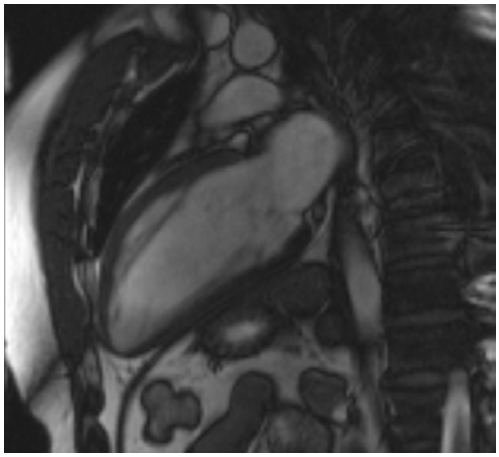
2.6.7.6 Flow quantification

The non –invasive measuring of blood flow is one of the biggest advantages of cardiovascular MR. Flow measurements are used for examining vessel pathologies or as a part of comprehensive cardiovascular MR examinations. Phase contrast images are generated for displaying flow and encoding the flow velocity. (Figure 2.6 e and f)

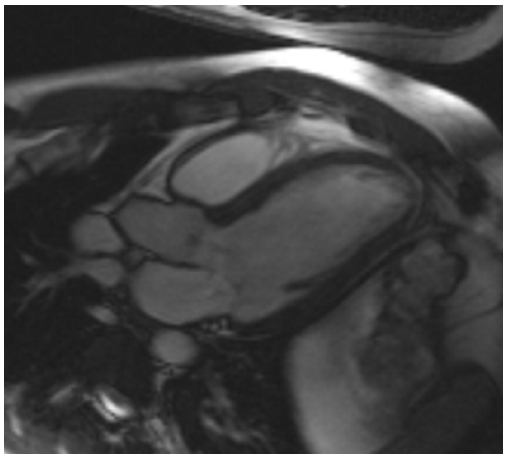
The flow velocity is displayed by respective grey values in the phase contrast images. Each pixel grey value represents a certain velocity (Table 2.9).

**Table 2.9** Flow Velocity Scale

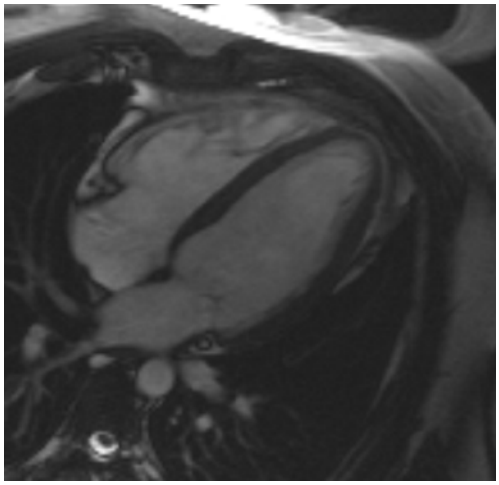
| Display | Flow Velocity |
|---|---|
| White | maximum in positive direction |
| Black | maximum in negative direction |
| medium grey | stationary tissue (no flow) |



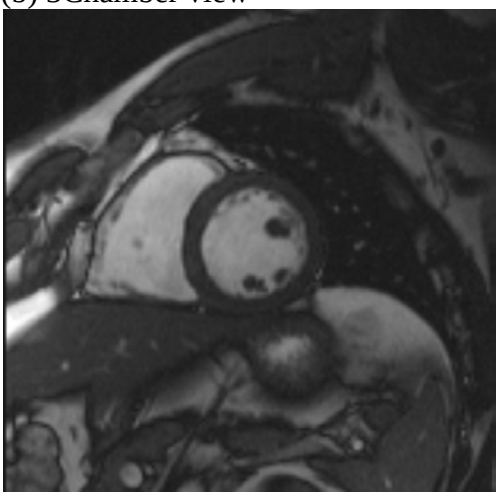
(a) 2Camber view



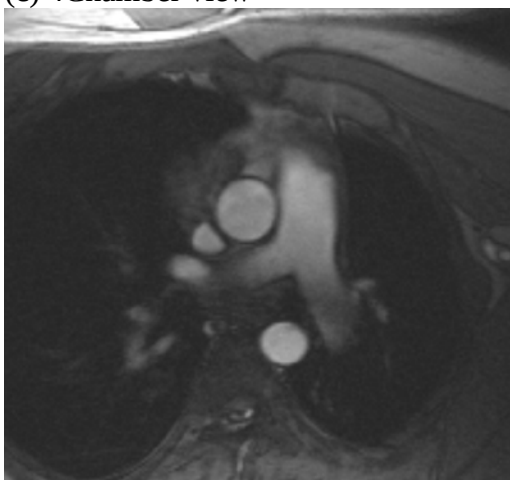
(b) 3Chamber view



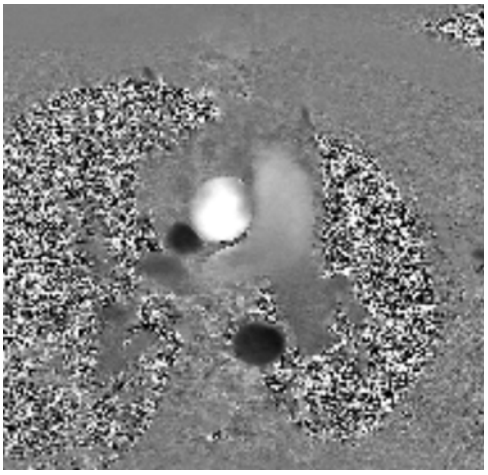
(c) 4Chamber view



(d) Short axis



(e) Flow compensated image



(f) Phase contrast image

**Figure 2.6** Standard views and segments (a) 2 chamber view, (b) 3 chamber view, (c) 4 chamber view (d) short axis view, (e) flow compensated image and (f) phase contrast image.

### 2.6.8 Global and regional function

Cardiac MRI is capable of imaging a selected volume of the heart in any orientation. This is performed by acquiring multiple slices over a specific volume, providing a 3D view of the anatomy. The acquisition of the volume that covers the heart enables measurement of global quantities such as ventricular mass, ventricular volume and ejection fraction. In contrast to global function, regional measurements (eg. wall thickening) provide assessments of specific regions of the heart that may be an accurate predictor of future cardiac events.

#### 2.6.8.1 MRI Sequences

The two most basic MRI pulse sequences are the spin-echo (SE) and gradient-echo (GE) sequences. These sequences provide information on anatomy and tissue characterization. Their clinical uses include evaluation for arrhythmogenic right ventricular cardiomyopathy, cardiac tumors, constrictive pericardial disease, vessel wall abnormalities and thoracic masses.

With cardiac MRI we can measure rapid motion such as the flow of blood using phase contrast (PC), also known as velocity encoding. Relatively slower motion, such as that of the myocardium can be images using MR tagging. [346, 347, 348, 349] MR tagging was introduced by Zerhouni et al. 1988[349] and Axel & Dougherty 1989[347]. MR tagging places markers noninvasively inside the tissue by manipulating the magnetization of the tissue using special encoding pulses. They appear in the acquired images as dark lines and accompany the motion of the myocardium during the cardiac cycle. This ability to place markers in the tissue is unique to MRI.

Gadolinium-enhanced 3D MR angiography provides concurrent non-invasive complete anatomical (arterial and venous supply) and functional (calculation of left-to-right shunt using phase-contrast-MRI performed in the ascending aorta, main pulmonary artery and anomalous pulmonary vein) diagnosis, avoiding the need for more traditional invasive techniques.

A summary of the available sequences and their potential application during cardiac MRI is listed in Table 2.10.

**Table 2.10** MRI sequences and their application to cardiac MRI [350]

| Technique | ECG Triggering | Appearance of blood flow | Dynamic cine[a] Vs. Static[b] | Clinical application |
|---|---|---|---|---|
| *Spin echo* | | | | |
| Standard spin echo | Yes | Dark | Static | Anatomy, tissue characterization |
| Fast spin echo | Yes | Dark | Static | Anatomy, tissue characterization, faster image acquisition relative to standard spin echo |
| *Gradient echo* | | | | |
| Segmented k-space fast gradient echo (or steady-state free precession) | Yes | Bright | Dynamic | Anatomy, ventricular fn., blood flow imaging |
| Phase contrast | Yes | Bright | Dynamic | Flow quant. and characterization |
| Tagging | Yes | Bright | Dynamic | Analysis of myocardial mechanics and flow |
| Gd-enhanced 3D MRA | No | Bright | Static | 3D anatomic dataset |
| MR fluoroscopy | No | Bright | Dynamic | Anatomy, fn., guidance of interventional procedures |
| Delayed enhancement | Yes | Intermediate | Static | Myocardial viability |

[a] Multiple images are obtained throughout the cardiac cycle in each anatomic location. The stacked images are then displayed on a computer screen in a cine-loop format.

[b] A single image is obtained in each anatomic location.

2.6.8.2 Black Blood Imaging

Black-blood imaging (Figure 2.7) improves conspicuity of the endocardial borders and helps demarcate intracardiac masses from normal structures. The improved delineation of vessel walls with SE also enables superior anatomic evaluation. GE, on the other hand, involves the application of only 1 section-selective excitation. After that excitation, blood contributes to the image even after it moves out of the imaging plane. Such contrast is termed bright-blood

imaging. Complex branching vessels, such as the pulmonary veins or arteries, are better depicted with this technique.

Another parameter that affects the appearance of the blood flow is the echo time (TE). With GE, the signal depends on gradient reversal, without the additional spin refocusing of SE. Spins that enter the section during acquisition produce heightened signal. The bright blood pool can be used to distinguish structures such as bronchi from vessels.

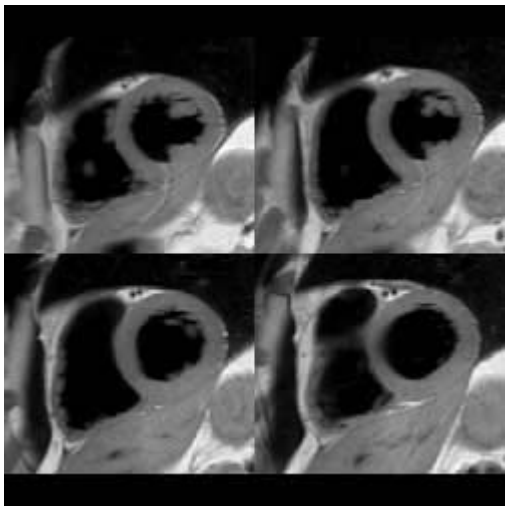


**Figure 2.7** Multi-slice black blood imaging, short axis view.

2.6.8.3 Spatial and temporal resolution

Spatial resolution is a concern with any imaging modality. Fortunately, the size of the major cardiac structures is well within the limit for MRI. Spatial resolution generally is determined by the field of view (FOV) and the number of phase-encoding steps. For comparable FOVs and matrix sizes, spatial resolution is equal with SE and GE techniques. Their major difference is with temporal resolution.

Adequate depiction of the atrial septum or valve leaflets depends on the temporal resolution, as well as the spatial resolution. Regarding time resolution, GE imaging has advantages compared with SE imaging. The assessment of dynamic heart structures is performed with cine GE acquisitions because its temporal resolution is better.

A trade-off exists between temporal resolution and spatial resolution. For typical static SE imaging, one may use a matrix of 256 x 256 and a FOV of 34 cm. To make a movie of the beating heart, one may select a GE technique and reduce the number of phase-encoding steps, for example, to 128. The spatial resolution decreases from 1.33 x 1.33 mm to 1.33 x 2.66 mm accordingly. That resolution is sufficient to depict cardiac wall motion and to calculate the ejection fraction, but higher resolution may be required if detailed evaluation of the cardiac valves is desired.

#### 2.6.8.4 Electrocardiographic Gating

The most important factor in the acquisition of diagnostic images is the quality of the MRI system's ECG gating. If the gating system lacks consistency or cannot tolerate irregularities of the cardiac rhythm, cardiac images are severely impaired. Without dependable gating, many pulse sequences become useless, and if those sequences are required, the examination is unlikely to yield interpretable data. The MRI unit may abort the acquisition of series because of excessive ectopy or failed triggering.

#### 2.6.8.5 Temporal resolution and imaging time

Functional evaluation of the cardiac chambers and internal structures requires good time resolution. Temporal resolution is a function of the TR, the heart rate, and the number of

phase-encoding steps and cardiac-imaging phases. The number of phase-encoding steps per segment depends on the matrix and number of segments. In the standard protocol a matrix with 128 phase-encoding steps and 20 phases per cardiac cycle results in a k-space segment that contains 6 phase-encoding steps.

The temporal resolution is equal to the TR multiplied by the number of phase-encoding steps, or 9.4 milliseconds x 128, which equals 1203 milliseconds per imaging phase. However, the effective temporal resolution is equal to the TR multiplied by the number of phase-encoding steps per k-space segment, or 9.4 milliseconds x 6, which equals 56.4 milliseconds. This time is within the accepted temporal resolution needed to stop cardiac motion of 70-80 milliseconds.

One difficulty in cardiac imaging is related to the heart rate. The TR is gated to the R-R interval for cardiac-triggered imaging. For standard SE techniques, 1 phase-encoding step is acquired for each section per cardiac cycle. A series with a 256 x 256 matrix requires 256 heartbeats to complete. In a patient with a heart rate of 60 bpm and an R-R interval of 1000 milliseconds, image acquisition requires 4 minutes 16 seconds. With the use of cardiac magnets, SE sequences are faster.

2.6.8.6 MRI assessment of ventricular function

Many methods of ventricular volume calculation are used. Rehr et al. 1985 [351] as well as Pearlman et al. 1992 [352] found excellent correlation between findings at volumetric analysis with MRI and findings with ventricular casts (0.99 correlation, 4.9 mL standard error). Accuracy increases with the inclusion of long-axis measurements. Three-dimensional

volumetric calculations are well correlated with ventriculographic findings and have low interstudy variability (<5%) compared with ventriculographic and echocardiographic results.

The first step in the calculation of ventricular volume is the selection of representative end-diastole (ED) and end-systole (ES) cardiac-phase images. According to Semelka et al. 1990 [353] either phase images that depict the largest and smallest ventricular volumes or the phase images obtained immediately before mitral valve closure (ie, ED) and opening (ie, ES) are chosen. Next, the right ventricle (RV) and left ventricle (LV) are traced along the endocardial margin on each section obtained in the selected ED and ES phases from the cardiac apex to the section just prior to one that depicts the mitral and tricuspid valves. The tracings should exclude trabeculations but may include papillary muscles inside the endocardial margin, as long as the procedure is performed in systole and diastole (see Figure 2.8 (a) and (b)).

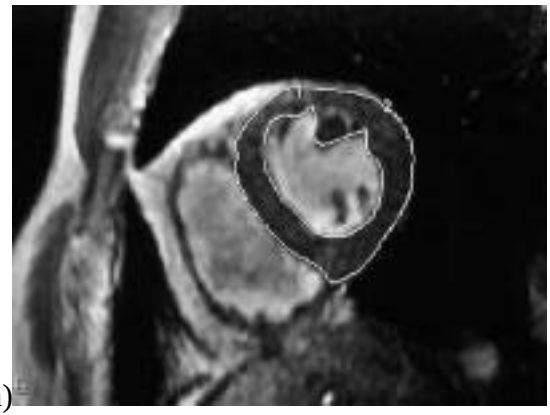
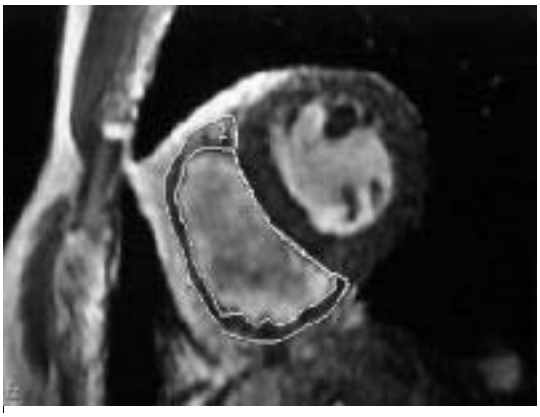
(a)  (b) 

**Figure 2.8**(a). Short-axis gradient-echo image (flip angle, 15°) illustrates volumetric analysis, with tracing of the endocardial border and exclusion of the papillary muscle superiorly. The epicardial margin also is traced for calculation of the myocardial mass, in which the septal mass assigned as part of the left ventricle. (b) Short-axis gradient-echo image (flip angle, 15°) of the ventricles illustrates volumetric calculation of the right ventricle, with a tracing of the right ventricular endocardial border. The epicardium also is traced for determination of the myocardial mass. Note that the septum is excluded when the epicardium is traced.

Calculations can be made as follows:

- ED and ES volumes for each section are totaled to yield the RV and LV end-diastolic volume (EDV) and end-systolic volume (ESV).
- The stroke volume (SV) equals the EDV minus the ESV, or SV = EDV - ESV.
- The ejection fraction (EF) equals the SV divided by the EDV times 100, or EF = (SV / EDV) X 100 to give a value reported as a percent.
- Cardiac output equals SV multiplied by the heart rate.

Ventricular and valvular parameters are shown in Table 2.9.

**Table 2.9:** Ventricular and Valvular Parameters*

| **Parameter** | **Men** | **Women** |
|---|---|---|
| LV EDV (mL) | 77-195 | 52-141 |
| RV EDV (mL) | 88-227 | 58-154 |
| LV ESV (mL) | 19-72 | 13-51 |
| RV ESV (mL) | 23-103 | 12-68 |
| LV EF (%) | 56-78 | 56-78 |
| RV EF (%) | 47-74 | 47-80 |
| LV SV (mL) | 51-133 | 33-97 |
| RV SV (mL) | 52-138 | 35-98 |
| Cardiac output (L/min) | 2.82-8.82 | 2.65-5.98 |
| LV mass (g) | 118-238 | 75-175 |
| RV mass (g) | 30-70 | 24-55 |
| Septal mass (g) | 40-82 | 26-58 |

*From Lorenz, 1999. [354]

The MRI sequence used for determination of ventricular function is gradient echo cine MRI. An ECG-triggered segmented k-space fast gradient echo sequence has been used extensively during 1990s and its accuracy and reproducibility in measuring left and right ventricular volumes, mass and ejection fraction has been validated. [355, 356, 357, 358] A newer gradient echo imaging sequence, steady-state free precision has been shown to provide a sharper contrast between the blood pool and the myocardium and to reduce motion-induced blurring during systole. Numerous studies have been performed in which cardiac MRI was employed to identify regional wall motion. [359, 360, 361, 362, 363] The ability to quantify both LV and RV volumes with a high degree of accuracy is well established for MRI [364]. The accuracy of LV mass by MRI is more than twice than that observed by echocardiography.[332] Assessment of severity of valvular lesions has been studied using CMR and quantitative measurements of regurgitant volume using MR phase velocity imaging have been reported.[365]

Stress induced wall motion abnormalities can be detected with a significantly higher diagnostic accuracy with MRI compared with echo in patients with suspected coronary artery disease; sensitivity increased from 74.3% to 86.2% and specificity from 69.8% to 85.7% (both $P<0.05$).[327] Cardiac MRI produces images with natural contrast between tissue and flowing blood thereby removing the need for a contrast agent in routine imaging. In addition it may prove advantageous in difficult to image obese patients, as CMR is not dependent on adequate acoustic windows for imaging [366] and is not limited by attenuation artefacts or limited spatial resolution related to radionuclide imaging.

### 2.6.9 LV function and structure in Obesity

A cardiovascular magnetic resonance imaging study of cardiac structure and function in the obese,[367] showed subjects had higher left and right ventricular mass and end-diastolic volumes. These early abnormalities in LV structure and function may have significant implications for determining myocardial dysfunction that is associated with increased cardiovascular disease caused by obesity.

Magnetic resonance methods have also allowed the quantification and characterization of atherosclerotic plaque[368,369] (Figure 2.9). A study using cardiovascular magnetic resonance imaging to assess the cross sectional area and elastic properties of the ascending thoracic and abdominal aorta in 21 clinically healthy obese young adult men and 25 men who were age matched lean controls,[370] demonstrated that obesity is associated with increased cross-sectional aortic area and decreased aortic elasticity.

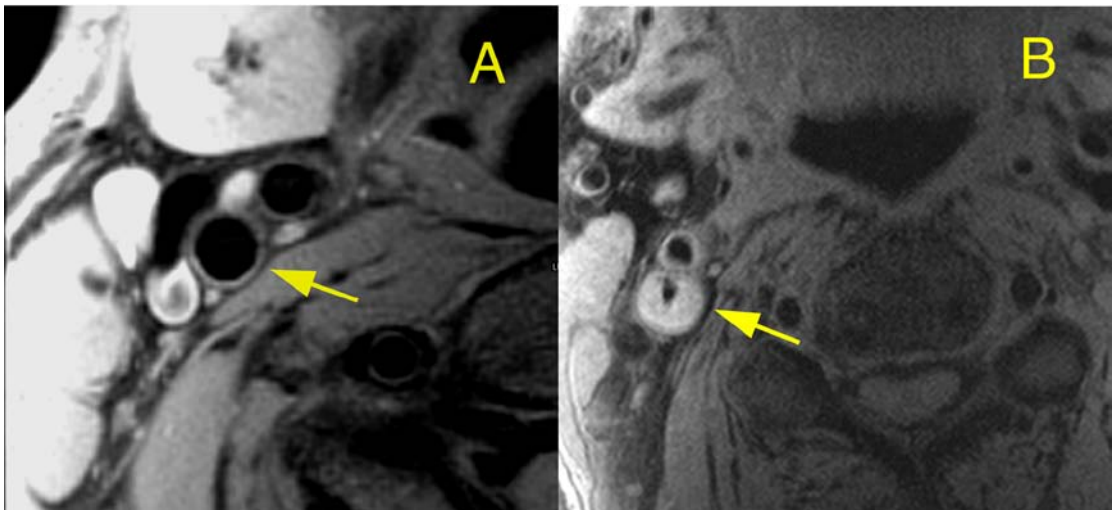



**Figure 2.9** Axial T1 weighted image of a normal internal carotid artery (Figure A) and significant atheroma in the internal carotid artery (Figure B).

Cardiac MRI provides excellent image quality that surpasses that of echocardiography. In the last 10 years, cardiac MRI techniques have progressively improved. No other noninvasive imaging modality provides the same degree of contrast and temporal resolution for the assessment of cardiovascular anatomy and pathology. Its emerging role as one of the main imaging modalities in clinical cardiology cannot be understated.

# CHAPTER 3

**Utility of magnetic resonance imaging in defining obesity related abnormalities in ventricular structure and function, and response to dietary intervention.**

## 3.1 Introduction

The prevalence of obesity has been increasing in western society.[371] Obese people have been reported to have greater left ventricular mass, greater wall thickness, and larger chamber size than those who are not obese,[372, 373] and the ratio between wall thickness and chamber radius (the relative wall thickness) is larger in obese people than in lean people.[Error! Bookmark not defined., 374] Left ventricular hypertrophy is an important risk factor for cardiovascular morbidity and mortality,[375] and an increase in relative wall thickness has been shown to increase overall cardiovascular risk.[376, 377] Otherwise healthy obese men have subtle cardiac abnormalities that can be detected by cardiac magnetic resonance imaging, including increased left and right ventricular mass and increased left and right ventricular end-diastolic volume (Danias et al. 2003)[378]. Moreover the effects of weight reduction using lifestyle and dietary changes on ventricular and vascular structure and function have not been clearly defined. Few studies have included detailed and comprehensive measures of the functional, mechanical and structural changes associated with obesity. Some trials demonstrated benefit,[379, 380, 381, 382, 383 384]and others no change.[385, 386]

The aim of this study is to (1) compare obese but otherwise normal males to age matched normal weight control group with regards to cardiovascular structure and function and (2) test the hypothesis that rapid weight loss, induced by a low calorie diet will improve obesity

related abnormalities in cardiovascular structure and function in men. Specifically we will determine the effects of obesity and diet-induced weight loss on internal carotid wall thickness (a marker of early atherosclerosis and thus vascular structure), aortic distensibility and forearm mediated dilatation (markers of vascular function) as well a LV mass (marker of ventricular structure) and EF (marker of ventricular function).

Furthermore we will examine the extent to which the effects are dependent on, or interrelated with, other cardiovascular risk factors (hypertension, abnormal glucose tolerance, hyperlipidaemia).

### 3.2 Methods

Obese, otherwise healthy, normotensive, non-smoking men on no medication were studied. A cohort of age-matched normal weight control males were also studied.

Exclusion criteria were diabetes mellitus (fasting plasma glucose levels of 7.8-11.1 mmol/L), impaired renal function, (including microalbuminuria), peripheral or autonomic neuropathy, hypertension (blood pressure >140/90 mm Hg), cardiovascular disease, psychiatric problems, use of drugs or alcohol abuse (500 g of alcohol per week in the previous 12-months). Obstructive sleep apnoea (OSA) was excluded based on the Berlin questionnaire (Score<5). The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital. Caucasian men only were enrolled because the cut-off points for the definition of obesity vary significantly by race.

Height was measured using a wall-mounted stadiometer. Waist circumference was measured three times, taken at the level of the narrowest point (or midway) between the lower costal border and the top of the iliac crest and read in the midaxillary line. The mean of the three measurements was used in analyses. Subjects were weighed on the Nuweigh JAC 929-300 platform scale (max 300kg, min 0.4 kg, e=0.02 kg). Resting systolic (SBP) and diastolic (DBP) blood pressures were measured by mercury sphygmomanometer after 10 minutes of seated rest. Two measurements were obtained and the mean values were used in analyses.

Weight loss was induced using a low calorie diet (~800 Kcal/day) KicStart™ (Pharmacy Health Solutions Pty Ltd, Sydney, Australia) over an 8 week period. A research dietician was available to assist with the implementation and monitoring of the low calorie diets.

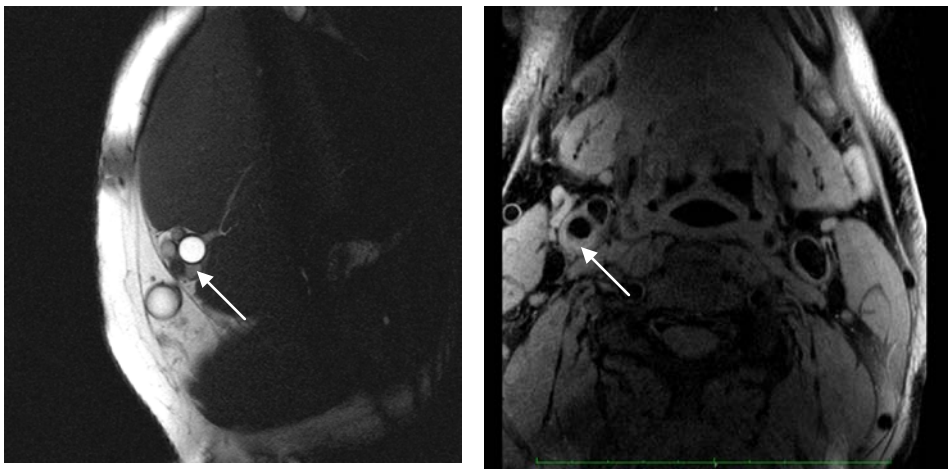
At baseline and 8 weeks ventricular and vascular structure and function were evaluated using Magnetic Resonance Imaging (MRI: 1.5 T Seimens Sonata). Arterial stiffness was evaluated via aortic distensibility in the descending aorta at the level of the pulmonary artery also using MRI. Endothelial function was measured using a brachial forearm cuff occlusion flow-mediated dilatation (FMD) technique using MRI, and data is shown as mean ±SEM. Ejection fraction (EF) was evaluated by a modified Simpson's rule.

Carotid artery imaging was performed using a two element array surface coil. Carotid repetition time/echo time (TR/TE) 45.3 ms/2.4 ms, field of view FOV 200 mm, in-plane resolution 0.52 mm, and slice thickness 3mm (Figure 3.1 b).

Vascular distensibility of the aorta was assessed using TrueFISP (fast imaging with steady state free precession) cine sequence. For aortic distensibility, sagittal-oblique scout images

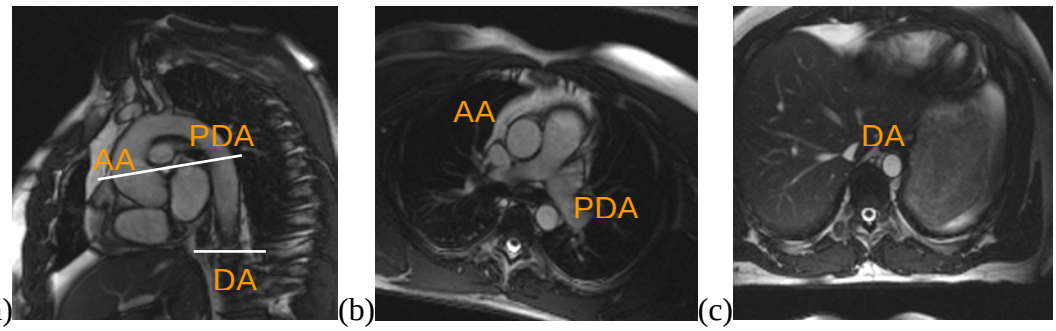
were acquired aligned with the aortic arch (Figure 3.2 a, b and c). A high-resolution gradient-echo pulse sequence with a velocity encoding gradient for phase contrast MRI was applied with time/echo (TR/TE) 40ms/1.4 ms, flip angle 40°, matrix size 256x192, FOV 320x240 mm, slice thickness 6 mm. Blood pressure monitoring was performed immediately pre and post scans.

For brachial artery imaging, a flexible surface coil was attached above the right elbow. Blood pressure was measured from the right arm using a brachial artery sphygmomanometer during brachial artery imaging. Magnetic resonance imaging of brachial artery area was performed at baseline and 1 min after reactive hyperaemia induced by release of a forearm cuff inflated to 50 mmHg above systolic pressure for 5 minutes. Magnetic resonance imaging data acquisition is then repeated before and 3 minutes after a sublingual spray of 400µg nitroglycerin (NTG). Cardiac-gated TrueFISP cine images of the brachial artery were acquired with the following parameters: TR/TE 56/3 ms, flip angle 66°, FOV 117x77 mm, matrix 384x252, 16 segments, 11 to 19 phases depending on heart rate (Figure 3.1 a). Endothelial function measured by MRI was performed after a minimum of 20 minutes sitting-rest and at a constant room temperature of 20 °C.



(a) (b)

**Figure 3.1** (a) MRI of brachial artery area- cardiac gated TrueFISP cine images, (b) Axial T1 weighted image of a carotid artery with atheroma in the internal carotid artery.




(a) (b) (c)

**Figure 3.2** (a) Coronal-sagittal oblique scout image aligned with the aortic arch and descending aorta, (b) and (C) show corresponding TrueFISP images in transverse orientation.

All MRI data was de-identified and analysed in a blinded fashion. For evaluation of vascular distensibilites, inner boundaries of the brachial, carotid and aortic walls were traced manually using image pro plus. Vascular distensibility (mm $Hg^{-1}$) was calculated as relative change in cross sectional area for a given pressure change according to the formula: Distensibility = $((A_{max} - A_{min})/A_{min}) \cdot (P_{max} - P_{min})$, where $A_{max}$=maximal(systolic) area ($mm^2$), $A_{min}$ = minimal (diastolic) area ($mm^2$), $P_{maz}$= systolic blood pressure (mm Hg) and $P_{min}$=diastolic blood pressure (mm Hg)[387].

### 3.3 Statistical Analysis

We analysed data from participants who completed the study. Statistical analysis was performed using SPSS 15. All results are expressed as mean values ± SEM, unless specified otherwise as (± SD). For assessment of functional differences pre and post weight loss a paired *t* test with a 95 % confidence interval was performed. A value of $p<0.05$ was considered significant. Pearson's correlation was performed evaluating the relationship between change in weight and waist circumference, with change in metabolic parameters, EF, endothelial function and aortic distensibility.

### 3.4 Results

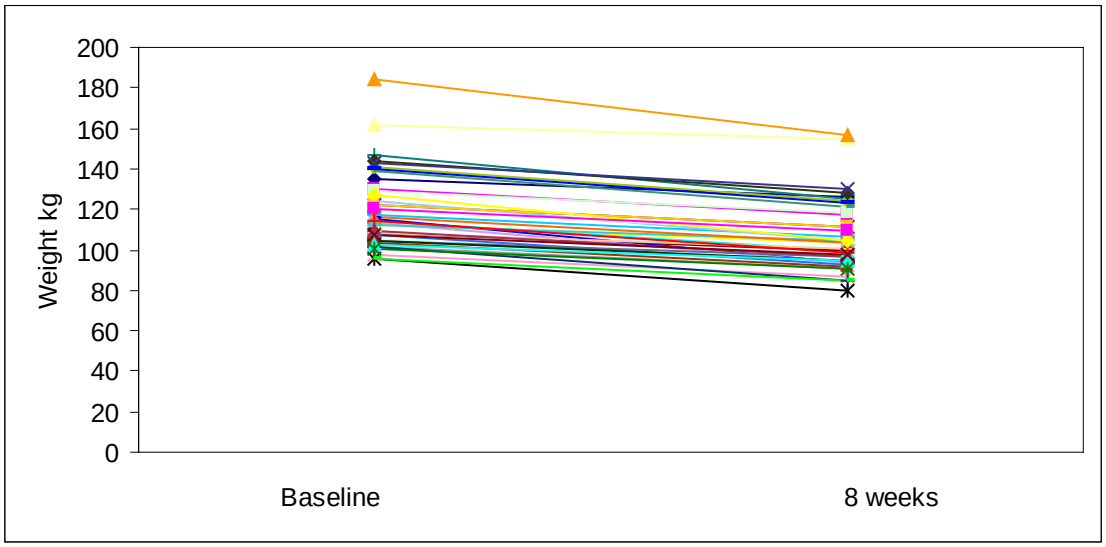
Sixty five obese men, were enrolled in the study. Ten men were unable to tolerate the MRI scan due to claustrophobia and withdrew. Baseline blood pressure was elevated (≥ 140/90) in 12 men and fasting glucose was elevated in 14 at a level consistent with the presence of type 2 diabetes mellitus (T2DM) (glucose levels of 7.8-11.1 mmol/L). All hypertensive men were in

the diabetic group. Fifty five obese men, mean age 43.3±9.9 yrs (18-65 yrs) completed the study. No adverse events were reported. At baseline, the mean BMI was 36.8±4.3 kg/$m^2$ (30-45 kg/$m^2$), mean waist circumference 111.2± 12.6 cm (104-152cm). All men lost weight (13.4 ± 4.7 kg, range 5.1-21.8kg, $p<0.01$ Figure 3.3a). There was a significant reduction in mean waist circumference (12.6 ± 5.4 cm, range 3.8-22.8 cm, $p<0.01$ Figure 3.3b). Only the 41 normal obese males without any other cardiovascular risk factors were subsequently analysed. A total of 10 normal age-matched controls were also studied (Table 3.1). Baseline comparison shows there are significant differences in weight, waist circumference, BMI, systolic and diastolic blood pressure, glucose, insulin, total triglycerides, total cholesterol, HDL, FMD, EF and aortic distensibility.

**Table 3.1** Characteristics at baseline for normal weight men (n=10) and obese men (n=41).

| **Characteristics** | **Baseline n=10** | **Baseline n=41** | **p Value** |
|---|---|---|---|
| Age | 43.4 ±1.4 | 44.6 ±1.4 | 0.94 |
| Weight (kg) | 81.7±1.4 | 118.5±2.6 | <0.01 |
| Waist Circumference (cm) | 89.2±0.98 | 121.6±1.6 | <0.01 |
| BMI (kg/$m^2$) | 24.8±0.55 | 36.6±0.57 | <0.01 |
| Systolic BP (mmHg) | 122.5±1.8 | 134.4±2.2 | <0.01 |
| Diastolic BP (mmHg) | 71.9±1.6 | 83.1±1.4 | <0.01 |
| Glucose (mmol/L) | 4.8±0.1 | 6.2±0.3 | <0.01 |
| Insulin (mU/L) | 4.6±0.29 | 15.3±1.4 | <0.01 |
| Total Triglycerides (mmol/L) | 1.3±0.16 | 1.8±0.12 | 0.04 |
| Total Cholesterol (mmol/L) | 4.5±0.16 | 5.2±0.14 | 0.02 |
| HDL Cholesterol (mmol/L) | 1.2±0.05 | 1.0±0.03 | <0.01 |
| LDL Cholesterol (mmol.L) | 3.2±0.13 | 3.3±0.12 | 0.82 |
| Mmass (g) | 168.9±12.2 | 175.5±5.7 | 0.63 |
| FMD% | 8.0±0.77 | 4.8±0.81 | 0.01 |
| EF% | 595±1.6 | 50.9±0.97 | <0.01 |
| Aortic Distensibility x$10^{-3}$ | 5.2±0.57 | 2.4±0.37 | <0.01 |

a)




b)

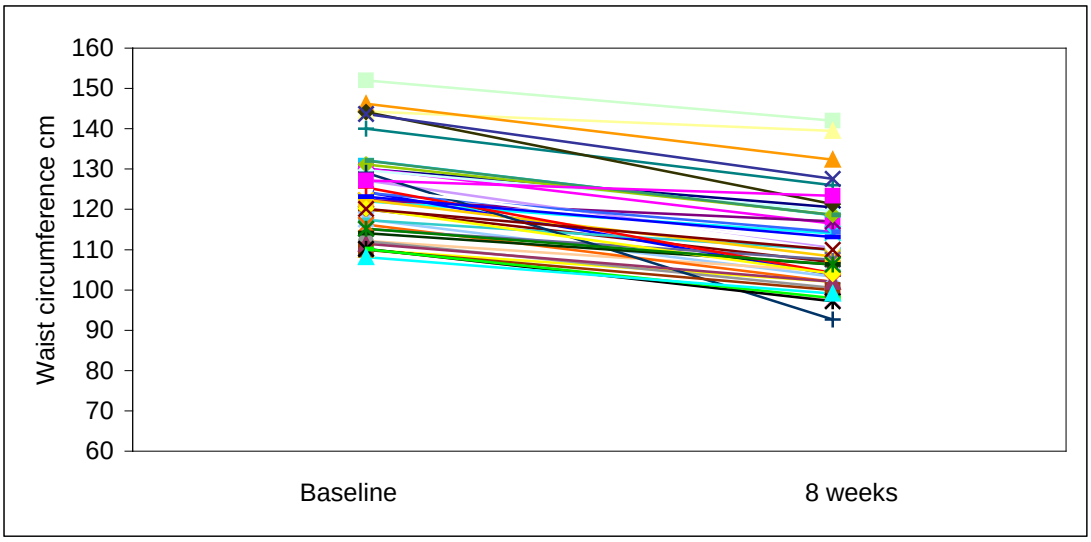



**Figure 3.3** (a) Weight loss induced using a low calorie diet at baseline and 8 weeks. (b) Waist circumference loss induced using a low calorie diet at baseline and 8 weeks.

**Characteristics of the subjects and baseline measurements n=55**

A total of 55 patients tolerated the cardiac magnetic resonance scans. Although none of the men were taking any medication, 29% percent (16/55) of men self reported having high blood

pressure BP ≥ 140/90. Nine percent of men (5/55) reported high blood cholesterol and 25 % (14/55) elevated glucose levels. This was confirmed in all men. None had any prior psychological illnesses. None of the men reported having been diagnosed with obstructive sleep apnoea. Five percent (3/55) of men reported taking over the counter medications such as vitamin and mineral supplements. Baseline characteristics of the men are shown in Table 3.1a.

**Table 3.1 a** Characteristics at baseline and following weight loss (n=55), mean ± Std. Error.

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 44.6 ±1.4 | | | |
| Weight (kg) | 118.5±2.6 | 104.9±2.4 | 0.000 | 13.5±0.65 |
| Waist Circumference (cm) | 121.6±1.6 | 109.2±1.6 | 0.000 | 12.4±0.69 |
| BMI ($kg/m^2$) | 36.6±0.57 | 29.1±0.56 | 0.000 | 7.4±0.25 |
| Systolic BP (mmHg) | 134.4±2.2 | 123.5±1.3 | 0.000 | 10.9±1.7 |
| Diastolic BP (mmHg) | 83.1±1.4 | 77.2±1.1 | 0.023 | 5.9±1.4 |
| Glucose (mmol/L) | 6.2±0.3 | 5.2±0.11 | 0.045 | 1.0±0.29 |
| Insulin (mU/L) | 15.3±1.4 | 8.9±1.0 | 0.000 | 6.2±0.93 |
| Total Triglycerides (mmol/L) | 1.8±0.12 | 1.2±0.08 | 0.001 | 0.54±0.12 |
| Total Cholesterol (mmol/L) | 5.2±0.14 | 4.4±0.12 | 0.002 | 0.69±0.15 |
| HDL Cholesterol (mmol/L) | 1.0±0.03 | 1.0±0.03 | 0.867 | 0.00±0.02 |
| LDL Cholesterol (mmol.L) | 3.3±0.12 | 2.8±0.10 | 0.023 | 0.44±0.12 |
| FMD% | 4.8±0.81 | 9.5±1.1 | 0.002 | 4.7±1.2 |
| EF% | 50.9±0.97 | 57.3±0.98 | 0.000 | 6.43±0.62 |

A decrease in weight was associated with a reduction in systolic and diastolic blood pressure, glucose, insulin, total and LDL cholesterol, and triglycerides (Table 3.1a).

The relationships between the measured variables at baseline are shown in Tables 3.1b. The relationships between changes in the outcome variables are shown in Tables 3.1c. There were

no significant relationships between measured parameters at baseline (Table 3.1b) and 8 weeks post weight loss (Table 3.1c).

**Table 3.1b** Relationship between variables at baseline (n=55)

| | W | WC |
|---|---|---|
| **BPSY** | -0.050 | -0.156 |
| **BPDIA** | -0.016 | -0.068 |
| **Glucose** | -0.194 | -0.298 |
| **Insulin** | 0.472 | 0.309 |
| **Trigs** | 0.206 | 0.132 |
| **TC** | -0.225 | -0.131 |
| **HDL** | -0.423 | -0.336 |
| **LDL** | -0.318 | -0.155 |
| **TCHDL** | 0.231 | 0.197 |
| **FMD** | -0.202 | -0.209 |
| **EF%** | -0.158 | 0.093 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

**Table 3.1c** Relationship between variables at 8 weeks post weight loss (n=55)

| | ΔW | ΔWC |
|---|---|---|
| **ΔBPSY** | 0.032 | -0.112 |
| **ΔBPDIA** | 0.131 | 0.085 |
| **ΔGlucose** | 0.055 | 0.117 |
| **ΔInsulin** | 0.222 | 0.271 |
| **ΔTrigs** | 0.389 | 0.395 |
| **ΔTC** | 0.365 | 0.424 |
| **ΔHDL** | 0.038 | -0.024 |
| **ΔLDL** | 0.313 | 0.351 |
| **ΔTCHDL** | 0.379 | 0.559 |
| **ΔFMD** | -0.072 | -0.119 |
| **ΔEF%** | -0.066 | -0.367 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

Baseline and follow-up clinical characteristics for normal obese men is represented in Table 3.2a and diabetic men in Table 3.3a.

**Baseline and follow-up changes pre and post weight loss in normal obese men n=41**

Therefore, a total of 41 men had no cardiovascular abnormalities/risk factors, and it is their data that we now present.

A decrease in weight was associated with a reduction in systolic and diastolic blood pressure, insulin, total and LDL cholesterol, and triglycerides (Table 3.2a).

**Table 3.2a** Baseline and follow-up changes pre and post weight loss n=41, mean ± Std. Error Mean – **normal obese males**

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 43.6 ±1.5 | | | |
| Weight (kg) | 119.5±2.9 | 106.1±2.7 | 0.000 | 13.3±0.74 |
| Waist Circumference (cm) | 123.9±1.8 | 111.5±1.8 | 0.000 | 12.4±0.89 |
| BMI ($kg/m^2$) | 36.9±0.67 | 29.5±0.62 | 0.000 | 7.4±0.30 |
| Systolic BP (mmHg) | 132.7±2.3 | 123.4±2.9 | 0.000 | 9.4±1.8 |
| Diastolic BP (mmHg) | 81.6±1.6 | 76.5±1.73 | 0.008 | 5.0±1.8 |
| Glucose (mmol/L) | 5.3±0.1 | 5.2±0.08 | 0.180 | 0.1±0.08 |
| Insulin (mU/L) | 15.3±1.5 | 8.6±0.91 | 0.000 | 6.7±1.1 |
| Total Triglycerides (mmol/L) | 1.8±0.124 | 1.3±0.1 | 0.002 | 0.46±0.14 |
| Total Cholesterol (mmol/L) | 5.1±0.16 | 4.5±0.14 | 0.005 | 0.54±0.18 |
| HDL Cholesterol (mmol/L) | 1.0±0.03 | 1.0±0.03 | 0.860 | 0.00±0.03 |
| LDL Cholesterol (mmol.L) | 3.2±0.14 | 2.9±0.11 | 0.030 | 0.34±0.15 |
| FMD% | 4.7±0.91 | 9.4±1.4 | 0.002 | 4.7±1.5 |
| EF% | 52±1.2 | 58±1.2 | 0.000 | 5.9±0.8 |

The relationships between the measured variables at baseline are shown in Tables 3.2b.

**Table 3.2b** Relationship between variables at baseline (n=41)

| | W | WC |
|---|---|---|
| **BPSY** | -0.185 | -0.222 |
| **BPDIA** | -0.009 | -0.034 |
| **Glucose** | -0.166 | -0.292 |
| **Insulin** | .352(*) | .441(**) |
| **Trigs** | 0.204 | 0.137 |
| **TC** | -0.249 | -0.248 |
| **HDL** | -.397(*) | -.498(**) |
| **LDL** | -.379(*) | -0.288 |
| **TCHDL** | 0.138 | 0.246 |
| **FMD** | -0.192 | -0.299 |
| **EF%** | -0.068 | 0.081 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

Baseline weight and waist circumference were associated with insulin, HDL, and LDL.

**Relationship between change in weight, waist circumference, metabolic parameters, EF and FMD, normal obese males.**

The correlation between measured parameters following rapid weight reduction is represented in Table 3.2c.

**Table 3.2c** Relationship between variables at 8 weeks post weight loss n=41.

| | ΔW | ΔWC | ΔBMI |
|---|---|---|---|
| **ΔSBP** | -0.028 | -0.104 | 0.186 |
| **ΔDBP** | 0.139 | 0.088 | 0.134 |
| **ΔGlucose** | -0.027 | 0.040 | 0.017 |
| **ΔInsulin** | .313(*) | .331(*) | .391(*) |
| **ΔTrigs** | .445(**) | .426(**) | 0.285 |
| **Δ TC** | .454(**) | .470(**) | .348(*) |
| **Δ HDL** | 0.210 | 0.041 | 0.147 |
| **Δ LDL** | .384(*) | .390(*) | 0.210 |
| **ΔTCHDL** | .385(*) | .596(**) | 0.278 |
| **ΔFMD** | -0.090 | -0.135 | -0.163 |
| **ΔEF%** | -0.121 | -.402(*) | -0.025 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

Significant correlations were observed between change in weight and change in insulin ($r=0.313$, $p<0.05$) total triglycerides ($r=0.445$, $p<0.01$), total cholesterol ($r=0.454$, $p<0.01$), and LDL ($r=0.384$, $p<0.05$). Likewise, a significant correlation was observed between change in waist circumference and change in insulin ($r=0.331$, $p<0.05$) total triglycerides ($r=0.426$, $p<0.01$), total cholesterol ($r=-0.470$, $p<0.01$), and LDL ($r=0.390$, $p<0.05$). Finally, a significant correlation was observed between change in waist circumference and change in EF ($r=-0.402$, $p<0.011$). There was no significant correlation between change in weight or waist circumference and FMD.

**Effects of weight loss on ventricular and vascular characteristics (normal obese men)**

At baseline obese men had a left ventricular mass of 175.5 ±5.7 g and at 8 weeks 148.2 ± 6.1, $p<0.001$.

Over the 8 week weight loss period an improvement in EF from 52 ± 1% to 58 ± 1% ($p<0.01$) was evident (Figure 3.4). A significant inverse correlation was observed between change in waist circumference ($r=-0.402$, $p<0.05$) with change in ejection fraction (Table 3.2 c).

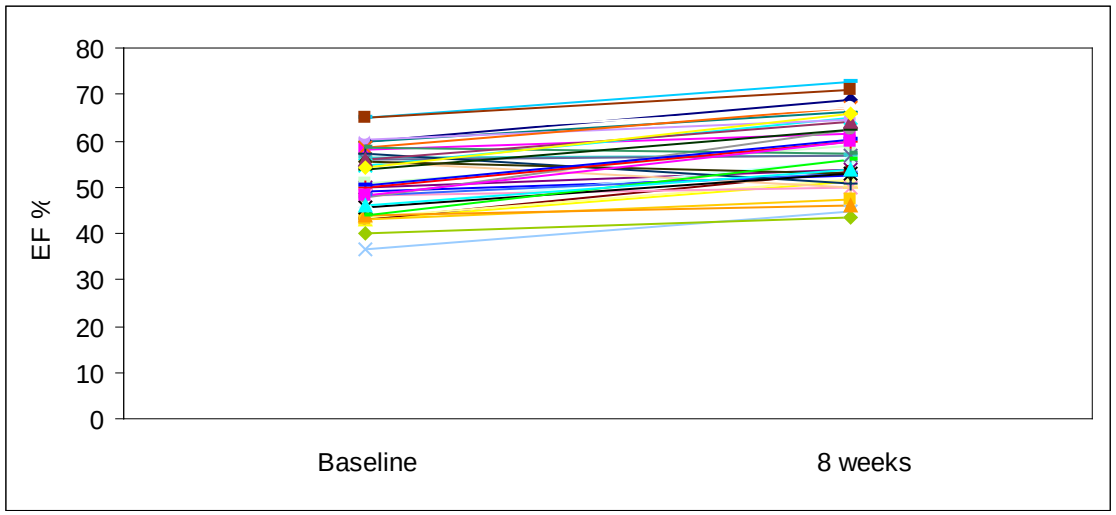



**Figure 3.4** Ejection fraction (EF) measured at baseline 52±1.2 % and at 8 weeks 58±1.2 %, Δ= 5.9±0.8 %, p=0.000.

Mean baseline brachial artery cross sectional areas acquired at end-diastole pre and post weight loss were (19.3±0.62 $mm^2$ vs. 18.7±0.56 $mm^2$, r=0.774). Hyperemia-induced dilation of the brachial artery was significantly reduced in obese men prior to weight loss, indicating impaired endothelial dysfunction. Following weight reduction at 8 weeks, FMD improved from 4.7±0.91% to 9.4±1.4% (p=0.002) (Figure 3.5).

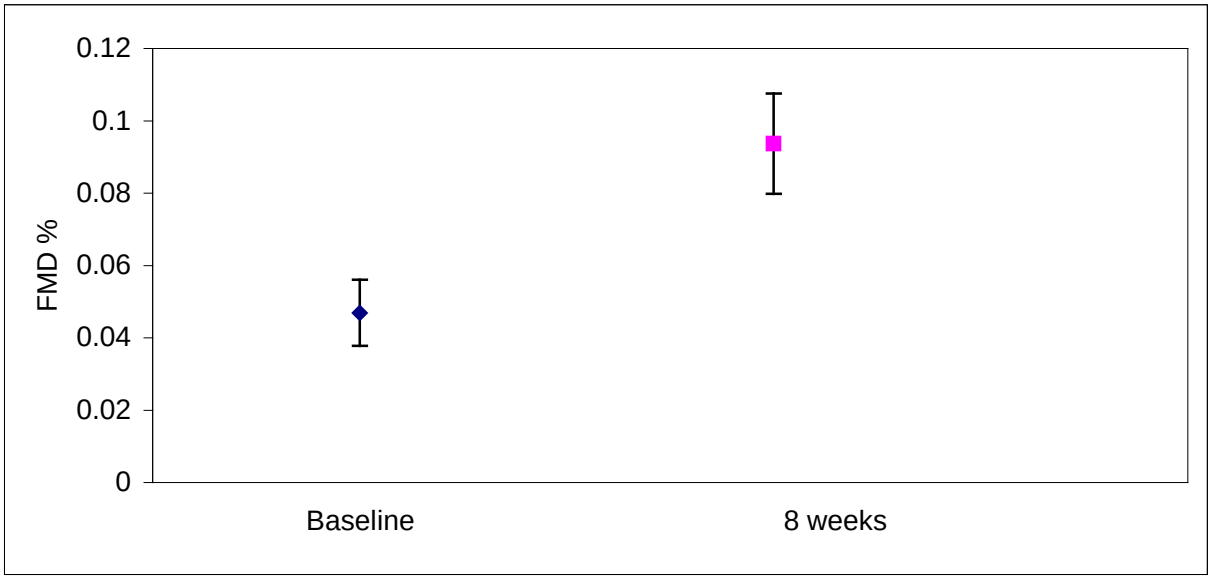



**Figure 3.5** Relative cross sectional area changes induced by hyperemia (flow-mediated dilation (FMD) representing endothelium-dependent relaxation. Baseline = 4.7±0.91%, 8 weeks = 9.4±1.4, Δ =4.7±1.5, p=0.002.

Comparison of cross sectional areas at different sites of the aorta acquired at diastole pre and post weight loss is as follows; in AA (846.23 ±28.4 $mm^2$ vs 812.46.6 ±22.42 $mm^2$, and DA 470.76 ±15.48 $mm^2$ vs 443.76 ±19.21 $mm^2$. Cross sectional areas of the aorta acquired at systole pre and post weight loss is as follows; in AA (932.9 ±29.3 $mm^2$ vs 902.1 ±26.0 $mm^2$, and DA (526.2 ±16.42 $mm^2$ vs 506.1 ±19.6 $mm^2$.

Magnetic resonance quantification of aortic distensibility revealed no significant improvement with weight loss AA (2.25±0.15 $10^{-3}$ $mmHg^{-1}$ vs 2.45 ±0.22 $10^{-3}$ $mmHg^{-1}$, p=0.19.

The average left and right common carotid vessel wall area measured pre and post weight loss (20.9 ±1.2 $mm^2$ vs 21.2 ±1.6 $mm^2$, p=0.832) was not significantly different.

**Diabetic Obese Men**

**Table 3.3a** Baseline and follow-up changes pre and post weight loss n=14, mean ± Std. Error Mean

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 47.4 ±3.5 | | | |
| Weight (kg) | 115.7±5.2 | 101.6±5.2 | 0.000 | 14.1±1.39 |
| Waist Circumference (cm) | 114.9±2.7 | 102.6±3.0 | 0.000 | 12.4±0.87 |
| BMI ($kg/m^2$) | 35.6±1.1 | 28.2±1.3 | 0.000 | 7.5±0.44 |
| Systolic BP (mmHg) | 139.3±5.4 | 123.9±2.1 | 0.004 | 15.4±4.3 |
| Diastolic BP (mmHg) | 87.5±3.0 | 78.9±2.4 | 0.000 | 8.6±1.6 |
| Glucose (mmol/L) | 9.2±0.7 | 5.5±0.38 | 0.000 | 3.7±0.73 |
| Insulin (mU/L) | 15.3±3.2 | 10.2±3.1 | 0.012 | 5.1±1.7 |
| Total Triglycerides (mmol/L) | 1.8±0.26 | 1.1±0.1 | 0.006 | 0.81±0.25 |
| Total Cholesterol (mmol/L) | 5.4±0.26 | 4.2±0.25 | 0.000 | 1.2±0.18 |
| HDL Cholesterol (mmol/L) | 1.1±0.06 | 1.1±0.06 | 0.547 | 0.03±0.05 |
| LDL Cholesterol (mmol.L) | 3.4±0.24 | 2.7±0.19 | 0.000 | 0.77±0.12 |

A decrease in weight was associated with a reduction in systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides, insulin and glucose.

The relationships between the measured variables at baseline are shown in Tables 3.3b.

**Table 3.3b** Relationship between variables at baseline (n=14)

| | W | WC |
|---|---|---|
| **W** | 1 | 0.406 |
| **WC** | 0.406 | 1 |
| **BPSY** | 0.283 | 0.174 |
| **BPDIA** | 0.045 | 0.163 |
| **Glucose** | -0.294 | 0.035 |
| **Insulin** | .769(**) | 0.039 |
| **Trigs** | 0.228 | 0.209 |
| **TC** | -0.105 | 0.532 |
| **HDL** | -0.470 | 0.295 |
| **LDL** | -0.110 | 0.424 |
| **TCHDL** | .532(*) | 0.110 |
| **FMD** | -0.213 | 0.069 |
| **EF%** | -.677(*) | -0.275 |

Weight (W), waist circumference (WC), Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

**Relationship between change in weight, waist circumference, metabolic parameters, EF and FMD.**

The correlation between measured parameters following rapid weight reduction is represented in Table 3.4.

**Table 3.4** Correlations (r) at 8 weeks post weight loss.

| | ΔW | ΔWC | ΔBMI |
|---|---|---|---|
| **ΔSBP** | 0.109 | -0.191 | -0.066 |
| **ΔDBP** | 0.109 | 0.063 | 0.135 |
| **ΔGlucose** | 0.049 | .567(*) | 0.392 |
| **ΔInsulin** | -0.017 | -0.034 | -0.182 |
| **ΔTrigs** | 0.229 | 0.337 | 0.177 |
| **ΔTC** | -0.002 | 0.184 | -0.064 |
| **ΔHDL** | -0.467 | -0.377 | -.552(*) |
| **ΔLDL** | -0.037 | 0.042 | -0.051 |
| **ΔTCHDL** | 0.358 | 0.471 | 0.331 |
| **ΔFMD** | 0.004 | 0.010 | -0.002 |
| **ΔEF%** | 0.073 | -0.085 | -0.370 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

A significant correlation observed between change in waist circumference and change in glucose ($r=0.567$, $p<0.05$).

There was no correlation between change in weight and EF ($r=0.073$, $p=0.822$) or FMD ($r=0.004$, $p=0.990$).

**Effects of weight loss on ventricular and vascular characteristics (diabetic obese men)**

At baseline obese men had a left ventricular mass of 189.5 ±8.8 g and at 8 weeks 158.3 ± 8.5, $p<0.001$.

Over the 8 week weight loss period an improvement in EF from 48.5 ± 2% to 56.7 ± 2% ($p<0.01$) was evident (Figure 3.6). Although EF improved at 8 weeks, this was not correlated significantly with the degree of change in weight or waist circumference.

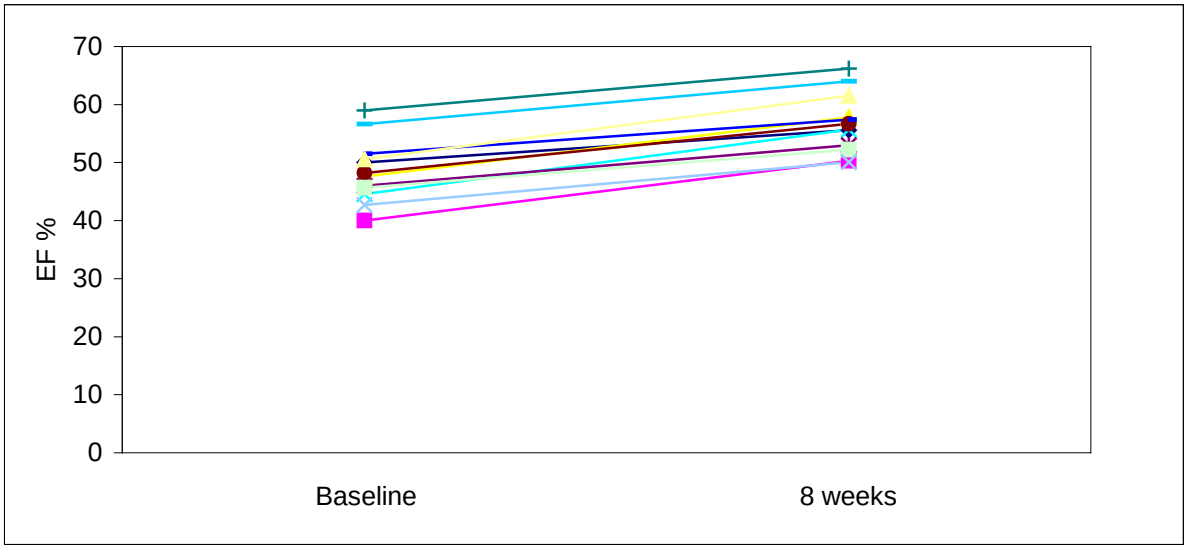



**Figure 3.6** Ejection fraction (EF) measured at baseline 48.5±1.6 % and at 8 weeks 56.7±1.5, Δ = 8.2±0.57 %, p = 0.000.

Following weight reduction at 8 weeks, FMD improved from 5.2±1.7 to 9.9±1.9 ($p<0.05$) (Figure 3.7).

Mean baseline brachial artery cross sectional areas acquired at end-diastole pre and post weight loss were (18.9±1.2 $mm^2$ vs. 18.3±0.90 $mm^2$, r=0.927). Hyperemia-induced dilation of the brachial artery was significantly reduced in obese men prior to weight loss, indicating impaired endothelial dysfunction.

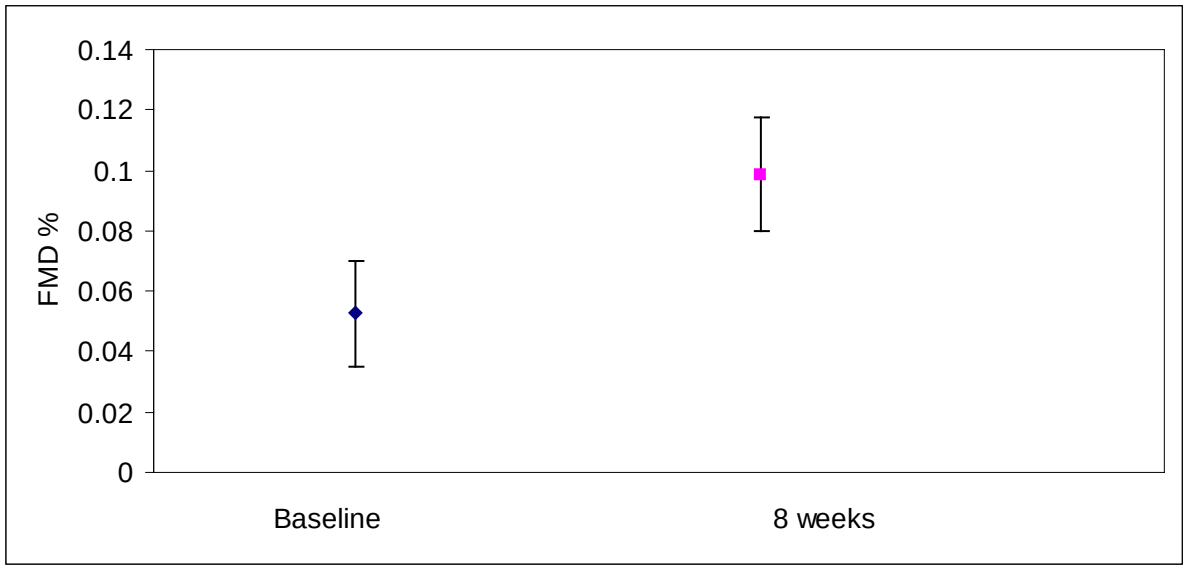



**Figure 3.7** Relative cross sectional area changes induced by hyperemia (flow-mediated dilation (FMD) representing endothelium-dependent relaxation. Baseline = 5.2 ± 1.7%, 8 weeks = 9.9 ± 1.9, Δ = 4.6 ± 1.6, p=0.007.

Comparison of cross sectional areas at different sites of the aorta acquired at diastole pre and post weight loss are as follows; in AA (815.0 ±71.3 $mm^2$ vs 760.3 ±61.25 $mm^2$, and DA (404.9 ±39.9 $mm^2$ vs 398.6 ±39.2 $mm^2$. Cross sectional areas of the aorta acquired at systole pre and post weight loss are as follows; in AA (907.2 ±76.4 $mm^2$ vs 854.9 ±69.7 $mm^2$, and DA (466.1 ±36.8 $mm^2$ vs 459.6 ±42.1 $mm^2$.

Magnetic resonance quantification of aortic distensibility revealed no significant improvement with weight loss AA (2.4±0.37 $10^{-3}$ $mmHg^{-1}$ vs 3.1 ±0.38 $10^{-3}$ $mmHg^{-1}$, p=0.13.

### 3.5 Discussion

We have shown that a weight loss program using VLCD over 8 weeks in otherwise healthy caucasian obese individuals is associated with an improvement in EF and FMD but no change in aortic compliance or carotid wall area. Interestingly, these changes did not appear to correlate with the degree of weight loss. This suggests that changes in factors associated with weight loss may be more important determinants of cardiovascular function in obesity than just weight alone. Furthermore, if any changes in vascular and ventricular structural elements (carotid wall area, LV mass) are to be seen with weight loss then > 8/52 may be required.

In this study we used cardiac MR to characterize cardiac structure and function in obese men and demonstrate an improvement following rapid weight reduction. Our study confirms findings from previous echocardiographic studies, which in selected populations have also reported left ventricular hypertrophy with obesity (Alpert et al. 1995[180]; Crisostomo et al. 1999 [388]). Obese men had higher left ventricular mass at baseline which significantly reduced following weight loss. Previous reports have also associated left ventricular mass with a variety of anatomical and functional cardiac parameters (Chen et al. 1998[389]).

Significant weight loss over an 8 week period in obese males improves left ventricular systolic function and endothelial function in both normal and diabetic men.

Although dramatic weight reduction induced by a very low calorie diet in our study was associated with significant improvement of metabolic parameters and endothelial dysfunction, the effect of drastic weight loss on arterial compliance in male patients was not significant in both diabetic and normal groups. Brook et al. 2004 showed that 3 months of weight loss improved the metabolic profile, but failed to improve endothelial function or vascular

compliance. Previous research has indicated that among older adults, aortic stiffness is associated with visceral adipose tissue specifically.[390] Wildman et al. 2003[391] found that body fat measures were among the strongest independent predictors of aortic stiffness in both young and older adults. Median aortic pulse wave velocity (aPWV) values were 40 to 90 cm/s higher for obese individuals compared with normal weight individuals. The results demonstrated that excess body weight has both short and long term effects on the vascular system, and this might be one mechanism by which obesity is associated with cardiovascular disease. This was the first population based study to report an effect of weight on vascular stiffness in adults as young as 20 years, and the strength of the association indicates that excess weight begins to affect the vascular system at a very early stage of vascular aging. Similar relations between aortic stiffness and body weight have been documented in elderly participants in both the Cardiovascular Health Study[392] and in the Health ABC Study, as well as among younger hypertensives[393] and individuals with a family history of hypertension.[394]

There are a number of mechanisms by which body weight might contribute to aortic stiffening, in both the short and long term. First, insulin resistance has been shown to accompany obesity.[395] Insulin resistance likely has vascular effects through both its associated hyperinsulinemia and increased glycemia. The effects of hyperinsulinemia on the vascular system are not yet completely understood but might include promotion of sodium reabsorption, [396, 397] stimulation of the sympathetic nervous system,[398, 399] and promotion of vascular smooth muscle cell growth,[400] all of which might contribute to increased aortic stiffness.

**Limitations of the study**

Not all patients could tolerate the cardiac MRI protocol due to claustrophobia (n=12). Furthermore, morbidly obese individuals (n=15) may be more likely to fail due to the physical constraints of the MRI machine. We do not have a control group of overweight males at baseline and 8 weeks. However regression to the mean is an unlikely explanation for the improvement in EF/FMD as individuals were not selected on the basis of these results, simply their weight.

## 3.6 Conclusion

Short term weight loss improves ejection fraction and flow mediated dilatation but not aortic compliance or carotid artery area. Further work is needed to address predictors of there improvements/sustainability of their benefits.

# CHAPTER 4

**The Effects of Diet-Induced Weight Loss on Sexual Function, Lower Urinary Tract Symptoms and Quality of Life in Obese Men.**

## 4.1 Introduction

Erectile dysfunction (ED) is associated with decreased quality of life in men,[401, 402, 403] and affects more than 100 million men worldwide. Factors that may be associated with ED include increasing age, behavioural and lifestyle factors (smoking), disease state (obesity, diabetes, obstructive sleep apnoea, heart disease, hypertension) medications (thiazide diuretics) and psychological factors including depression and anxiety.[404, 405] Apart from the clear association with prostate disease there is also a significant relationship between lower urinary tract symptoms (LUTS)[406, 407] and obesity[408], and cardiovascular risk factors[409, 410] (in particular hypertension), diabetes mellitus[411] and depression[412]. An association between ED and LUTS has also been described[413]. While plasma T is associated with sexual desire[414, 415, 416], the relationship of any measure of T to erectile function is less clear.

Obesity is associated with cardiovascular disease and endothelial dysfunction/and possibly by similar mechanisms ED and LUTS. Obesity is also associated with lowered plasma T and decreased sexual and overall quality of life. Accordingly the aim of this study was to test the hypothesis that rapid weight loss, induced by a low calorie diet, will reverse not only cardiovascular disease but also obesity related sexual and lower urinary tract abnormalities in men. Specifically we aimed to determine the effects of obesity and diet-induced weight loss on: Erectile dysfunction (ED), sexual desire (SD), androgen levels and lower urinary tract

symptoms (LUTS). We also sought to determine the relationships between improvements in weight, metabolic state and changes in each of these problems as well as the relationships between changes in each with the other and improvements in cardiovascular function.

**4.2 Methods**

Fifty-five obese, otherwise healthy, normotensive, non-smoking men on no medication, age 43.6±1.5 yrs, (24-65 yrs), (mean ±SEM, (range)); BMI 36.9±0.67kg/$m^2$ and waist circumference 123.9±1.8cm, (108-152cm) were studied.

Exclusion criteria were diabetes mellitus (fasting plasma glucose levels of 7.8-11.1 mmol/L), impaired renal function, (including microalbuminuria), pelvic trauma, prostate disease, peripheral or autonomic neuropathy, hypertension (blood pressure >140/90 mm Hg), cardiovascular disease, psychiatric problems, use of drugs or alcohol abuse (500 g of alcohol per week in the previous 12-months). The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

Height was measured using a wall-mounted stadiometer. Waist circumference was measured three times, taken at the level of the narrowest point (or midway) between the lower coastal border and the top of the iliac crest and read in the mid-axillary line. The mean of the three measurements was used in the analyses. Subjects were weighed on the Nuweigh JAC 929-300 platform scale (max 300kg, min 0.4 kg, e=0.02 kg). Resting systolic (SBP) and diastolic (DBP) blood pressures were measured by mercury sphygmomanometer after 10 minutes of seated rest. Systolic pressure was recorded at the appearance of the first and diastolic pressure at the forth Korotkov sound. Two measurements were obtained and the mean of the values used in analyses.

Weight-loss was induced over 8 weeks using 3 sachets of Kicstart™, a nutritionally complete very low calorie diet (VLCD) (450 Kcal/day) and one small meal (~400 Kcal/day) over 8 weeks. A research dietician was available to assist with the implementation and monitoring of the low calorie diets.

ED (international index of erectile function (IIEF)), SD (sexual desire inventory 2 (SDI-2)), and LUTS (international prostate symptom scale (IPSS)) and physical and mental health (SF-36) were evaluated at baseline and after weight-loss (as described in section 2.3.2). Subjects were reviewed every two weeks. At each visit, weight, waist circumference and seated blood pressure were measured and caloric intake adjusted if necessary to ensure a weight loss of 1-2kg.

**4.3 Statistical Analysis**

We analysed data from participants who completed the study. Statistical analysis was performed using SPSS 15. All results are expressed as mean values ± SEM, unless specified otherwise as (± SD). For assessment pre and post weight loss a paired *t* test with a 95 % confidence interval was performed. A value of $p<0.05$ was considered significant. The significance of any relationships between various measurements at baseline and the relationship between the change in weight and waist circumference with change in IIEF, SDI, IPSS, total and free testosterone levels, SHBG, SF-36 and OSA at 8 weeks were determined using Pearson's correlation and multivariate analysis. Similar methods were used to determine relationships between ED, LUTS, and measurement of cardiovascular function at baseline and the after 8 weeks. Analyses were performed only for the men who completed the study.

## 4.4 Results

Sixty five men were enrolled in the study. Ten men were unable to tolerate the MRI scan due to claustrophobia and withdrew. Baseline blood pressure was elevated (≥ 140/90) in 12 men and fasting glucose was elevated in 14 at a level consistent with the presence of type 2 diabetes mellitus (T2DM) (glucose levels of 7.8-11.1 mmol/L). All hypertensive men were in the diabetic group. Fifty five obese men, mean age 43.3±9.9 yrs (18-65 yrs) completed the study. No adverse events were reported. At baseline, the mean BMI was 36.8±4.3 kg/$m^2$ (30-45 kg/$m^2$), mean waist circumference 111.2± 12.6 cm (104-152cm). All men lost weight (13.4 ± 4.7 kg, range 5.1-21.8kg, $p<0.01$). There was a significant reduction in mean waist circumference (12.6 ± 5.4 cm, range 3.8-22.8 cm, $p<0.01$). Normal obese and diabetic men were initially analysed together then separately to determine associations between measured parameters.

### Characteristics of the subjects and baseline measurements n=55

Although none of the men were taking any medication, 29% percent (16/55) of men self reported having high blood pressure BP≥ 140/90. Nine percent of men (5/55) reported high blood cholesterol and 25 % (14/55) elevated glucose levels. This was confirmed in all men. One subject reported having an enlarged prostate. None had any prior psychological illnesses. Overall, 9% (5/55) of men reported having a vasectomy. None of the men reported having been diagnosed with obstructive sleep apnoea. Five percent (3/55) of men reported taking over the counter medications such as vitamin and mineral supplements. Baseline characteristics of the men are shown in Table 4.1a. All men walked for sport, physical activity

or recreation in the two weeks prior to their clinic visit, and participated in moderate intensity exercise (Table 4.4).

**Changes in measured parameter in response to weight loss n=55**

The measured variables prior to and following weight loss shown in Table 4.1b. All men lost weight (13.5 ± 0.65 kg, 5.0-27.7kg) and decreased waist circumference (12.4 ± 0.69 cm, 3.8 – 36.4 cm). A reduction in weight was associated with a reduction in systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and insulin.

The relationships between the measured variables at baseline are shown in Tables 4.1b and d, and between measures of sexual and lower urinary tract function and cardiovascular function (chapter 3) in Table 4.1c. The relationships between changes in the outcome variables are shown in Tables 4.2a-c.

There were no significant relationships between baseline weight and waist circumference and testosterone, SHBG, cFT, erectile function, sexual desire or lower urinary tract symptoms (Table 4.1 b-d). Likewise, there were no associations between the change in weight or waist circumference and T, SHBG, cFT, erectile function, sexual desire or lower urinary tract symptoms (Table 4.2 a-c)**.**

**Table 4.1 a** Characteristics at baseline and following weight loss (n=55), mean ± Std. Error.

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 44.6 ±1.4 | | | |
| Weight (kg) | 118.5±2.6 | 104.9±2.4 | 0.000 | 13.5±0.65 |
| Waist Circumference (cm) | 121.6±1.6 | 109.2±1.6 | 0.000 | 12.4±0.69 |
| BMI ($kg/m^2$) | 36.6±0.57 | 29.1±0.56 | 0.000 | 7.4±0.25 |
| Systolic BP (mmHg) | 134.4±2.2 | 123.5±1.3 | 0.000 | 10.9±1.7 |
| Diastolic BP (mmHg) | 83.1±1.4 | 77.2±1.1 | 0.023 | 5.9±1.4 |
| Glucose (mmol/L) | 6.2±0.3 | 5.2±0.11 | 0.045 | 1.0±0.29 |
| Insulin (mU/L) | 15.3±1.4 | 8.9±1.0 | 0.000 | 6.2±0.93 |
| Total Triglycerides (mmol/L) | 1.8±0.12 | 1.2±0.08 | 0.001 | 0.54±0.12 |
| Total Cholesterol (mmol/L) | 5.2±0.14 | 4.4±0.12 | 0.002 | 0.69±0.15 |
| HDL Cholesterol (mmol/L) | 1.0±0.03 | 1.0±0.03 | 0.867 | 0.00±0.02 |
| LDL Cholesterol (mmol.L) | 3.3±0.12 | 2.8±0.10 | 0.023 | 0.44±0.12 |
| Testosterone (mmol/L) | 22.6±1.3 | 25.9±1.7 | 0.005 | 3.7±1.1 |
| SHBG (mmol/L) | 19.6±1.1 | 27.8±1.4 | 0.000 | 6.6±0.92 |
| cFT (mmol/L) | 0.64±0.04 | 0.66±0.04 | 0.431 | 0.03±0.03 |
| IIEF | 18.7±0.25 | 21.0±0.28 | 0.000 | 2.2±0.17 |
| SDI | 70.4±0.46 | 80.45±0.29 | 0.000 | 10.0±0.45 |
| IPSS | 18.8±0.19 | 12.2±0.20 | 0.000 | -6.6±0.21 |
| FMD% | 4.8±0.81 | 9.5±1.1 | 0.002 | 4.7±1.2 |
| EF% | 50.9±0.97 | 57.3±0.98 | 0.000 | 6.43±0.62 |

**Table 4.1b** Relationship between variables at baseline (n=55)

| | W | WC | BPSY | BPDIA | Glucose | Insulin | Trigs | TC | HDL | LDL | TCHDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **T** | -0.086 | -0.072 | -0.072 | -0.063 | -0.207 | -0.119 | -0.193 | -0.194 | 0.062 | -0.155 | -0.205 |
| **SHBG** | -0.190 | -0.081 | 0.271 | 0.238 | 0.057 | -0.313 | -0.383 | -0.168 | 0.245 | -0.050 | -0.375 |
| **cFT** | -0.114 | -0.124 | -0.037 | -0.064 | -0.209 | -0.053 | -0.066 | -0.163 | 0.045 | -0.146 | -0.152 |
| **IIEF** | -0.206 | -0.048 | 0.262 | 0.261 | 0.316 | -0.014 | -0.164 | 0.152 | 0.255 | 0.209 | -0.088 |
| **SDI** | 0.042 | 0.137 | -0.158 | -0.176 | -0.324 | 0.115 | -0.079 | -0.201 | -0.168 | -0.149 | 0.001 |
| **IPSS** | 0.012 | 0.020 | -0.161 | -0.312 | -0.111 | -0.083 | -0.141 | 0.035 | 0.180 | 0.059 | -0.141 |

Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol). *p≤0.05, **p≤0.01

**Table 4.1c** Relationship between variables at baseline n=55 subjects (obese normal and diabetic men).

| | FMD | EF% | PF | RP | BP | GH | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|---|---|---|
| **T** | -0.060 | 0.033 | 0.116 | 0.040 | 0.139 | 0.014 | -0.005 | -0.067 | -0.013 | -0.236 |
| **SHBG** | -0.051 | 0.254 | -0.018 | 0.023 | 0.027 | 0.113 | 0.074 | 0.049 | 0.068 | -0.044 |
| **cFT** | -0.017 | -0.060 | 0.161 | 0.077 | 0.099 | -0.042 | -0.021 | -0.066 | 0.018 | -0.210 |
| **IIEF** | 0.182 | -0.034 | -0.109 | 0.105 | -0.041 | -0.074 | -0.040 | 0.042 | 0.089 | -0.045 |
| **SDI** | -0.088 | 0.194 | -0.106 | -0.141 | -0.116 | -0.079 | -0.320 | -0.131 | -0.148 | -0.351 |
| **IPSS** | 0.168 | -0.103 | -0.150 | -0.055 | 0.123 | -0.138 | 0.014 | -0.108 | -0.253 | -0.247 |

Flow mediated dilatation (FMD), Ejection fraction (EF), Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH). *p≤0.05, **p≤0.01

**Table 4.1d** Relationship between variables at baseline n=55 subjects (obese normal and diabetic men).

| | T | SHBG | cFT | IIEF | SDI | IIPS |
|---|---|---|---|---|---|---|
| **T** | 1 | 0.270 | 0.921 | -0.332 | 0.297 | 0.176 |
| **SHBG** | 0.270 | 1 | -0.022 | -0.047 | 0.111 | 0.116 |
| **cFT** | 0.921 | -0.022 | 1 | -0.289 | 0.236 | 0.106 |
| **IIEF** | -0.332 | -0.047 | -0.289 | 1 | -0.329 | 0.015 |
| **SDI** | 0.297 | 0.111 | 0.236 | -0.329 | 1 | -0.028 |
| **IPSS** | 0.176 | 0.116 | 0.106 | 0.015 | -0.028 | 1 |

Testosterone (T), sex hormone-binding globulin (SHBG), calculated free testosterone (cFT), erectile dysfunction (IIEF), sexual desire (SDI), lower urinary tract symptoms (LUTS). *p≤0.05, **p≤0.01

**Table 4.2a** Relationship between variables at 8 weeks post weight loss n=55 (obese normal and diabetic subjects).

| | Δ W | Δ WC | Δ BPSY | Δ BPDIA | Δ Glucose | Δ Insulin | Δ Trigs | Δ TC | Δ HDL | Δ LDL | Δ TCHDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Δ T** | 0.165 | 0.014 | -0.137 | -0.028 | -0.085 | 0.111 | -0.123 | -0.014 | 0.019 | 0.033 | -0.079 |
| **Δ SHBG** | 0.476 | 0.347 | 0.060 | 0.028 | 0.170 | 0.092 | 0.307 | 0.393 | 0.191 | 0.299 | 0.278 |
| **Δ cFT** | 0.034 | -0.085 | -0.233 | -0.091 | -0.163 | 0.122 | -0.233 | -0.178 | -0.117 | -0.035 | -0.166 |
| **Δ IIEF** | 0.115 | -0.015 | -0.135 | -0.264 | 0.013 | 0.168 | -0.002 | 0.082 | -0.040 | 0.093 | 0.087 |
| **Δ SDI** | 0.051 | -0.047 | 0.177 | 0.148 | 0.235 | -0.006 | 0.113 | 0.183 | 0.162 | 0.092 | 0.028 |
| **Δ IPSS** | -0.074 | -0.019 | 0.043 | 0.069 | 0.129 | 0.063 | -0.039 | -0.060 | -0.139 | -0.091 | 0.058 |

**Table 4.2b** Relationship between variables at 8 weeks post weight loss n=55 (obese normal and diabetic subjects).

| | Δ FMD | Δ EF% | Δ PF | Δ RP | Δ BP | Δ GH | Δ VT | Δ SF | Δ RE | Δ MH |
|---|---|---|---|---|---|---|---|---|---|---|
| **Δ T** | 0.094 | -0.101 | 0.164 | 0.012 | -0.157 | -0.075 | 0.031 | -0.045 | 0.024 | -0.023 |
| **Δ SHBG** | 0.057 | 0.004 | 0.006 | 0.015 | -0.145 | 0.051 | -0.227 | 0.059 | -0.005 | -0.008 |
| **Δ cFT** | 0.090 | -0.130 | 0.177 | 0.022 | -0.163 | -0.070 | 0.109 | -0.054 | 0.036 | -0.052 |
| **Δ IIEF** | -0.187 | -0.005 | 0.059 | 0.007 | 0.150 | -0.088 | -0.050 | 0.070 | -0.001 | -0.179 |
| **Δ SDI** | 0.027 | 0.094 | -0.126 | -0.281 | -0.055 | -0.106 | -0.214 | -0.233 | -0.036 | -0.364 |
| **Δ IPSS** | -0.093 | 0.186 | -0.049 | -0.094 | -0.008 | -0.003 | 0.030 | -0.153 | -0.314 | -0.215 |

**Table 4.2c** Relationship between variables at 8 weeks post weight loss n=55 (obese normal and diabetic subjects).

| | Δ T | Δ SHBG | Δ cFT | Δ IIEF | Δ SDI | Δ IPSS |
|---|---|---|---|---|---|---|
| **Δ T** | 1 | 0.385 | 0.893 | 0.289 | 0.059 | 0.014 |
| **Δ SHBG** | 0.385 | 1 | 0.005 | -0.043 | 0.006 | -0.134 |
| **Δ cFT** | 0.893 | 0.005 | 1 | 0.341 | 0.023 | 0.128 |
| **Δ IIEF** | 0.289 | -0.043 | 0.341 | 1 | 0.261 | 0.144 |
| **Δ SDI** | 0.059 | 0.006 | 0.023 | 0.261 | 1 | -0.191 |
| **Δ IPSS** | 0.014 | -0.134 | 0.128 | 0.144 | -0.191 | 1 |

**Baseline and follow-up changes pre and post weight loss in normal obese men n=41**

**Table 4.3a** Baseline and follow-up changes pre and post weight loss n=41, mean ± Std. Error Mean – **normal obese males**

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 43.6 ±1.5 | | | |
| Weight (kg) | 119.5±2.9 | 106.1±2.7 | 0.000 | 13.3±0.74 |
| Waist Circumference (cm) | 123.9±1.8 | 111.5±1.8 | 0.000 | 12.4±0.89 |
| BMI (kg/m$^2$) | 36.9±0.67 | 29.5±0.62 | 0.000 | 7.4±0.30 |
| Systolic BP (mmHg) | 132.7±2.3 | 123.4±2.9 | 0.000 | 9.4±1.8 |
| Diastolic BP (mmHg) | 81.6±1.6 | 76.5±1.73 | 0.008 | 5.0±1.8 |
| Glucose (mmol/L) | 5.3±0.1 | 5.2±0.08 | 0.180 | 0.1±0.08 |
| Insulin (mU/L) | 15.3±1.5 | 8.6±0.91 | 0.000 | 6.7±1.1 |
| Total Triglycerides (mmol/L) | 1.8±0.124 | 1.3±0.1 | 0.002 | 0.46±0.14 |
| Total Cholesterol (mmol/L) | 5.1±0.16 | 4.5±0.14 | 0.005 | 0.54±0.18 |
| HDL Cholesterol (mmol/L) | 1.0±0.03 | 1.0±0.03 | 0.860 | 0.00±0.03 |
| LDL Cholesterol (mmol.L) | 3.2±0.14 | 2.9±0.11 | 0.030 | 0.34±0.15 |
| Testosterone (nmol/L) | 24.2±1.6 | 28.2±2.0 | 0.003 | 4.0±1.3 |
| SHBG (nmol/L) | 19.6±1.3 | 26.3±1.7 | 0.000 | 6.7±0.96 |
| cFT (nmol/L) | 0.69±0.05 | 0.72±0.05 | 0.390 | 0.03±0.04 |
| IIEF | 18.3±0.2 | 20.5±0.3 | 0.000 | 2.2±0.20 |
| SDI | 71.2±0.4 | 80.7±0.3 | 0.000 | 9.0±0.42 |
| IPSS | 18.9±0.22 | 12.2±0.2 | 0.000 | -6.8±0.2 |
| FMD% | 4.7±0.91 | 9.4±1.4 | 0.002 | 4.7±1.5 |
| EF% | 52±1.2 | 58±1.2 | 0.000 | 5.9±0.8 |

Erectile function (IIEF score) improved in 37 men (Figure 4.1 a). SDI and IPSS scores improved in all men (Figure 4.1b and c). The mean IIEF 18.3 ± 0.2; SDI-71.2 ± 0.4, and IPSS 18.9 ± 0.22 scores prior to weight loss improved post weight loss: IIEF 20.5 ± 0.3, $p<0.0001$; SDI-2 80.7 ± 0.3, $p<0.0001$; and IPSS 12.2 ± 0.2, $p< 0.0001$ (Table 4.3a). Plasma Total

Testosterone (Figure 4.2a) and SHBG (Figure 4.2b) both increased but there was no significant increase in calculated free testosterone (cFT).

The relationships between the measured variables at baseline are shown in Tables 4.3b and c. The relationships between changes in the outcome variables are shown in Tables 4.3d and e. Baseline Insulin (r=-0.347, p<0.05), Triglycerides (r=-0.353, p<0.05) and TCHDL (r=-0.312, p<0.05) were related to baseline SHBG. Baseline diastolic blood pressure (r=-0.356, p<0.05) was negatively associated with prostate symptoms.

Baseline SHBG (r=0.311, p<0.05) and IPSS (r=0.362, p<0.05) were positively associated with sexual desire (Table 4.3 c).There were no significant relationships between baseline weight and waist circumference and testosterone, SHBG, cFT, erectile function, sexual desire or lower urinary tract symptoms (Table 4.3 b).

**Table 4.3b** Relationship between variables at baseline n=41.

| | W | WC | BPSY | BPDIA | Glucose | Insulin | Trigs | TC | HDL | LDL | TCHDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **T** | -0.163 | -0.139 | -0.005 | 0.047 | -0.135 | -0.157 | -0.293 | -0.108 | 0.207 | -0.043 | -0.257 |
| **SHBG** | -0.233 | -0.155 | 0.081 | 0.105 | 0.041 | .347(*) | .353(*) | -0.201 | 0.164 | -0.094 | .312(*) |
| **cFT** | -0.209 | -0.179 | 0.116 | 0.090 | -0.137 | -0.116 | -0.182 | -0.077 | 0.238 | -0.021 | -0.251 |
| **IIEF** | -0.173 | 0.068 | 0.072 | 0.142 | -0.151 | 0.078 | -0.032 | 0.141 | 0.121 | 0.179 | 0.016 |
| **SDI** | -0.167 | 0.030 | -0.301 | -0.159 | -0.106 | 0.054 | -0.077 | 0.051 | -0.016 | 0.099 | 0.082 |
| **IPSS** | -0.014 | -0.054 | -0.165 | .356(*) | 0.149 | -0.149 | -0.191 | 0.034 | 0.291 | 0.042 | -0.243 |

**Table 4.3c** Relationship between variables at baseline n=41.

| | T | SHBG | cFT | IIEF | SDI | IPSS |
|---|---|---|---|---|---|---|
| **T** | 1 | .426(**) | .919(**) | -0.252 | 0.268 | 0.199 |
| **SHBG** | .426(**) | 1 | 0.154 | -0.259 | .311(*) | 0.274 |
| **cFT** | .919(**) | 0.154 | 1 | -0.162 | 0.166 | 0.085 |
| **IIEF** | -0.252 | -0.259 | -0.162 | 1 | -0.204 | -0.017 |
| **SDI** | 0.268 | .311(*) | 0.166 | -0.204 | 1 | 0.144 |
| **IIPS** | 0.199 | 0.274 | 0.085 | -0.017 | 0.144 | 1 |
| **IPSS** | -0.033 | 0.143 | -0.056 | -0.215 | .362(*) | 0.277 |

A reduction in weight (r=0.466, p<0.01) and waist circumference (r=0.336, p<0.01) was associated with an improvement in SHBG (Table 4.3 d). There is also a direct relationship

between an improvement in TC (r=0.462, p<0.05), HDL (r=0.340, p<0.05) and LDL (r=0.399, p<0.05) with SHBG. A negative association between glucose (r=-0.324, p<0.05) and cFT is also evident. There was no association between an improvement in erectile dysfunction, sexual desire or LUTS and testosterone, SHBG and cFT (table 4.3 e).

**Table 4.3d** Relationship between variables at 8 weeks post weight loss n=41.

| | **Δ W** | **Δ WC** | **Δ BPSY** | **Δ BPDIA** | **Δ Glucose** | **Δ Insulin** | **Δ Trigs** | **Δ TC** | **Δ HDL** | **Δ LDL** | **Δ TCHDL** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **ΔT** | 0.130 | -0.037 | 0.021 | 0.014 | -0.179 | 0.217 | -0.100 | -0.049 | -0.070 | -0.030 | -0.029 |
| **ΔSHBG** | .466(**) | .336(*) | 0.295 | -0.022 | 0.192 | 0.281 | 0.240 | .462(**) | .340(*) | .399(*) | 0.264 |
| **ΔcFT** | -0.003 | -0.114 | -0.183 | -0.044 | -.324(*) | 0.197 | -0.164 | -0.218 | -0.250 | -0.113 | -0.097 |
| **ΔIIEF** | 0.092 | -0.053 | -0.022 | -0.278 | 0.111 | 0.232 | 0.067 | 0.085 | -0.073 | 0.047 | 0.147 |
| **ΔSDI** | -0.024 | -0.130 | 0.225 | 0.075 | 0.035 | -0.124 | -0.006 | 0.019 | 0.129 | -0.055 | -0.109 |
| **ΔIPSS** | -0.135 | -0.040 | 0.009 | 0.069 | 0.148 | 0.169 | -0.024 | -0.085 | -0.145 | -0.146 | 0.017 |

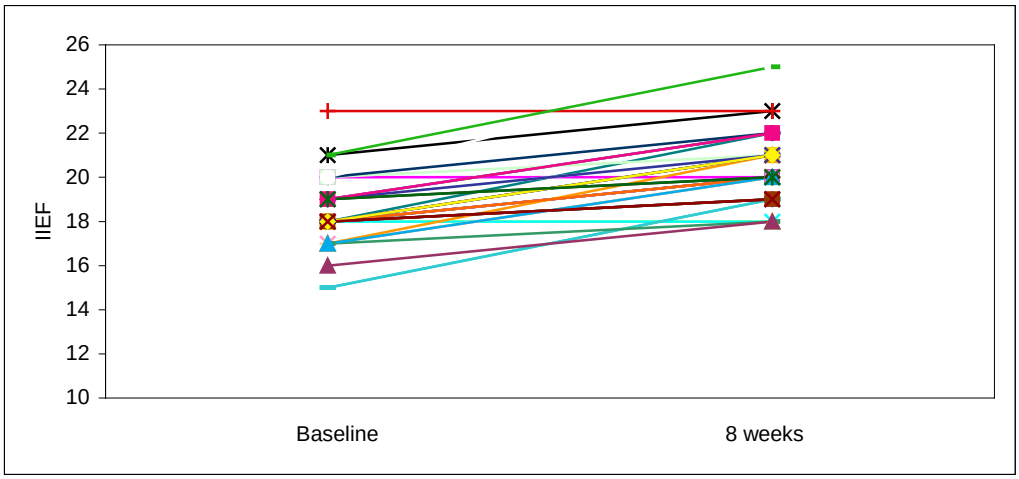
**Table 4.3e** Relationship between variables at 8 weeks post weight loss n=41.

| | **Δ T** | **Δ SHBG** | **Δ cFT** | **Δ IIEF** | **Δ SDI** | **Δ IPSS** |
|---|---|---|---|---|---|---|
| **Δ T** | 1 | .379(*) | .888(**) | 0.224 | -0.164 | 0.111 |
| **Δ SHBG** | .379(*) | 1 | -0.009 | -0.022 | -0.072 | -0.185 |
| **Δ cFT** | .888(**) | -0.009 | 1 | 0.282 | -0.168 | 0.240 |
| **Δ IIEF** | 0.224 | -0.022 | 0.282 | 1 | 0.070 | 0.147 |
| **Δ SDI** | -0.164 | -0.072 | -0.168 | 0.070 | 1 | -0.206 |
| **Δ IPSS** | 0.111 | -0.185 | 0.240 | 0.147 | -0.206 | 1 |

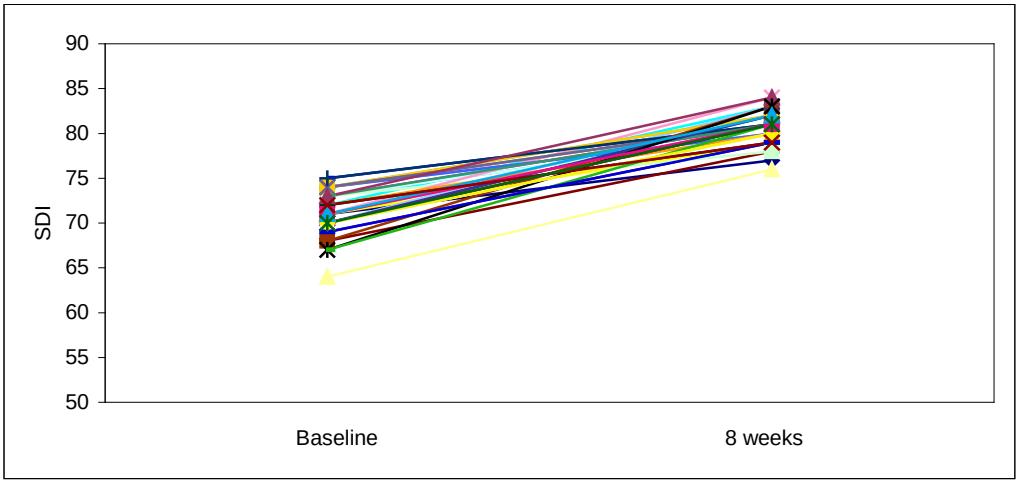
**Table 4.4:** Mean number of weekly minutes of walking, moderate intensity exercise and vigorous intensity exercise in **norma**l obese men.

| | Baseline |
|---|---|
| Minutes of walking per week | 674.9 ± 217.8 |
| Minutes of moderate intensity | 446.3 ± 218.0 |
| Minutes of vigorous intensity | nil |

a)




b)




c)

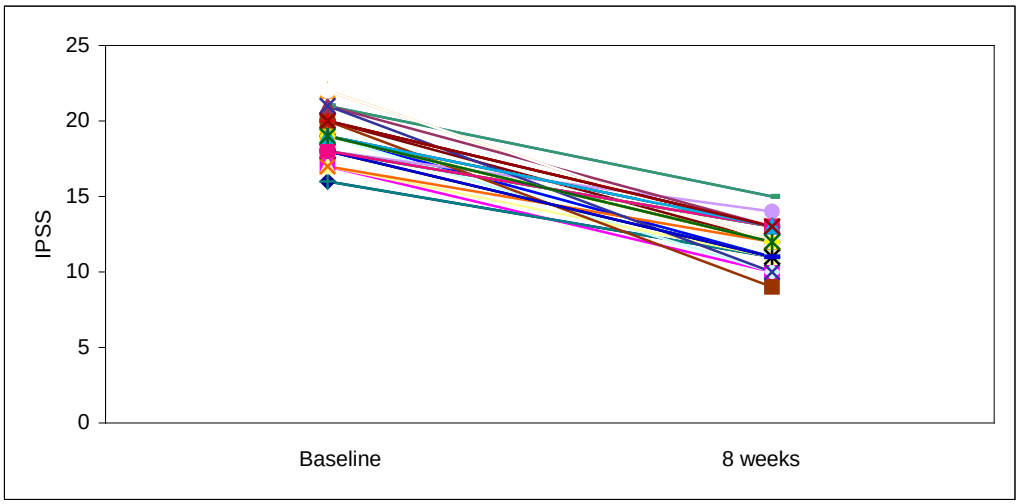
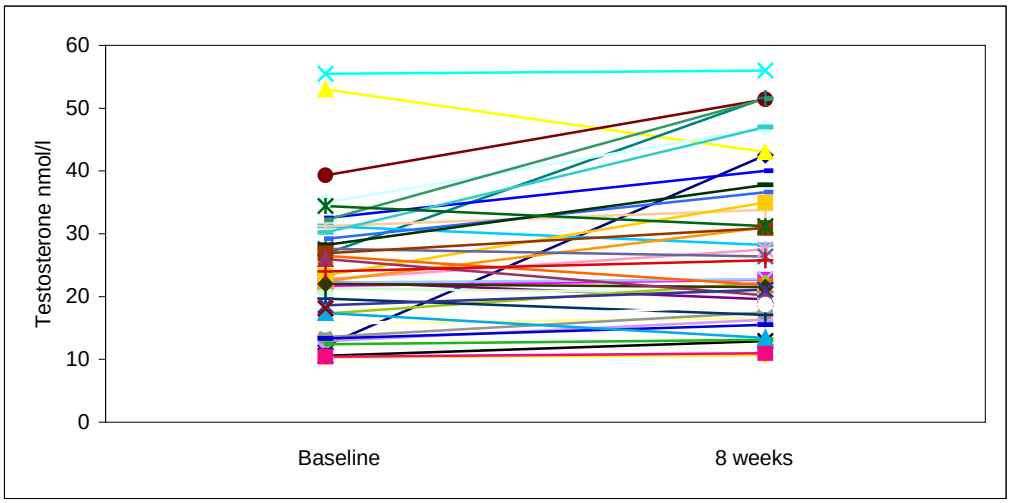



**Figure 4.1** (a) Individual changes in erectile function score at baseline and 8 weeks, (b) Individual changes in sexual desire score at baseline and 8 weeks, (c) Individual changes in IPSS score at baseline and 8 weeks.

a)




b)

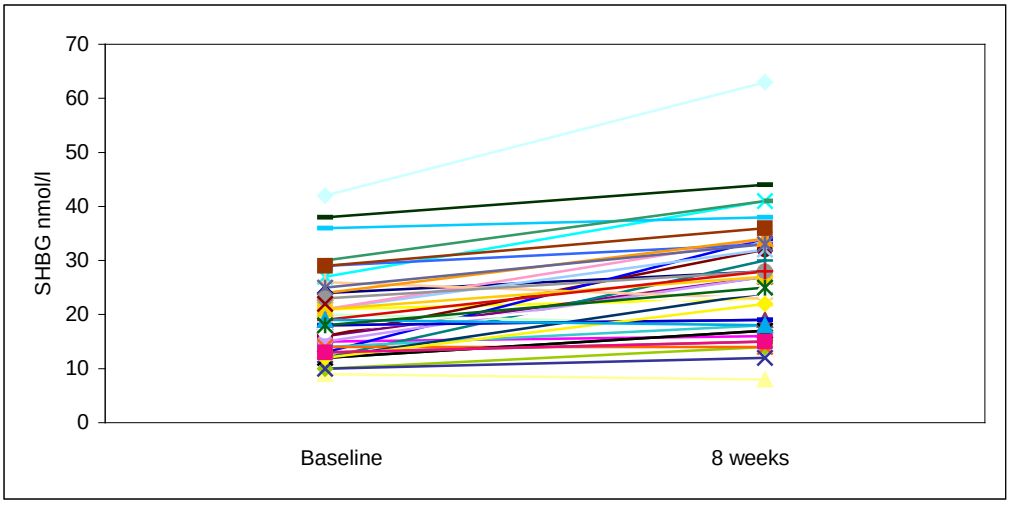



**Figure 4.2** (a) Individual changes in testosterone at baseline and 8 weeks, (b) Individual changes in SHBG at baseline and 8 weeks.

**Relationship between weight, waist circumference, and testosterone, SHBG, cFT IIEF, SDI and IPSS.**

The correlation between measured parameters at baseline (Table 4.5 a-d) and following rapid weight reduction is represented in Tables 4.5e – h.

**Table 4.5a** Relationship between baseline weight, waist circumference, and testosterone, SHBG, cFT IIEF, SDI and IPSS n=41.

| | W | WC |
|---|---|---|
| **T** | -0.163 | -0.139 |
| **SHBG** | -0.233 | -0.155 |
| **cFT** | -0.209 | -0.179 |
| **IIEF** | -0.173 | 0.068 |
| **SDI** | -0.167 | 0.030 |
| **IPSS** | -0.014 | -0.054 |

Table 4.5a, there was no significant relationship between baseline weight and waist circumference with testosterone, SHBG, cFT, erectile function, sexual desire or lower urinary tract symptoms.

**Table 4.5b** Relationship between baseline testosterone, SHBG, cFT and IIEF, SDI and IPSS n=41.

| | T | SHBG | cFT |
|---|---|---|---|
| **IIEF** | -0.252 | -0.259 | -0.162 |
| **SDI** | 0.268 | .311(*) | 0.166 |
| **IPSS** | 0.199 | 0.274 | 0.085 |

Table 4.5b, there was a positive association between baseline SHBG and baseline sexual desire ($r=0.311$, $p<0.05$).

**Table 4.5c** Relationships between baseline FMD and ejection fraction with testosterone, SHBG, cFT IIEF, SDI, IPSS n=41.

| | **FMD** | **EF%** |
|---|---|---|
| **T** | 0.029 | 0.029 |
| **SHBG** | 0.008 | 0.170 |
| **cFT** | 0.076 | -0.041 |
| **IIEF** | 0.073 | -0.166 |
| **SDI** | -0.050 | 0.314 |
| **IPSS** | 0.088 | -0.084 |

Table 4.5c, there are no associations between cardiac function, sexual function and lower urinary tract symptoms.

In the multivariate analysis as shown in Table 4.5d, total testosterone, SHBG and cFT were associated with baseline weight.

**Table 4.5d** Relationship between variables at baseline. Multivariate analysis n=41.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **IIEF** | Weight | .059 | **T** | Weight | .019 |
| | WC | .741 | | WC | .192 |
| **SDI** | Weight | .162 | **SHBG** | Weight | .025 |
| | WC | .637 | | WC | .640 |
| **IPSS** | Weight | .947 | **cFT** | Weight | .008 |
| | WC | .546 | | WC | .016 |

**Table 4.5e** Relationship between change in weight, waist circumference, and testosterone, SHBG, cFT IIEF, SDI and IPSS n=41.

| | **Δ Weight** | **Δ WC** |
|---|---|---|
| **Δ T** | 0.130 | -0.037 |
| **Δ SHBG** | .466(**) | .336(*) |
| **Δ cFT** | -0.003 | -0.114 |
| **Δ IIEF** | 0.092 | -0.053 |
| **Δ SDI** | -0.024 | -0.130 |
| **Δ IPSS** | -0.135 | -0.040 |

Table 4.5e, a significant relationship was observed between change in SHBG and change in weight ($r=0.466$, $p<0.01$) and change in waist circumference ($r=0.336$, $p<0.05$).

**Table 4.5f** Relationship between change in testosterone, SHBG, cFT and IIEF, SDI and IPSS n=41.

| | **Δ T** | **Δ SHBG** | **Δ cFT** |
|---|---|---|---|
| **Δ IIEF** | 0.224 | -0.022 | 0.282 |
| **Δ SDI** | -0.164 | -0.072 | -0.168 |
| **Δ IPSS** | 0.111 | -0.185 | 0.240 |

Table 4.5f, there was no significant relationship between the change in either T or cFT and either erectile function, sexual desire or lower urinary tract symptoms**.**

**Table 4.5g** Relationships between change in FMD and ejection fraction with testosterone, SHBG, cFT IIEF, SDI, IPSS n=41.

| | **Δ FMD** | **Δ EF%** |
|---|---|---|
| **Δ T** | 0.106 | -0.047 |
| **ΔSHBG** | -0.082 | -0.029 |
| **Δ cFT** | 0.146 | -0.071 |
| **Δ IIEF** | -0.111 | -0.004 |
| **Δ SDI** | 0.128 | 0.149 |
| **Δ IPSS** | 0.014 | 0.090 |

Table 4.5g, there are no associations between measured parameters.

In the multivariate analysis IIEF, SDI, IPSS and FAI were not associated with weight loss or reduction in waist circumference (Table 4.5 h).

**Table 4.5 h** Relationship between variables at 8 weeks post weight loss. Multivariate analysis n=41.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **Δ IIEF** | Δ Weight | .327 | **Δ T** | Δ Weight | .058 |
| | Δ WC | .330 | | Δ WC | .816 |
| **Δ SDI** | Δ Weight | .454 | **Δ SHBG** | Δ Weight | .531 |
| | Δ WC | .585 | | Δ WC | .970 |
| **Δ IPSS** | Δ Weight | .722 | **Δ cFT** | Δ Weight | .179 |
| | Δ WC | .302 | | Δ WC | .984 |

**Physical and mental health**

The mean SF-36 quality of life scores for normal obese men from baseline to 8 weeks are summarised in Table 4.6.

Patients reported a significant improvement in physical functioning (p=0.001), bodily pain (p=0.000), general health (p=0.000), vitality (p=0.000), social functioning (p=0.018) and mental health (p=0.000) following 8 weeks of rapid weight reduction.

**Table 4.6** Mean change in quality of life scores from Baseline to 8 weeks in obese men.

| **Quality of Life Measure** | **Baseline** | **8 weeks** | **Δ** | **p value** |
|---|---|---|---|---|
| Physical Functioning | 69.3 ± 4.0 | 78.7 ± 3.0 | 9.4 ± 2.7 | 0.001 |
| Role Physical | 89.6 ± 4.5 | 95.1 ± 2.2 | 5.5 ± 4.3 | 0.212 |
| Bodily pain | 79.7 ± 2.7 | 84.9 ± 2.1 | 5.3 ± 1.3 | 0.000 |
| General Health | 57.8 ± 2.2 | 69.0 ± 1.6 | 11.2 ± 1.1 | 0.000 |
| Vitality | 57.6 ± 1.7 | 67.0 ± 1.3 | 9.4 ± 1.2 | 0.000 |
| Social functioning | 97.3 ± 2.6 | 99.4 ± 2.2 | 2.1 ± 0.9 | 0.018 |
| Role emotional | 91.9 ± 3.8 | 96.8 ± 2.3 | 4.9 ± 2.7 | 0.083 |
| Mental health | 70.2 ± 1.7 | 74.1 ± 1.3 | 3.9 ± 0.7 | 0.000 |

**Relationship between weight, waist circumference, sexual function and quality of life measures.**

The correlations between measured parameters at baseline (Table 4.7 a and b) and following rapid weight reduction are represented in Tables 4.7c and d.

**Table 4.7a** Relationship between baseline weight, waist circumference, testosterone, sexual function and Physical and mental health measures n=41.

| | Weight | WC | T | SHBG | cFT | ED | SDI | IPSS |
|---|---|---|---|---|---|---|---|---|
| **PF** | -.427(**) | -.461(**) | 0.100 | 0.100 | 0.137 | -0.096 | -0.109 | -0.241 |
| **RP** | -.447(**) | -.322(*) | 0.085 | 0.100 | 0.132 | 0.014 | -0.060 | -0.211 |
| **BP** | -0.126 | -0.148 | 0.087 | 0.160 | 0.006 | -0.014 | -0.059 | 0.001 |
| **GH** | -0.143 | 0.015 | -0.067 | 0.273 | -0.158 | -0.034 | -0.158 | -0.267 |
| **VT** | -0.184 | -0.181 | -0.064 | 0.119 | -0.085 | -0.138 | -0.245 | -0.040 |
| **SF** | -0.258 | -0.188 | -0.109 | 0.067 | -0.108 | 0.008 | -0.065 | -0.258 |
| **RE** | -.353(*) | -.310(*) | 0.040 | -0.011 | 0.109 | 0.021 | -0.086 | -0.277 |
| **MH** | -0.203 | -.318(*) | -0.271 | -0.086 | -0.229 | -0.038 | -.447(**) | -0.291 |

Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH), erectile dysfunction (ED), sexual desire (SD) and lower urinary tract symptoms (LUTS). *$p \leq 0.05$, **$p \leq 0.01$

Baseline weight and waist circumference were related to baseline physical functioning (r=-0.427, p<0.01; r=-0.461, p<0.01), role physical (r=-0.447, p<0.01; r=-322, p<0.05), and role emotional (r=-0.353, p<0.05; r=-0.310, p<0.05)**.** Baseline mental health was associated with waist circumference (r=-0.318, p<0.05).

Baseline sexual desire (r=-0.447, p<0.05) was related to initial mental health (Table 4.7a).

In the multivariate analysis as shown in Table 4.7b, mental health was related to sexual desire (r=0.008, p<0.01). Baseline general health was associated with IPSS (r=0.026, p<0.05).

**Table 4.7b** Relationship between variables at baseline. Multivariate analysis n=41.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **T** | PF | 438 | **IIEF** | PF | .645 |
| | RP | .313 | | RP | .809 |
| | BP | .343 | | BP | .826 |
| | GH | .697 | | GH | .913 |
| | VT | .665 | | VT | .305 |
| | SF | .672 | | SF | .939 |
| | RE | .423 | | RE | .882 |
| | MH | .508 | | MH | .342 |
| **SHBG** | PF | .193 | **SDI** | PF | .383 |
| | RP | .144 | | RP | .659 |
| | BP | .836 | | BP | .459 |
| | GH | .069 | | GH | .149 |
| | VT | .264 | | VT | .076 |
| | SF | .299 | | SF | .766 |
| | RE | .370 | | RE | .686 |
| | MH | .338 | | MH | .008 |
| **cFT** | PF | .314 | **IPSS** | PF | .131 |
| | RP | .220 | | RP | .183 |
| | BP | .363 | | BP | .695 |
| | GH | .491 | | GH | .026 |
| | VT | .796 | | VT | .851 |
| | SF | .817 | | SF | .114 |
| | RE | .311 | | RE | .115 |
| | MH | .775 | | MH | .141 |

**Table 4.7c** Relationships between change in weight, waist circumference, sexual function and Physical and mental health measures n=41.

| | Δ Weight | Δ WC | Δ T | Δ SHBG | Δ cFT | Δ ED | Δ SD | Δ LUTS |
|---|---|---|---|---|---|---|---|---|
| **Δ PF** | 0.203 | 0.044 | 0.211 | 0.086 | 0.182 | 0.086 | -0.037 | -0.170 |
| **Δ RP** | 0.203 | -0.049 | 0.081 | 0.056 | 0.057 | 0.089 | -0.130 | -0.232 |
| **Δ BP** | -0.058 | 0.195 | -0.231 | 0.060 | -.335(*) | 0.171 | 0.015 | -0.110 |
| **Δ GH** | 0.046 | -0.013 | -0.079 | -0.067 | -0.059 | -0.088 | -0.060 | -0.222 |
| **Δ VT** | 0.046 | -0.050 | 0.036 | -0.083 | 0.052 | -0.088 | -0.131 | -0.020 |
| **Δ SF** | .324(*) | 0.097 | -0.034 | 0.116 | -0.032 | 0.109 | -0.072 | -.394(*) |
| **Δ RE** | -0.075 | 0.029 | 0.024 | 0.031 | 0.023 | 0.025 | 0.072 | -.412(**) |
| **Δ MH** | 0.293 | .348(*) | 0.037 | 0.114 | -0.033 | -0.166 | -0.293 | -0.248 |

Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH). *$p \leq 0.05$, **$p \leq 0.01$

A reduction in weight was associated with sustained improvement in social functioning ($r=0.324$, $p<0.05$), and cFT ($r=-0.335$, $p<0.05$) was with an improvement in Bodily pain. An improvement in prostate symptoms was associated with an improvement in social functioning ($r=-0.394$, $p<0.05$) and role emotional ($r=-0.412$, $p<0.05$) (Table 4.7c). A reduction in waist circumference was associated with improved mental health ($r=0.348$. $p<0.05$).

In the multivariate analysis as shown in Table 4.7d, 8 weeks of dietary intervention showed improvements in social functioning ($r=0.005$, $p<0.01$) and role emotional ($r=0.008$, $p<0.01$) was related to an improvement in IPSS.

**Table 4.7d** Relationship between variables at 8 weeks post weight loss. Multivariate analysis n=41.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| Δ**T** | ΔPF | .812 | Δ**IIEF** | ΔPF | .753 |
| | ΔRP | .930 | | ΔRP | .483 |
| | ΔBP | .192 | | ΔBP | .064 |
| | ΔGH | .847 | | ΔGH | .840 |
| | ΔVT | .641 | | ΔVT | .572 |
| | ΔSF | .111 | | ΔSF | .316 |
| | ΔRE | .563 | | ΔRE | .780 |
| | ΔMH | .686 | | ΔMH | .430 |
| Δ**SHBG** | ΔPF | .943 | Δ**SDI** | ΔPF | .705 |
| | ΔRP | .910 | | ΔRP | .256 |
| | ΔBP | .344 | | ΔBP | .517 |
| | ΔGH | .814 | | ΔGH | .532 |
| | ΔVT | .464 | | ΔVT | .383 |
| | ΔSF | .157 | | ΔSF | .261 |
| | ΔRE | .764 | | ΔRE | .928 |
| | ΔMH | .804 | | ΔMH | .023 |
| Δ**cFT** | ΔPF | .918 | Δ**IPSS** | ΔPF | .205 |
| | ΔRP | .988 | | ΔRP | .092 |
| | ΔBP | .055 | | ΔBP | .801 |
| | ΔGH | .861 | | ΔGH | .152 |
| | ΔVT | .737 | | ΔVT | .719 |
| | ΔSF | .127 | | ΔSF | .005 |
| | ΔRE | .457 | | ΔRE | .008 |
| | ΔMH | .718 | | ΔMH | .073 |

**Diabetic Men**

**Baseline and follow-up changes pre and post weight loss diabetic obese men**

Baseline characteristics of the men are shown in Table 4.8a. The relationships between the baseline (Table 4.8 b and c) and follow up variables are shown in Tables 4.8 d and e. Baseline blood pressure was elevated (≥ 140/90) in 12 men and fasting glucose elevated in 14 (glucose levels of 7.8-11.1 mmol/L). All hypertensive men were in the diabetic group.

Fourteen men completed the study, lost weight (14.1 ± 1.39 kg, 5.0-27.7kg) and decreased waist circumference (12.4 ± 0.87 cm, 3.8 – 36.4 cm).

Systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and insulin, glucose decreased following weight loss. All men walked for sport, physical activity or recreation in the two weeks prior to their clinic visits, and participated in moderate intensity exercise (Table 4.9).

ED (Figure 4.3a), SDI (Figure 4.3b) and IPSS (Figure 4.3c) scores improved in all men. The mean IIEF 19.8 ± 0.6; SDI-68.2 ± 1.3, and IPSS 18.5 ± 0.34 scores prior to weight loss improved post weight loss: IIEF 22.3 ± 0.7, $p<0.0001$; SDI-2 79.8 ± 0.8, $p<0.0001$; and IPSS 12.5 ± 0.54, $p<0.0001$ (Table 4.8). There was no significant increase in calculated free testosterone (cFT) or testosterone levels (Figure 4.4a), however SHBG increased (Figure 4.4b).

**Table 4.8a** Baseline and follow-up changes pre and post weight loss n=14, mean ± Std. Error Mean – **Diabetic Males**

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 47.4 ±3.5 | | | |
| Weight (kg) | 115.7±5.2 | 101.6±5.2 | 0.000 | 14.1±1.39 |
| Waist Circumference (cm) | 114.9±2.7 | 102.6±3.0 | 0.000 | 12.4±0.87 |
| BMI ($kg/m^2$) | 35.6±1.1 | 28.2±1.3 | 0.000 | 7.5±0.44 |
| Systolic BP (mmHg) | 139.3±5.4 | 123.9±2.1 | 0.004 | 15.4±4.3 |
| Diastolic BP (mmHg) | 87.5±3.0 | 78.9±2.4 | 0.000 | 8.6±1.6 |
| Glucose (mmol/L) | 9.2±0.7 | 5.5±0.38 | 0.000 | 3.7±0.73 |
| Insulin (mU/L) | 15.3±3.2 | 10.2±3.1 | 0.012 | 5.1±1.7 |
| Total Triglycerides (mmol/L) | 1.8±0.26 | 1.1±0.1 | 0.006 | 0.81±0.25 |
| Total Cholesterol (mmol/L) | 5.4±0.26 | 4.2±0.25 | 0.000 | 1.2±0.18 |
| HDL Cholesterol (mmol/L) | 1.1±0.06 | 1.1±0.06 | 0.547 | 0.03±0.05 |
| LDL Cholesterol (mmol.L) | 3.4±0.24 | 2.7±0.19 | 0.000 | 0.77±0.12 |
| Testosterone (nmol/L) | 18.5±1.6 | 21.3±2.4 | 0.199 | 2.8±2.1 |
| SHBG (nmol/L) | 19.5±2.5 | 26.2±2.8 | 0.014 | 6.7±2.4 |
| cFT (nmol/L) | 0.53±0.06 | 0.53±0.06 | 0.980 | 0.00±0.06 |
| IIEF | 19.8±0.6 | 22.3±0.7 | 0.000 | 2.5±0.33 |
| SDI | 68.2±1.3 | 79.8±0.8 | 0.000 | 11.6±1.2 |
| IIPS | 18.5±0.34 | 12.5±0.54 | 0.000 | -6.0±0.36 |
| FMD% | 5.2±1.7 | 9.9±1.9 | 0.007 | 4.6±1.6 |
| EF% | 48.5±1.6 | 56.7±1.5 | 0.000 | 8.2±0.57 |

Baseline systolic ($r=0.637$, $p<0.05$) and diastolic blood pressure ($r=0.573$, $p<0.05$) and TCHDL ($r= -0.550$, $p<0.05$) were related to baseline SHBG. Baseline LDL was associated to testosterone ($r=-0.642$, $p<0.05$) and cFT ($r=-0.580$, $p<0.05$) (Table 4.8 b).

An improvement in LDL was associated with testosterone (r=0.593, p<0.05) and cFT (r=0.647, p<0.05) (Table 4.8d).

Table 4.8 e shows a positive association between an improvement in IIEF with testosterone (r=0.535, p<0.05) and SDI (r=0.596, p<0.05) 8 weeks post weight loss.

**Table 4.8b** Relationship between variables at baseline n=14.

| | W | WC | BPSY | BPDIA | Glucose | Insulin | Trigs | TC | HDL | LDL | TCHDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **T** | 0.136 | -0.383 | -0.125 | -0.224 | 0.102 | -0.004 | 0.287 | -0.476 | -0.373 | -.642(*) | 0.047 |
| **SHBG** | -0.088 | 0.100 | .637(*) | .573(*) | 0.156 | -0.244 | -0.454 | -0.082 | 0.449 | 0.068 | -.550(*) |
| **cFT** | 0.143 | -0.408 | -0.332 | -0.371 | -0.004 | 0.151 | 0.419 | -0.381 | -0.513 | -.580(*) | 0.278 |
| **IIEF** | -0.226 | 0.114 | 0.419 | 0.283 | 0.182 | -0.166 | -0.485 | 0.028 | 0.402 | 0.209 | -0.350 |
| **SDI** | 0.266 | -0.018 | 0.114 | -0.010 | -0.049 | 0.220 | -0.066 | -0.514 | -0.277 | -0.467 | -0.104 |
| **IIPSS** | 0.045 | 0.063 | -0.088 | -0.092 | -0.124 | 0.088 | 0.028 | 0.153 | -0.054 | 0.189 | 0.223 |

**Table 4.8c** Relationship between variables at baseline n=14.

| | T | SHBG | cFT | IIEF | SDI | IIPS | IPSS |
|---|---|---|---|---|---|---|---|
| **T** | 1 | -0.332 | .918(**) | -0.424 | 0.243 | -0.155 | 0.183 |
| **SHBG** | -0.332 | 1 | -.661(*) | 0.306 | -0.121 | -0.330 | -0.274 |
| **cFT** | .918(**) | -.661(*) | 1 | -0.456 | 0.223 | 0.032 | 0.275 |
| **IIEF** | -0.424 | 0.306 | -0.456 | 1 | -0.246 | 0.270 | 0.122 |
| **SDI** | 0.243 | -0.121 | 0.223 | -0.246 | 1 | -0.496 | -0.190 |
| **IPSS** | -0.155 | -0.330 | 0.032 | 0.270 | -0.496 | 1 | .752(**) |

**Table 4.8d** Relationship between variables at 8 weeks post weight loss n=14.

| | ΔW | ΔWC | ΔBPSY | ΔBPDIA | ΔGlucose | ΔInsulin | ΔTrigs | ΔTC | ΔHDL | ΔLDL | ΔTCHDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **ΔT** | 0.284 | 0.295 | -0.452 | -0.189 | -0.006 | -0.278 | -0.154 | 0.292 | 0.333 | .593(*) | -0.206 |
| **ΔSHBG** | 0.509 | 0.515 | -0.274 | 0.222 | 0.334 | -0.321 | 0.464 | 0.359 | -0.109 | 0.068 | 0.371 |
| **ΔcFT** | 0.163 | 0.080 | -0.344 | -0.314 | -0.188 | -0.184 | -0.434 | 0.114 | 0.373 | .647(*) | -0.400 |
| **ΔIIEF** | 0.160 | 0.190 | -0.474 | -0.365 | -0.241 | -0.002 | -0.273 | -0.061 | 0.036 | 0.285 | -0.223 |
| **ΔSDI** | 0.131 | 0.176 | 0.012 | 0.307 | 0.075 | 0.303 | 0.200 | 0.470 | 0.189 | 0.392 | 0.119 |
| **ΔIPSS** | 0.054 | 0.107 | -0.035 | -0.188 | -0.238 | -0.233 | -0.283 | -0.404 | -0.229 | -0.180 | -0.028 |

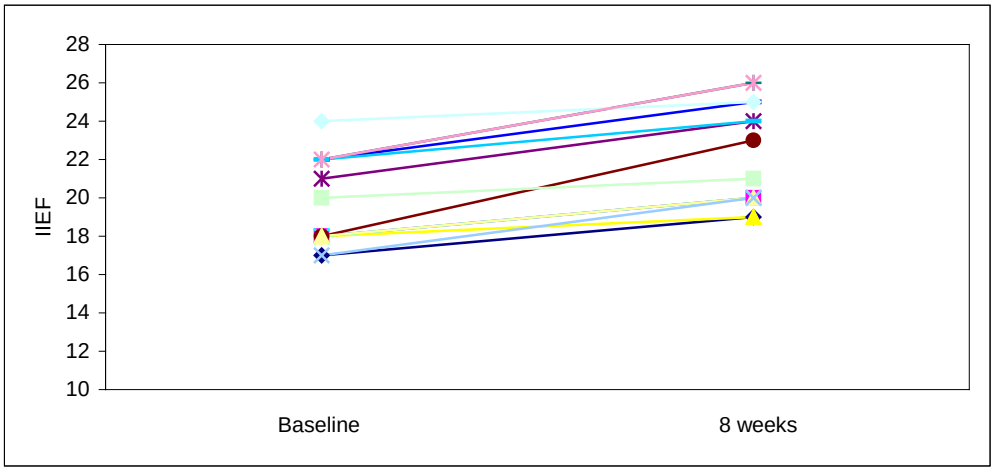
**Table 4.8e** Relationship between variables at 8 weeks post weight loss n=14.

| | **ΔT** | **ΔSHBG** | **ΔcFT** | **ΔIIEF** | **ΔSDI** | **ΔIPSS** |
|---|---|---|---|---|---|---|
| **ΔT** | 1 | 0.424 | .910(**) | .535(*) | 0.529 | -0.280 |
| **ΔSHBG** | 0.424 | 1 | 0.038 | -0.092 | 0.098 | -0.038 |
| **ΔcFT** | .910(**) | 0.038 | 1 | .586(*) | 0.460 | -0.248 |
| **ΔIIEF** | .535(*) | -0.092 | .586(*) | 1 | .596(*) | 0.046 |
| **ΔSDI** | 0.529 | 0.098 | 0.460 | .596(*) | 1 | -0.452 |
| **ΔIPSS** | -0.280 | -0.038 | -0.248 | 0.046 | -0.452 | 1 |

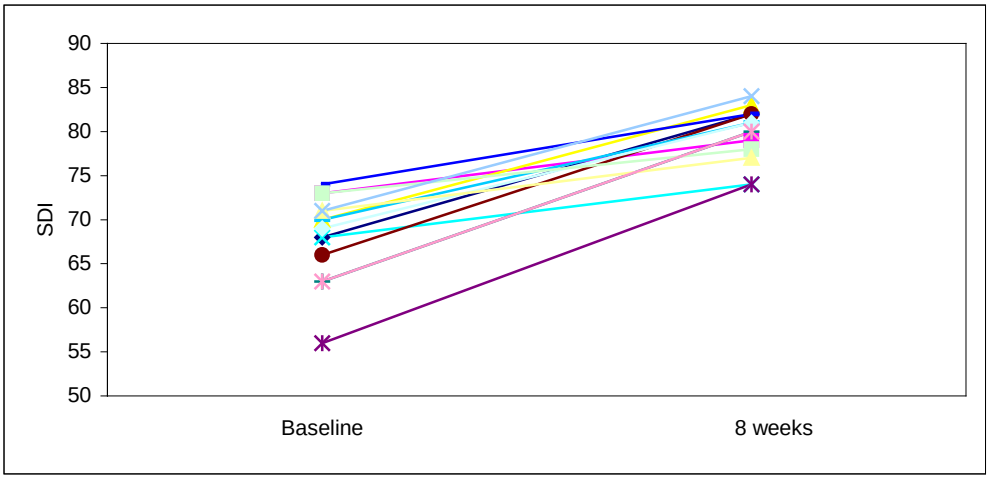
**Table 4.9:** Mean number of weekly minutes of walking, moderate intensity exercise and vigorous intensity exercise in **diabetic** obese men.

| | Baseline |
|---|---|
| Minutes of walking per week | 473.3 ± 105.6 |
| Minutes of moderate intensity | 70.1 ± 7.1 |
| Minutes of vigorous intensity | nil |

a)




b)




c)

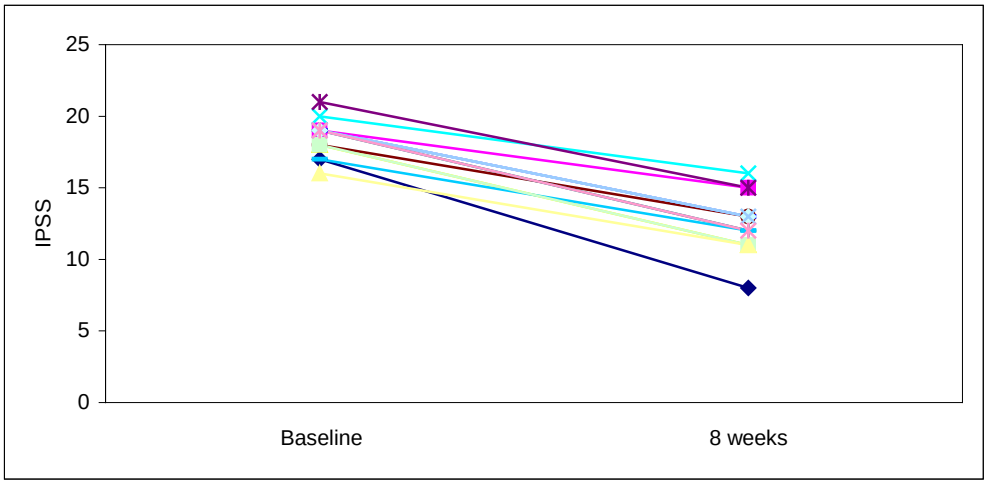
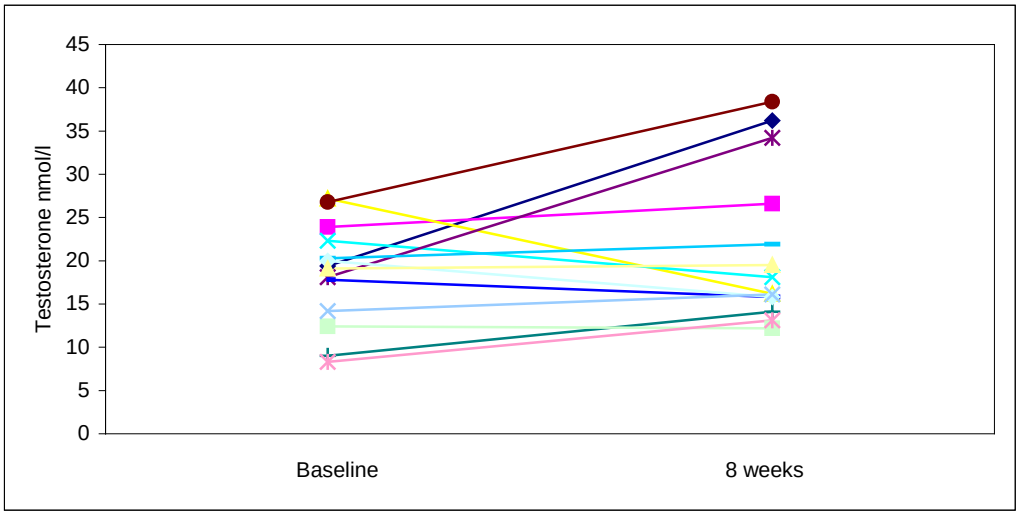



**Figure 4.3** (a) Individual changes in erectile function score at baseline and 8 weeks, (b) Individual changes in sexual desire score at baseline and 8 weeks, (c) Individual changes in IPSS score at baseline and 8 weeks. Diabetic men

a)




b)

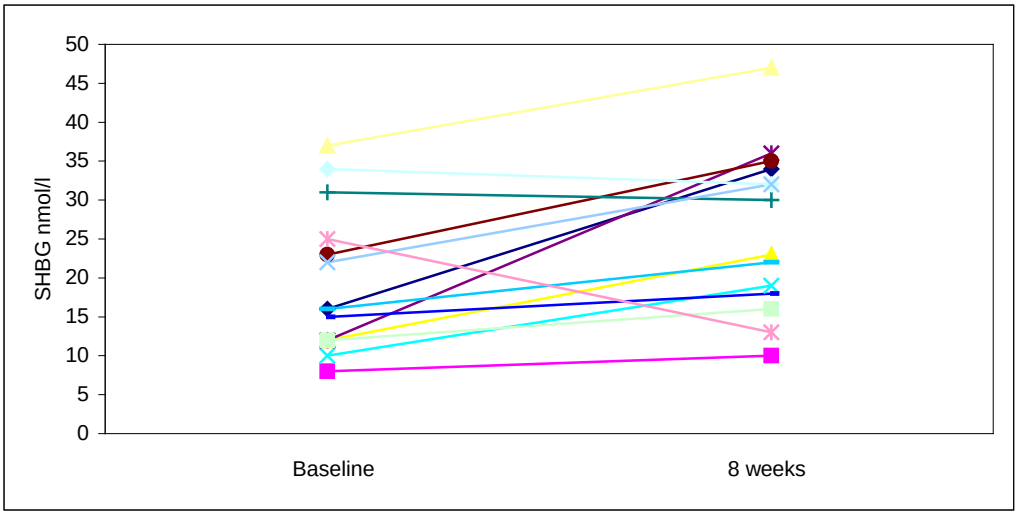



**Figure 4.4** (a) Individual changes in testosterone at baseline and 8 weeks, (b) Individual changes in SHBG at baseline and 8 weeks. Diabetic men

**Relationship between weight, waist circumference, and testosterone, SHBG, IIEF, SDI, IPSS, EF and FMD.**

The correlation between measured parameters at baseline and following rapid weight reduction is represented in Table 4.10a, b, c and d.

**Table 4.10a** Relationships between baseline weight, waist circumference, and testosterone, SHBG, cFT, IIEF, SDI, IPSS n=14.

| | **W** | **WC** |
|---|---|---|
| **T** | 0.136 | -0.383 |
| **SHBG** | -0.088 | 0.100 |
| **cFT** | 0.143 | -0.408 |
| **IIEF** | -0.226 | 0.114 |
| **SDI** | 0.266 | -0.018 |
| **IPSS** | 0.045 | 0.063 |

Table 4.10a, there was no significant relationship between baseline weight/waist circumference and Testosterone, SHBG, cFT and erectile function, sexual desire or lower urinary tract symptoms.

**Table 4.10 b** Relationships between baseline testosterone, cFT and IIEF and IIEF, SDI, IPSS n=14.

| | **T** | **cFT** | **IIEF** |
|---|---|---|---|
| **IIEF** | -0.424 | -0.456 | 1 |
| **SDI** | 0.243 | 0.223 | -0.246 |
| **IPSS** | -0.155 | 0.032 | 0.270 |

Table 4.10 b, there was no baseline relationships between testosterone, CFT with erectile dysfunction, sexual desire and lower urinary tract symptoms.

**Table 4.10c** Relationships between baseline FMD and ejection fraction with testosterone, SHBG, cFT IIEF, SDI, IPSS n=14.

| | **FMD** | **EF%** |
|---|---|---|
| **T** | -0.365 | -0.342 |
| **SHBG** | -0.197 | 0.522 |
| **cFT** | -0.273 | -0.456 |
| **IIEF** | 0.388 | .639(*) |
| **SDI** | -0.117 | -0.189 |
| **IPSS** | 0.380 | -0.364 |

Table 4.10c, baseline ejection fraction was positively associated with erectile dysfunction ($r=0.639$, $p<0.05$).

**Table 4.10d** Relationship between variables at baseline. Multivariate analysis n=14.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **IIEF** | Weight | .499 | **T** | Weight | .969 |
| | WC | .749 | | WC | .060 |
| **SDI** | Weight | .324 | **SHBG** | Weight | .980 |
| | WC | .930 | | WC | .042 |
| **IPSS** | Weight | .435 | **cFT** | Weight | .985 |
| | WC | .895 | | WC | .037 |

Table 4.10 d shows baseline SHBG and cFT are related to baseline waist circumference.

**Table 4.10e** Relationships between change in weight, waist circumference, and testosterone, SHBG, cFT, IIEF, SDI, IPSS n=14.

| | **∆W** | **∆WC** |
|---|---|---|
| **∆ T** | 0.284 | 0.295 |
| **∆SHBG** | 0.509 | 0.515 |
| **∆ cFT** | 0.163 | 0.080 |
| **∆ IIEF** | 0.160 | 0.190 |
| **∆ SDI** | 0.131 | 0.176 |
| **∆ IPSS** | 0.054 | 0.107 |

There was no association between the amount of weight lost or reduction in waist circumference and the change in plasma testosterone, erectile function, sexual desire or LUTS in diabetic obese men (Table 4.10 e).

**Table 4.10 f** Relationships between change in testosterone, cFTand IIEF and IIEF, SDI, IPSS n=14.

| | **Δ T** | **Δ cFT** | **Δ IIEF** |
|---|---|---|---|
| **Δ IIEF** | .535(*) | .586(*) | 1 |
| **Δ SDI** | 0.529 | 0.460 | 0.598(*) |
| **Δ IPSS** | -0.280 | -0.248 | 0.046 |

Table 4.10f, significant relationships were observed between the change in plasma total testosterone and change in IIEF ($r=0.535$, $p<0.05$), change in cFT and change in IIEF ($r=0.586$, $p<0.05$). A significant relationship was also observed between an improvement in IIEF and sexual desire ($r=0.596$, $p<0.05$).

**Table 4.10g** Relationships between change in FMD and ejection fraction with testosterone, SHBG, cFT IIEF, SDI, IPSS n=14.

| | **Δ FMD** | **Δ EF%** |
|---|---|---|
| **Δ T** | 0.027 | -0.500 |
| **ΔSHBG** | 0.494 | -0.096 |
| **Δ cFT** | -0.208 | -0.525 |
| **Δ IIEF** | -0.505 | -0.217 |
| **Δ SDI** | -0.173 | -0.386 |
| **Δ IPSS** | -.537(*) | .662(*) |

Table 4.10g, Baseline FAI ($r=-0.587$, $p<0.05$) and IIEF ($r=0.639$, $p<0.05$) were associated to baseline EF. IPSS scores were significantly correlated with change in ejection fraction($r=0.662$, $p<0.05$) and change in FMD ($r=-0.537$, $p<0.05$) (Table 4.10f).

**Table 4.10h** Relationship between variables at 8 weeks post weight loss. Multivariate analysis n=14.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| Δ **IIEF** | Δ Weight | .144 | Δ **T** | Δ Weight | .183 |
| | Δ WC | .172 | | Δ WC | .271 |
| Δ **SDI** | Δ Weight | .156 | Δ **SHBG** | Δ Weight | .012 |
| | Δ WC | .680 | | Δ WC | .314 |
| Δ **IPSS** | Δ Weight | .536 | Δ **cFT** | Δ Weight | .252 |
| | Δ WC | .400 | | Δ WC | .241 |

In the multivariate analysis as shown in Table 4.10h an improvement in SHBG was associated with weight loss. IIEF, SDI, IPSS, FAI and cFT were not associated with weight loss or waist circumference.

**Physical and mental health**

For diabetic obese men (Table 4.11) patients reported a significant improvement in physical functioning (p=0.026), general health (p=0.000), vitality (p=0.017), and mental health (p=0.000) after 8 weeks of dieting and exercise.

**Table 4.11** Mean change in quality of life scores from Baseline to 8 weeks in **Diabetic men**.

| **Quality of Life Measure** | **Baseline** | **8 weeks** | **Δ** | **p value** |
|---|---|---|---|---|
| Physical Functioning | 69.6 ± 7.1 | 80.7 ± 3.6 | 11.1 ± 4.4 | 0.026 |
| Role Physical | 85.7 ± 9.7 | 91.1 ± 4.2 | 5.4 ± 7.0 | 0.459 |
| Bodily pain | 75.7 ± 5.7 | 82.0 ± 3.6 | 6.3 ± 3.4 | 0.088 |
| General Health | 52.2 ± 3.3 | 69.7 ± 7.3 | 17.5 ± 2.9 | 0.000 |
| Vitality | 59.6 ± 4.3 | 67.5 ± 1.9 | 7.9 ± 2.9 | 0.017 |
| Social functioning | 95.5 ± 3.8 | 97.3 ± 3.5 | 1.8 ± 2.2 | 0.435 |
| Role emotional | 95.2 ± 4.8 | 97.6 ± 2.4 | 2.4 ± 2.4 | 0.336 |
| Mental health | 72.0 ± 2.7 | 74.3 ± 2.2 | 2.3 ± 0.8 | 0.014 |

**NB Higher score indicates better quality of life.**

**Relationship between weight, waist circumference, and quality of life measures – Diabetic obese men.**

The correlations between measured parameters at baseline (Table 4.12 a and b) and following rapid weight reduction are represented in Tables 4.12c-e.

**Table 4.12a** Relationship between baseline weight, waist circumference, sexual function and Physical and mental health measures n=14.

| | **Weight** | **WC** | **T** | **SHBG** | **cFT** |
|---|---|---|---|---|---|
| **PF** | -0.280 | 0.249 | 0.248 | -0.308 | 0.301 |
| **RP** | -0.382 | 0.473 | -0.218 | -0.136 | -0.149 |
| **BP** | -0.329 | -0.096 | 0.293 | -0.258 | 0.346 |
| **GH** | -0.088 | 0.352 | 0.180 | -0.364 | 0.269 |
| **VT** | -0.524 | -0.007 | 0.306 | -0.001 | 0.226 |
| **SF** | -0.179 | 0.231 | 0.076 | -0.004 | 0.065 |
| **RE** | -.672(**) | 0.309 | -0.266 | 0.354 | -0.401 |
| **MH** | 0.001 | .577(*) | 0.032 | 0.079 | -0.057 |

Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH).*$p \leq 0.05$, **$p \leq 0.01$

Table 4.12a, baseline weight was negatively associated with role emotional (r= -0.672, $p<0.01$). Baseline waist circumference was positively associated to mental health (r=0.577, $p<0.05$).

In the multivariate analysis as shown in Table 4.12b there were no associations between baseline physical and mental health parameters and testosterone, SHBG, cFT, IIEF, SDI and IPSS.

**Table 4.12b** Relationship between variables at baseline. Multivariate analysis n=14.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **T** | PF | .583 | **IIEF** | PF | .855 |
| | RP | .389 | | RP | .485 |
| | BP | .899 | | BP | .913 |
| | GH | .555 | | GH | .661 |
| | VT | .413 | | VT | .880 |
| | SF | .735 | | SF | .797 |
| | RE | .224 | | RE | .829 |
| | MH | .181 | | MH | .474 |
| **SHBG** | PF | .517 | **SDI** | PF | .587 |
| | RP | .267 | | RP | .495 |
| | BP | .995 | | BP | .545 |
| | GH | .405 | | GH | .471 |
| | VT | .626 | | VT | .231 |
| | SF | .968 | | SF | .655 |
| | RE | .273 | | RE | .340 |
| | MH | .223 | | MH | .300 |
| **cFT** | PF | .632 | **IIPS** | PF | .958 |
| | RP | .353 | | RP | .873 |
| | BP | .952 | | BP | .470 |
| | GH | .602 | | GH | .924 |
| | VT | .543 | | VT | .874 |
| | SF | .832 | | SF | .351 |
| | RE | .198 | | RE | .647 |
| | MH | .179 | | MH | .902 |

**Table 4.12c** Relationship between change in weight, waist circumference, sexual function and Physical and mental health measures n=14**.**

| | **ΔWeight** | **ΔWC** | **Δ T** | **ΔSHBG** | **Δ cFT** |
|---|---|---|---|---|---|
| **ΔPF** | 0.304 | 0.126 | 0.023 | -0.166 | 0.172 |
| **Δ RP** | 0.306 | -0.080 | -0.217 | -0.075 | -0.107 |
| **ΔBP** | 0.232 | 0.051 | -0.013 | -0.416 | 0.204 |
| **Δ GH** | 0.410 | 0.131 | -0.015 | 0.211 | -0.042 |
| **Δ VT** | -0.035 | 0.044 | 0.001 | -0.444 | 0.242 |
| **Δ SF** | -0.394 | 0.200 | -0.078 | -0.019 | -0.119 |
| **Δ RE** | -0.191 | -0.052 | -0.004 | -0.153 | 0.095 |
| **Δ MH** | -0.075 | 0.194 | -0.354 | -0.351 | -0.216 |

Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH).*p≤0.05, **p≤0.01

Table 4.12c, there were no significant associations between improvements in testosterone, SHBG, FAI, and cFT levels with physical and mental parameters.

In the multivariate analysis as shown in Table 4.12d, an improvement in sexual desire was related to social functioning (r=0.024, p<0.05). Like wise cFT was associated with social functioning (r=0.017, p<0.05).

**Table 4.12d** Relationship between variables at 8 weeks post weight loss. Multivariate analysis n=14.

| | Dependent Variable | Sig. | | Dependent Variable | Sig. |
|---|---|---|---|---|---|
| **ΔT** | ΔPF | .633 | **ΔIIEF** | ΔPF | .769 |
| | ΔRP | .327 | | ΔRP | .973 |
| | ΔBP | .828 | | ΔBP | .963 |
| | ΔGH | .647 | | ΔGH | .980 |
| | ΔVT | .938 | | ΔVT | .878 |
| | ΔSF | .017 | | ΔSF | .788 |
| | ΔRE | .582 | | ΔRE | .375 |
| | ΔMH | .793 | | ΔMH | .554 |
| **ΔSHBG** | ΔPF | .753 | **ΔSDI** | ΔPF | .707 |
| | ΔRP | .360 | | ΔRP | .368 |
| | ΔBP | .889 | | ΔBP | .805 |
| | ΔGH | .529 | | ΔGH | .585 |
| | ΔVT | .739 | | ΔVT | .505 |
| | ΔSF | .023 | | ΔSF | .027 |
| | ΔRE | .493 | | ΔRE | .718 |
| | ΔMH | .632 | | ΔMH | .150 |
| **ΔcFT** | ΔPF | .491 | **ΔIPSS** | ΔPF | .444 |
| | ΔRP | .276 | | ΔRP | .653 |
| | ΔBP | .713 | | ΔBP | .689 |
| | ΔGH | .595 | | GH | .877 |
| | ΔVT | .755 | | ΔVT | .627 |
| | ΔSF | .017 | | ΔSF | .272 |
| | ΔRE | .744 | | ΔRE | .191 |
| | ΔMH | .755 | | ΔMH | .586 |

**Table 4.12e** Relationship between change in sexual function and physical and mental health measures n=14.

| | **Δ IIEF** | **ΔSDI** | **ΔIPSS** |
|---|---|---|---|
| **ΔPF** | -0.048 | -0.357 | 0.362 |
| **Δ RP** | -0.269 | -.627(*) | 0.431 |
| **ΔBP** | 0.108 | -0.166 | 0.196 |
| **Δ GH** | -0.217 | -0.389 | 0.234 |
| **Δ VT** | 0.059 | -0.292 | 0.238 |
| **Δ SF** | 0.000 | -0.429 | 0.427 |
| **Δ RE** | -0.118 | -0.346 | 0.424 |
| **Δ MH** | -0.166 | -0.517 | 0.150 |

Physical Functioning (PF), Role Physical (RP), Bodily pain (BP), General Health (GH), Vitality (VT), Social functioning (SF), Role emotional (RE), Mental health (MH).*p≤0.05, **p≤0.01

Table 4.12e shows an improvement in sexual desire is associated with role physical (r=-0.627, p<0.05).

## 4.5 Discussion

In this study, we analysed the relationship between obesity and erectile dysfunction, testosterone, sexual desire and lower urinary tract symptoms. This chapter aimed to determine whether ED, SDI, testosterone and LUTS improved following rapid induced weight loss.

### Normal obese men baseline

Total testosterone, SHBG and FAI were related to weight and waist circumference.

In normal obese men total testosterone and cFT were associated with erectile dysfunction. Baseline SHBG was associated with baseline sexual desire. Baseline weight and waist circumference were related to baseline Physical functioning.

Similar relationships were also reported in other studies. Zohdy et al. 2007[417] evaluated the effect of obesity on serum total testosterone (TT) level and penile duplex parameters in men with erectile dysfunction (ED). A significant negative correlation between BMI and TT was detected. Paick et al. 2007[418] evaluated the effects of risk factors for ED or cardiovascular disease on the disease severity in impotent men. There was no correlation between scores of IIEF or EF domain. On the multivariate model used, hypertensive patients had 26-fold higher risk of severe ED than those without hypertension. Kratzik et al. 2005[419] investigated the impact of age, body mass index and testosterone on erectile dysfunction. Increase in BMI by 1 kg/m reduced IIEF-5 by 0.141, independent of age. Multiple logistic regression analyses confirmed the influence of increased age and higher BMI on the risk of ED. Severe cases of ED (IIEF-5 score 7 or less) were significantly associated with a decrease in T. Shao et al.

2005[420] evaluated the degree of sexual dysfunction in men with benign prostatic hyperplasia (BPH) accompanied by LUTS, and to assess the correlation between sexual dysfunction and urinary symptoms and age. There was statistically significant correlation between age and sexual symptom scores for erection, IIEF-5 scores and IPSS as well as between IPSS and sexual symptom scores for erection and overall satisfaction. IIEF-5 scores were significantly correlated with sexual symptom scores for each of the three categories (sexual drive, erection and ejaculation). Serum testosterone did not correlate to age, IIEF-5 scores and sexual function, nor did peak urinary flow rate and total prostatic volume to IPSS, IIEF-5 scores and sexual function.

**Normal obese men and weight loss**

A reduction in weight was associated with a reduction in systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and insulin. ED improved in 37 men, SDI and IPSS scores improved in all. Testosterone and SHBG both increased but there was no significant increase in calculated free testosterone (cFT).

IIEF, SDI, IPSS and FAI were not associated with weight loss or reduction in waist circumference. The lack of association of sexual dysfunctions of desire and erectile function with abdominal obesity, as estimated by waist circumference was surprising. It appears that obesity related metabolic disorders such as diabetes is more likely to impact on sexual function than obesity. Patients reported a significant improvement in physical functioning, bodily pain, general health, vitality, social functioning and mental health following 8 weeks of rapid weight reduction. Likewise, FAI and cFT was associated with an improvement in Bodily pain.

Burgmer et al. 2007[421] evaluated depressive symptoms, self-esteem and health-related quality of life 2 years after bariatric surgery. Statistical analyses revealed a significant decrease in depressive symptoms and a significant improvement in self-esteem and physical health-related quality of life. Shiri et al. 2007 [422] examined the impact of bariatric surgery in terms of positive psychological growth and development. Mental and physical health was assessed using the SF-36. Positive impact was apparent in all dimensions including greater appreciation of life, increased sense of personal strength and improvement in relating to others. Kinzl et al. 2007[423] investigated age, gender, weight loss, and preoperative psychiatric disorders with regard to quality of life measures (QOL) after LAGB. No difference was seen in satisfaction with weight loss among the age groups. Some correlations were seen between the amount of weight loss and QOL scores in females, but not in males. Greater weight loss showed a statistically significant positive correlation to self-esteem, physical activity, social relationships, sexuality, and eating pattern. The majority of morbidly obese patients showed psychological and interpersonal improvement after surgery. Titi et al. 2007 [424] reported on weight loss, QOL, and health outcomes following laparoscopic adjustable gastric banding (LAGB). Sixty-four patients (79%) reported improvement in their QOL including self-esteem, physical activity, social involvement, and ability to work. Seventy-one patients had initial obesity related comorbidity. In 61 of these patients (86%) their comorbidities resolved or improved.

**Diabetic obese men**

There was no association between initial weight/waist circumference with testosterone, erectile dysfunction, sexual desire and LUTS in diabetic obese men. Baseline FAI and IIEF were associated to baseline ejection fraction.

In other studies, Kapoor et al. 2007[425] investigated the relationship between ED and total, bioavailable and free testosterone levels in 198 men with type 2 diabetes. In addition, they examined the associations of various cardiovascular risk factors involved in the development of ED in type 2 diabetic men. Bioavailable and free testosterone levels were significantly lower in men with ED than those without ED. Sex hormone-binding globulin levels were also reduced, but there was no significant difference in total testosterone (TT) levels between men with and without ED. The severity of ED as assessed by International Index of Erectile Function scores was significantly associated with TT, bioavailable testosterone and calculated free testosterone levels. ED was more frequently observed in men with hypertension and a higher waist circumference. This study has shown that ED is associated with low bioavailable and free testosterone levels, age, visceral adiposity and hypertension in type 2 diabetic men. Guo et al. 2005[426] investigated the correlative factors affecting the IIEF-5 scores of the patient with type 2 diabetic mellitus. There was significant negative correlation between IIEF-5 scores and age, BMI, FPG, 2hPG, INS, GHbA1c and AR ($P < 0.05$), and significant positive correlation between IIEF-5 scores and NO ($P < 0.05$).

**Diabetic obese men and weight loss**

Systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and insulin, glucose decreased following weight loss. ED, SDI and IPSS scores improved in all men. There was no significant increase in calculated free testosterone (cFT) or testosterone levels,

however SHBG increased. Diabetic patients presented improvements in only physical functioning, general health, vitality and mental health after 8 weeks of dieting and exercise.

There was no association between weight loss/reduction in waist circumference with testosterone, erectile dysfunction, sexual desire and LUTS in diabetic obese men. A significant correlation was observed between an improvement in testosterone and IIEF. Likewise, an association exists between cFT and IIEF. A significant correlation was also observed between an improvement in IIEF and sexual desire. IPSS scores were significantly correlated with an increase in ejection fraction and FMD.

A previous diabetic study demonstrated weight loss and related metabolic improvement have been associated with improved sexual function.[427] Niskanen et al. 2004 showed rapid weight loss with successful weight maintenance in abdominally obese men with the metabolic syndrome brings about a sustained increase in fT levels. The dramatic increase in SHBG attenuated initially during weight maintenance but remained elevated.

Interventions focused on modifiable health behaviours may represent a safe strategy to improve erectile function and reduce cardiovascular risk in obese patients.

**4.6 Conclusion**

In this group of men, obesity was associated with mild/moderate erectile dysfunction, and significant LUTS, which together with sexual desire improved following rapid diet, induced weight loss, but was not directly related to the amount of weight loss or changes in metabolic state. Patients reported a significant improvement in physical functioning, bodily pain, general health, vitality, social functioning and mental health following 8 weeks of rapid weight reduction.

# CHAPTER 5

## Effects of Weight Loss on Pericardial Adipose Tissue Measured by Magnetic Resonance Imaging

### 5.1 Introduction

There is considerable evidence that regional fat distribution plays an important part in the development of an unfavourable metabolic and cardiovascular risk profile with modest increases in body mass index[428]. Pericardial adipose tissue (PAT) is a metabolically active tissue that generates local release of fatty acids and various bioactive molecules (for example leptin, adiponectin, and inflammatory cytokines), which might significantly affect cardiac muscle function or the responsiveness of coronary arteries  Furthermore, PAT mass may reflect intra-abdominal visceral fat, or be a marker of increased ectopic fat deposition in general (liver and skeletal muscle) which is associated with all features of metabolic syndrome.[429, 430, 431]  It has been shown in both imaging[432, 433] and autopsy studies [434, 435, 436, 437] that PAT mass and body weight and overall fat mass are related.

The assessment of PAT by MRI could be a simple and practical tool for cardiovascular risk stratification that requires investigation.  Currently, there is very limited information relating to the measurement and consequences of increased PAT. Previous studies determined the amount of PAT by measuring the right ventricular PAT thickness by echocardiography.[438,439] We have recently validated a novel CMR technique for estimating PAT, and shown it to be superior to right ventricular pericardial adipose tissue thickness estimations, when compared to PAT mass at autopsy.[440]

In this study, we used a unique CMR technique to measure PAT in obese Caucasian males, and to: (i) relate this volume to other anthropometric indices and metabolic and functional parameters, (ii) assess the changes in PAT after an 8 week very low calorie diet, and (iii) determine the relationship of these changes in PAT to anthropometric indices, metabolic parameters, ventricular and vascular function.

## 5.2 Methods

Obese male subjects (BMI>30kg/$m^2$) who were non diabetic, with no significant cardiovascular risk factors were enrolled. Pericardial adipose tissue burden was measured using CMR and transthoracic echocardiography as described below (section 5.3).

The protocol used for weight loss, and time points of evaluation and data collected is as described (Chapter 3, section 3.2).

## 5.3 Imaging

### 1. Magnetic Resonance Imaging

Standard steady state free precision cine imaging was performed as per a standard clinical CMR study, using a 1.5T CMR unit (Siemens Sonata, Erlangen). Consecutive end-diastolic images were acquired using the short-axis stack from the mitral valve plane through to the apex and using Image Pro Plus (v4, MediaCybernetics, Maryland, USA) regions of PAT were traced and their area calculated as previously described. The two and four chamber sagital-oblique views were used for reference to establish boundaries between contiguous areas of similar signal intensity. A modified Simpson's rule was then used to calculate epicardial fat

volume. All MRI data was re-identified and analysed in a blinded fashion. Intra-observer variability <5%.

**2. Echocardiography**

Complete transthoracic 2-dimensional echocardiograms were obtained. Standard parasternal and apical views were obtained in the partial left decubitus position using the Vivid 7, GE Vingmed (Milwaukee, Wisconsin) and images digitally stored. The echocardiograms were reviewed for measurement of left ventricular dimensions and PAT thickness. Echocardiograms of 15 patients were randomly selected and repeated measurements of PAT thickness were blindly performed to assess intraobserver and interobserver variability.

PAT was identified as a space or layer anterior to the right ventricle with decreased echoreflectivity compared with the myocardium and pericardium as described by Iacobellis et al.[441, 442] and Chaowalit et al. 2006 [443] The largest dimension of this space in end-diastole measured from trailing edge to leading edge was considered the maximum epicardial fat thickness in both the parasternal long and mid ventricular short axis views. For mid-ventricular parasternal short axis assessment, maximum epicardial fat thickness was measured between the mid-chordal level and the tip of the papillary muscles.

**5.4 Statistical Analysis**

Statistical analysis was performed using SPSS 15. All results are expressed as mean values ± SEM. Anthropometric variables and epicardial fat thickness at baseline and at 8 weeks were compared using Student *t* test. A value of $p<0.05$ was considered significant. Pearson's correlation was performed evaluating the correlation with change in weight and waist circumference with change in epicardial fat.

## 5.5 Results

### Characteristics of the subjects and baseline measurements

A total of 30 male patients were enrolled. At baseline the cohort had a mean age 44 ± 8 yrs (18-65yrs), BMI of 36 ± 4 kg/m$^2$ (30-45 kg/m$^2$), their weight was 115 ± 16 kg and waist circumference 122 ± 12 cm (104-152 cm) (Table 5.1).

### Changes in measured parameters in response to weight loss

All men lost weight (13.4 ± 0.8 kg, 5.0-27.7kg) and decreased waist circumference (13.7 ± 1.32 cm, 3.8 – 36.4 cm). A reduction in weight was associated with a reduction in systolic blood pressure, total and LDL cholesterol, triglycerides and insulin (Table 5.1).

**Table 5.1** Baseline and follow-up changes pre and post weight loss, mean ± Std. Error Mean

| **Characteristics** | **Baseline** | **8 Weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| Age (yrs) | 43.7 ±1.6 | | | |
| Weight (kg) | 115.0±3.2 | 101.6±2.9 | 0.000 | 13.4±0.80 |
| Waist Circumference (cm) | 121.8±2.5 | 108.0±2.4 | 0.000 | 13.7±1.32 |
| BMI (kg/m$^2$) | 36.3±0.83 | 28.5±0.73 | 0.000 | 7.7±0.31 |
| Systolic BP (mmHg) | 132.1±3.0 | 123.3±2.0 | 0.001 | 8.8±2.2 |
| Diastolic BP (mmHg) | 79.8±1.9 | 76.5±1.5 | 0.151 | 3.3±2.3 |
| Glucose (mmol/L) | 5.8±0.41 | 5.0±0.14 | 0.102 | 0.71±0.42 |
| Insulin (mU/L) | 15.0±1.9 | 7.0±0.7 | 0.000 | 8.0±1.6 |
| Total Triglycerides (mmol/L) | 1.7±0.2 | 1.0±0.07 | 0.001 | 0.7±0.19 |
| Total Cholesterol (mmol/L) | 5.2±0.19 | 4.4±0.18 | 0.000 | 0.75±0.18 |
| HDL Cholesterol (mmol/L) | 1.0±0.03 | 1.1±0.04 | 0.519 | 0.02±0.03 |
| LDL Cholesterol (mmol.L) | 3.4±0.18 | 2.9±0.15 | 0.002 | 0.49±0.14 |
| EF %* | 53.4±1.4 | 58.9±1.4 | 0.000 | 5.5±0.93 |
| FMD* | 4.3±1.1 | 6.3±1.5 | 0.000 | 2.0±1.8 |
| Epicardial fat volume cm$^3$ * | 86.9±5.34 | 65.9±4.7 | 0.000 | 21.0±2.2 |

*****measured by MRI

The baseline PAT volume measured by CMR was reduced significantly by 24 ± 2.4 % from 86.9±5.34 $cm^3$ to 65.9±4.7 $cm^3$ ($p<0.01$) as shown in Table 5.1 and Figure 5.1a. The PAT volume reduction can be clearly seen in Figure 5.1b.

Our results demonstrate that volumetric quantification of epicardial fat using CMR is feasible and yields superior reproducibility compared to thickness and area measurements. This is consistent with a recent study showing that a magnetic resonance imaging based volumetric approach was highly reproducible (CV 5%). [433]

**Cardiac Magnetic Resonance Imaging**

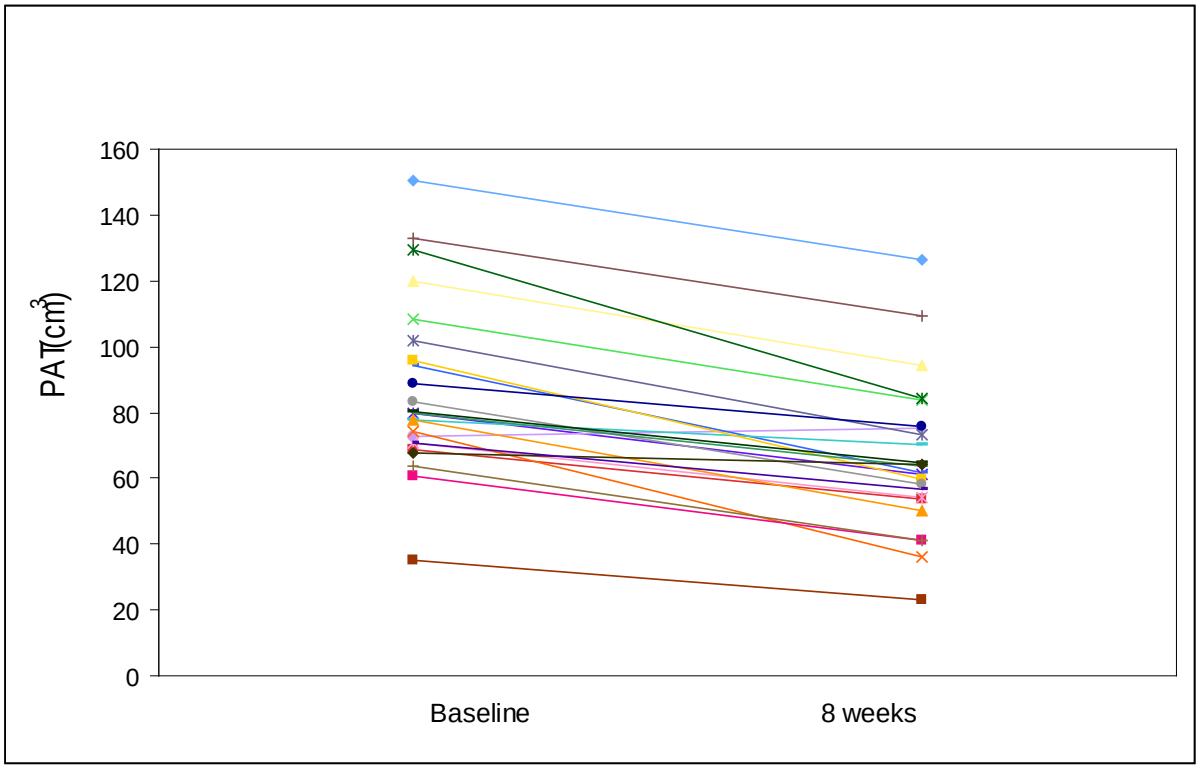



Figure 5.1a PAT volume at baseline and 8 weeks post dietary intervention

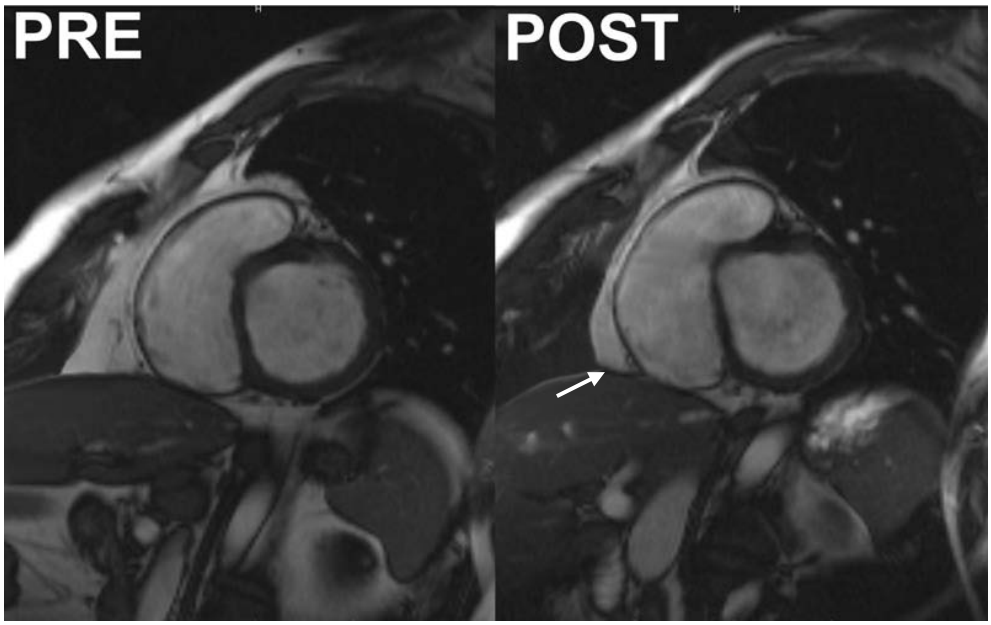



**Figure 5.1b** CMR images showing a reduction in pericardial adipose tissue (white arrow) taken at baseline and at 8 weeks of caloric restriction.

**Echocardiography**

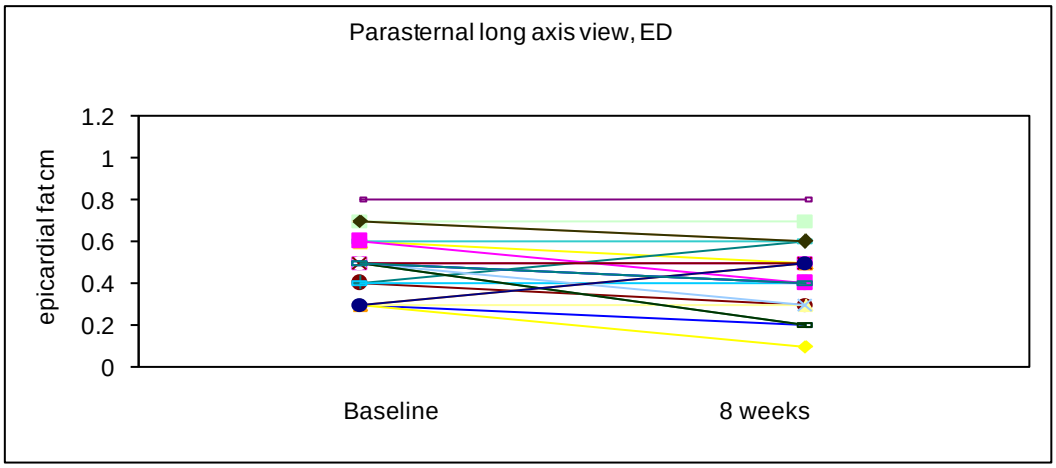
In our study, PAT thickness varied from 3.0 to 9.0 mm in obese men as measured by echocardiography (Table 5.2). Our obese patients had similar baseline epicardial fat thicknesses (3.0 to 10.5 mm) as patients reported by Willens et al.2007.[444]

The greatest reduction of PAT thickness, 1.16 ± 0.30 mm, was identified in the parasternal short axis view, end diastole. Figure 5.2 shows changes in PAT thickness at baseline and 8 weeks.

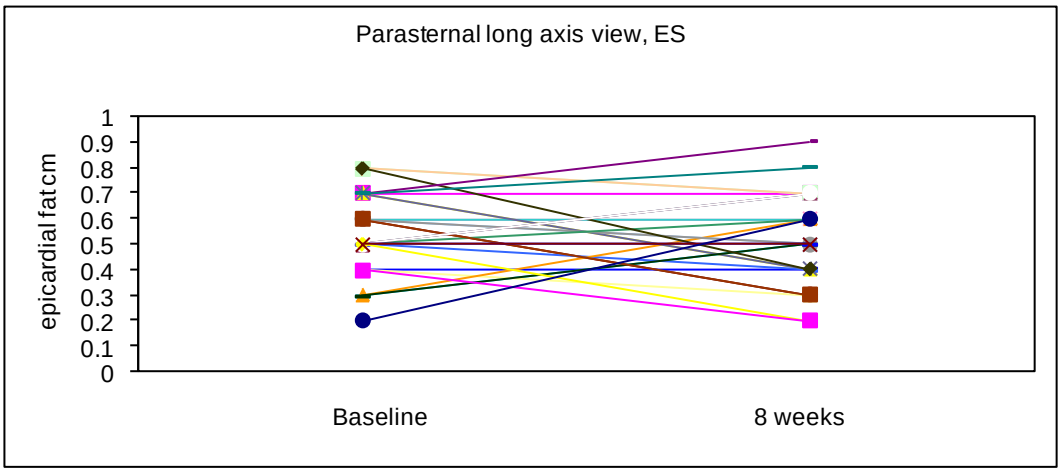
**Table 5.2** PAT cm ± SEM measured by echocardiography. Parasternal long view, end diastole (PSLAX ED), parasternal long view, end systole (PSLAX ES), parasternal short axis view, end diastole (PSSAX ED), and parasternal short axis view, end systole (PSSAX ES).

| | **Baseline** | **8 weeks** | **p Value** | **Δ** |
|---|---|---|---|---|
| PSLAX ED | 0.496 ± 0.027 | 0.431 ± 0.032 | 0.016 | 0.065 ± 0.020 |
| PSLAX ES | 0.545 ± 0.030 | 0.524 ± 0.033 | 0.596 | 0.021 ± 0.031 |
| PSSAX ED | 0.535 ± 0.031 | 0.419 ± 0.030 | 0.002 | 0.116 ± 0.030 |
| PSSAX ES | 0.581 ± 0.031 | 0.497 ± 0.027 | 0.010 | 0.084 ± 0.026 |

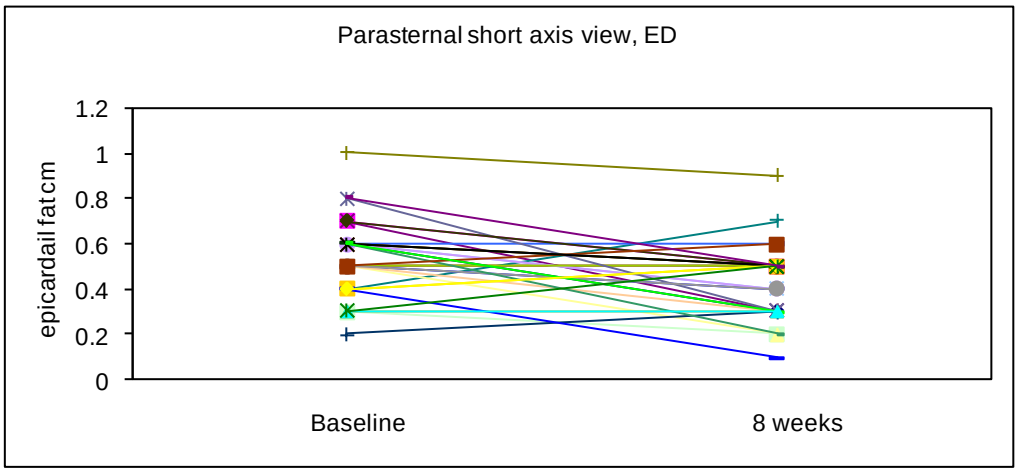
a)


Parasternal long axis view, ED
epicardial fat cm
1.2
1
0.8
0.6
0.4
0.2
0
Baseline
8 weeks

b)


Parasternal long axis view, ES
epicardial fat cm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Baseline
8 weeks

c)




d)

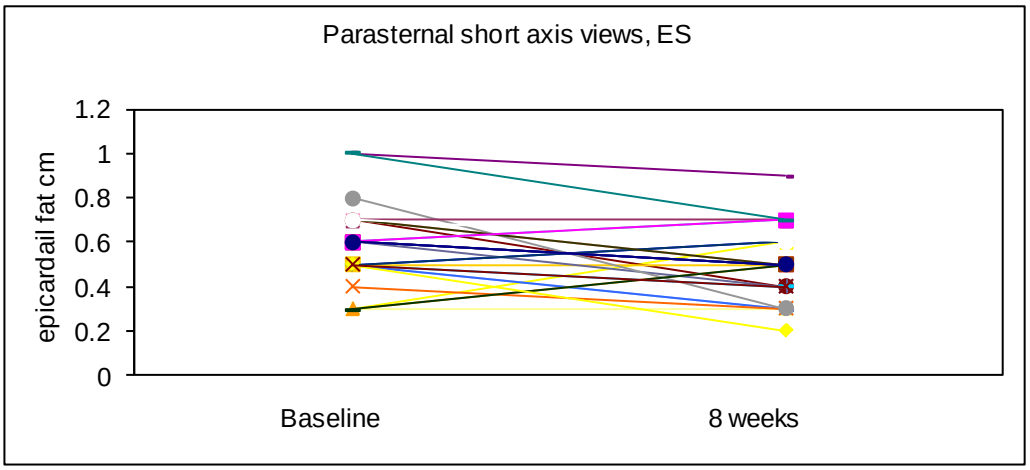



**Figure 5.2** (a) Parasternal long view, end diastole, (b) parasternal long view, end systole, (c) parasternal short axis view, end diastole, and (d) parasternal short axis view, end systole at baseline and 8 weeks.

**Relationship between change in weight, waist circumference, EF, FMD and epicardial fat.**

The correlation between measured parameters at baseline (Table 5.3a) and following rapid weight reduction is represented in Table 5.3b.

**Table 5.3a** Relationship between variables at baseline n=30.

| | W | WC | BPSY | BPDIA | Glucose | Insulin | Trigs | TC | HDL | LDL | FMD | EF% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PSLAXED#** | .076 | .143 | -.010 | -.180 | -.352 | .104 | .259 | -.050 | .062 | -.100 | .073 | -.140 |
| **PSLAXES#** | -.180 | .025 | .045 | -.180 | -.179 | -.106 | .204 | .162 | .296 | .134 | .079 | .050 |
| **PSSA ED#** | -.014 | -.083 | .123 | -.190 | -.059 | .058 | .240 | .084 | -.036 | .072 | .425* | -.042 |
| **PSSAXES#** | .048 | .306 | -.370* | -.289 | -.063 | -.179 | .143 | .252 | .043 | .226 | .085 | .040 |
| **VOLcm$^3$*** | .106 | .175 | .255 | .183 | -.222 | .155 | -.142 | -.529** | -.363 | -.505* | -.100 | -.195 |

* measured by MRI, # measured by echo. Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

Table 5.3a, baseline PAT thickness as measured by echocardiography in the parasternal short axis view, end systole (PSSAXES) view was negatively associated with baseline systolic blood pressure (p=-0.370, p<0.01). Baseline PAT volume as measured by MRI was related to TC (p=-0.529, p<0.01) and LDL (p=-0.505, p<0.05).

**Table 5.3b** Relationship between variables at 8 weeks post weight loss n=30.

| | W | WC | BPSY | BPDIA | Glucose | Insulin | Trigs | TC | HDL | LDL | FMD | EF% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PSLAXED#** | .077 | -.118 | -.096 | .264 | .348 | -.015 | .030 | -.151 | .036 | -.115 | .153 | -.107 |
| **PSLAXES#** | .146 | -.100 | -.372* | .287 | .198 | -.184 | -.036 | .034 | -.016 | .212 | -.059 | -.059 |
| **PSSAXED#** | -.209 | -.460** | -.371* | -.012 | .014 | -.104 | -.356* | -.281 | -.171 | -.113 | .339 | .092 |
| **PSSAXES#** | -.392* | -.534** | .076 | .067 | .053 | .001 | -.240 | -.271 | -.209 | -.398* | .208 | .395* |
| **VOLcm$^3$*** | .020 | .068 | .204 | .258 | .117 | .136 | -.113 | .041 | .202 | -.161 | -.191 | -.024 |

* measured by MRI, # measured by echo. Systolic BP (BPSY), Diastolic BP (BP DIA), Total Triglycerides (Trigs), Total Cholesterol (TC), High density lipoprotein (HDL) Cholesterol, Low density lipoprotein (LDL) Cholesterol), Flow mediated dilatation (FMD) and Ejection fraction (EF). *p≤0.05, **p≤0.01

Table 5.3b, a decrease in PAT thickness as measured by echocardiography was significantly associated with changes in weight, waist circumference, systolic blood pressure, triglycerides, and LDL. There is a lack of association with change in PAT volume as measured by CMR with weight loss, reduction in waist circumference, BP, glucose, insulin, triglycerides, HDL, LDL, EF, and FMD.

## 5.6 Discussion

We have shown that with a unique CMR technique, we have been able to assess PAT in obese caucasian males. Furthermore, we have shown that an 8 week VLCD intervention leads to a decrease in the PAT amount as measured by mri and echocardiography. PAT may be an important marker of cardiovascular risk in obese males.

This is the first study to show a reduction in PAT volume is associated with caloric restriction with further studies required to establish whether this is ultimately associated with improved myocardial function.

### Limitations of the study

Not all patients could tolerate the cardiac MRI protocol due to claustrophobia (n=10). Furthermore, morbidly obese individuals may be more likely to fail due to the physical constraints of the MRI machine.

## 5.7 Conclusion

Short term weight loss using VLCD over 8 weeks leads to a reduction in PAT volume as measured by CMR.

## 6.0 CONCLUSIONS

Obesity is increasing in prevalence. It is associated with many risk factors and is independently associated with cardiovascular disease. New technologies have assisted our understanding of the spectrum of abnormalities, although the precise mechanism by which they occur and interact to exacerbate overall cardiovascular risk remains to be determined. Obesity is potentially reversible and accordingly it is important to determine not only the relationship between obesity and cardiovascular function and structure but also the potential for reversibility with weight loss. A large and relatively rapid initial weight loss is associated with better maintenance of weight loss but the safety and overall benefit of this approach for cardiovascular dysfunction has not previously been defined.

Because the blood vessels in the penis are similar to those that supply the myocardium and because of the established relationship between erectile dysfunction and cardiovascular disease we sought to establish the nature of erectile function in men in this study. Moreover because of the relationship that is known to occur between erectile dysfunction and lower urinary tract symptoms we also sought to evaluate irritative and obstructive lower urinary tract symptoms at baseline and in response to weight loss.

Additionally obesity is associated with decreased plasma testosterone and men with low testosterone are susceptible to a number of consequences including loss of lean body mass, further increases in fat mass, and compromised erectile dysfunction and poor sexual desire. We therefore also determined the relationship between testosterone, erectile dysfunction and sexual desire at baseline and following rapid weight reduction.

The specific hypotheses addressed in this thesis were:

The effects of obesity and diet-induced weight loss, and the extent to which the effects are dependent on, or interrelated with, other cardiovascular risk factors (hypertension, abnormal glucose tolerance, hyperlipidaemia, and symptoms of obstructive sleep apnoea) on:

(i) Vascular and cardiac function using novel Magnetic Resonance Imaging (MRI) based methodology to evaluate left ventricular and vascular structure and function.

(ii) Erectile dysfunction, sexual desire, plasma androgen levels and lower urinary tract symptoms.

(iii) Pericardial adipose tissue assessed using echocardiography and MRI.

We used cardiac magnetic resonance imaging (CMR) to evaluate ventricular and vascular structure and function. The data indicate that severe obesity per se, in the absence of other significant cardiovascular risk factors or symptoms of cardiovascular disease, is associated with left ventricular and endothelial dysfunction. Rapid weight loss induced over an 8 week period was safe and improved left ventricular systolic function and endothelial function. There was a trend for improvement in aortic distensibility. Moreover in men with Type 2 diabetes cardiovascular function was significantly more impaired than in non diabetic men but similarly with weight loss induced by low calorie diet there was a significant improvement in ventricular systolic function and endothelial function, and a trend for improvement in aortic distensibility.

The failure to find a correlation between baseline weight, metabolic parameters and cardiovascular function and structure or change in weight loss and metabolic parameters and cardiac function and structure is consistent with the notion that some other factor associated

with the obesity and responsive to rapid weight loss is mediating the effect. It is possible that the amount of weight loss exceeded a critical threshold for benefit, but it seems equally or perhaps more plausible that a change in some other factor is responsible. In obese men erectile dysfunction has been shown to be most closely related to markers of inflammation rather than the degree of obesity or metabolic disturbance (Esposito et al 2004). Furthermore improvements in endothelial function in response to weight loss have been shown to relate most closely to reductions in pro-inflammatory cytokines and adhesion molecules (Ziccardi et al 2002).

Although we have examined plasma levels of a marker (CML) for advanced glycosylation end products and did not find any association with the degree of obesity or any metabolic, cardiac or sexual parameter (data not shown) we do not have markers of tissue AGE which are more relevant. Inflammatory cytokines have also not been measured due to time course required for the completion of this work, but these will hopefully be available in the near future.

In addition to the other benefits patients reported improvements in physical functioning, bodily pain, general health, vitality, social functioning and mental health following 8 weeks of rapid weight reduction. This suggests that not only is the rapid weight loss feasible and safe but improves overall well-being as well as cardiovascular and sexual function. We noted a relationship between improvement in cFT and improvement in physical functioning and bodily pain which is consistent with the known association between plasma androgens and physical functioning (Christos S et al 1995). In this group of men, obesity was associated with mild/moderate erectile dysfunction, and significant LUTS, which together with sexual

desire improved following rapid diet induced weight loss, but was not directly related to the amount of weight lost or changes in measured metabolic state.

Pericardial adipose tissue (PAT) covers 80% of the heart and constitutes 20% of its weight. PAT mass is related to the amount of abdominal fat and the risk of coronary atherosclerosis. Epicardial fat mass may be a sensitive indicator of cardiovascular risk. The third aim of this study was to (i) determine the relationship between obesity and PAT volume and (ii) effectively evaluate the impact of caloric restriction and associated weight reduction on epicardical fat volume via cardiac magnetic resonance imaging (CMR). This is the first study to show a reduction in PAT volume is associated with caloric restriction.

Having advanced our understanding in this field in these areas still a number of questions remain and will be the focus of future work in this area. Specific issues for future research will include mechanisms of benefit of weight loss in improving ventricular and vascular function. We have seen that the degree of weight loss was not a good predictor of improvement in these cardiovascular indices. The potential role of serological markers of inflammation in inducing the initial abnormalities needs to be elucidated. Therefore, reductions in such inflammatory markers with weight loss may explain some of the cardiovascular benefits. The levels of these inflammatory markers may be imperfectly related to weight. This future research will allow us a better understanding of the mechanisms of benefit of weight loss, and therefore potentially assist us in better managing individuals who are overweight or obese with or at risk of cardiovascular disease. Furthermore, the maintenance of these benefits of weight loss over longer terms (12months and beyond) requires analysis, and this is planned. Furthermore, the feasibility and potential benefit of

acute and long-term weight reduction in overweight or obese individuals with diabetes mellitus remains uncertain. Our preliminary work suggests similar benefits in diabetic and non-diabetic populations, although this is in small numbers. Future research efforts directed specifically at this population will be important. Finally, the confirmation that these improvements in cardiovascular surrogates of structure and function reflect a benefit in hard cardiovascular outcomes will clearly require longer-term study of larger numbers of individuals.

In summary, this shows that short-term (8 week) weight loss with a very low calorie diet is associated with improvements in ventricular and vascular function, and in sexual function and LUTS as well as a reduction in pericardial adipose tissue. Future research efforts as described above have arisen as a result of this work, and will further advance our understanding about the cardiovascular benefits of dietary weight loss.

**APPENDIX 1: SF36 GENERAL HEALTH AND WELL BEING**

These first questions ask for your views about your health, how you feel and how well you are able to do your usual activities. Please answer each question.

**1. In general would you say your health is:** ***(tick one box only)***

- ❑ 1 Excellent
- ❑ 2 Very good
- ❑ 3 Good
- ❑ 4 Fair
- ❑ 5 Poor

**2. Compared to one year ago, how would you rate your health in general now?** ***(tick one box only)***

- ❑ 1 Much better now than one year ago
- ❑ 2 Somewhat better now than one year ago
- ❑ 3 About the same as one year ago
- ❑ 4 Somewhat worse now than one year ago
- ❑ 5 Much worse now than one year ago

***The next questions relate to activities you might do during a typical day. Please tell us if your health now limits you a lot, limits you a little or does not limit you at all in these activities.***

**3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**5. Lifting or carrying groceries?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**6. Climbing several flights of stairs?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**7. Climbing one flight of stairs?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**8. Bending, kneeling or stooping?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**9. Walking more than one kilometre?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**10. Walking half a kilometre?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**11. Walking 100 metres?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

**12. Bathing or dressing yourself?** ***(tick one box only)***

- ❑ 1 Yes, limited a lot
- ❑ 2 Yes, limited a little
- ❑ 3 No, not limited at all

***The following four questions ask you about your physical health and your daily activities.***

During the last four weeks have you ....

**13. Had to cut down on the amount of time you spent on work or other activities as a result of your physical health?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**14. Accomplished less than you would like as a result of your physical health?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**15. Been limited in the kind of work or other activities as a result of your physical health?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**16. Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

***The following three questions ask you about your emotions and your daily activities.***

During the past four weeks have you ....

**17. Had to cut down on the amount of time you spent on work or other activities as a result of any emotional problems such as feeling depressed or anxious?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**18. Accomplished less than you would like as a result of any emotional problems?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**19. Had to not do work or other activities as carefully as usual as a result of any emotional problems?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**20. During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? Has it interfered:** ***(tick one box only)***

- ❑ 1 Not at all
- ❑ 2 Slightly
- ❑ 3 Moderately
- ❑ 4 Quite a bit
- ❑ 5 Extremely

**21. How much bodily pain have you had during the past four weeks?** ***(tick one box only)***

- ❑ 1 None
- ❑ 2 Very mild
- ❑ 3 Mild
- ❑ 4 Moderate
- ❑ 5 Severe
- ❑ 6 Very severe

**22. During the past four weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?** ***(tick one box only)***

- ❑ 1 Not at all
- ❑ 2 A little bit
- ❑ 3 Moderately
- ❑ 4 Quite a bit
- ❑ 5 Extremely

***These questions are about how you feel and how things have been with you during the <u>past four weeks</u>. For each question please give the one answer that comes closest to the way you have been feeling.***

How much during the <u>past four weeks</u>:

**23. Did you feel full of life?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**24. Have you been a very nervous person?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**25. Have you felt so down in the dumps that nothing could cheer you up?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**26. Have you felt calm and peaceful?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**27. Did you have a lot of energy?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**28. Have you felt down?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**29. Did you feel worn out?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**30. Have you been a happy person?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

**31. Did you feel tired?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time

6 None of the time

**32. During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc)?** ***(tick one box only)***

- ❑ 1 All the time
- ❑ 2 Most of the time
- ❑ 3 A good bit of the time
- ❑ 4 Some of the time
- ❑ 5 A little of the time
- ❑ 6 None of the time

***How true or false is each of the following statements for you?***

**33. "I seem to get sick a little easier than other people".** ***(tick one box only)***

- ❑ 1 Definitely true
- ❑ 2 Mostly true
- ❑ 3 Don't know
- ❑ 4 Mostly false
- ❑ 5 Definitely false

**34. "I am as healthy as anybody I know".** ***(tick one box only)***

- ❑ 1 Definitely true
- ❑ 2 Mostly true
- ❑ 3 Don't know
- ❑ 4 Mostly false
- ❑ 5 Definitely false

**35. "I expect my health to get worse".** ***(tick one box only)***

- ❑ 1 Definitely true
- ❑ 2 Mostly true
- ❑ 3 Don't know
- ❑ 4 Mostly false
- ❑ 5 Definitely false

**36. "My health is excellent".** ***(tick one box only)***

- ❑ 1 Definitely true
- ❑ 2 Mostly true
- ❑ 3 Don't know
- ❑ 4 Mostly false
- ❑ 5 Definitely false

**EXERCISE**

The next questions are about exercise you may do for sport, recreation or fitness.

**1. In the last two weeks, did you do any walking for sport, recreation or fitness?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**2. How many times did you do any walking for exercise in the last two weeks?**

- ❑ 1 Enter number of times

  _____
- ❑ 2 Don't know

**3. What was the total amount of time you spent walking in the last two weeks?**

- ❑ 1 Enter number of hours

  _____
- ❑ 2 Enter number of minutes

  _____

**4. In the last 2 weeks, (apart from walking) did you do any exercise which caused a moderate increase in your heart rate or breathing?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**5. How many times did you do any moderate exercise in the last two weeks?**

- ❑ 1 Enter number of times

  _____
- ❑ 2 Don't know

**6. What was the total amount of time you spent doing moderate exercise in the last two weeks?**

- ❑ 1 Enter number of hours

  _____
- ❑ 2 Enter number of minutes

  _____

**7. In the last 2 weeks, did you do any other exercise which caused a large increase in your heart rate or breathing, that is, vigorous exercise?** ***(tick one box only)***

- ❑ 1 Yes
- ❑ 2 No

**8. How many times did you do any vigorous exercise in the last two weeks?**

- ❑ 1 Enter number of times

  _____
- ❑ 2 Don't know

**9. What was the total amount of time you spent doing vigorous exercise in the last two weeks?**

- ❑ 1 Enter number of hours

  _____
- ❑ 2 Enter number of minutes

  _____

**FAMILY HISTORY**

**10. Do, or did, any of your relatives have diabetes? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather
- ❑ 7 Other *(please specify)*

  _____
- ❑ 8 No
- ❑ 9 Don't know

**11. Do, or did, any of your relatives have heart disease, for example, heart attack or heart failure? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather
- ❑ 7 Other *(please specify)*

  _____
- ❑ 8 No
- ❑ 9 Don't know

**12. Have any of your relatives ever had a stroke? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather
- ❑ 7 Other *(please specify)*

  _____
- ❑ 8 No
- ❑ 9 Don't know

**13. Do, or did, any of your relatives have high blood pressure? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather
- ❑ 7 Other *(please specify)*

  _____
- ❑ 8 No
- ❑ 9 Don't know

**14. Are or have any of your relatives ever been obese? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather
- ❑ 7 Other *(please specify)*

  _____
- ❑ 8 No
- ❑ 9 Don't know

**15. Do, or did, any of your relatives have osteoporosis (brittle bones)? (Blood/first degree relations only)** ***(tick all that apply)***

- ❑ 1 Mother
- ❑ 2 Father
- ❑ 3 Sister
- ❑ 4 Brother
- ❑ 5 Grandmother
- ❑ 6 Grandfather

❑ 7 Other *(please specify)*

_____

❑ 8 No
❑ 9 Don't know

**16. Do, or did, any of your male relatives have prostate cancer? (Blood/first degree relations only) *(tick all that apply)***

❑ 1 Father
❑ 2 Brother
❑ 3 Grandfather
❑ 4 Other *(please specify)*

_____

❑ 5 No
❑ 6 Don't know

**SMOKING**

**17. Do you currently smoke? *(tick one box only)***

❑ 1 Yes
❑ 2 No *(If no…go to* ↓Medication use*)*
❑ 3 Occasionally

**18. How many cigarettes do you usually smoke a day?**

❑ 1 Enter number of cigarettes
❑ 2 Less than one
❑ 3 Only smoke cigars or pipes

**19. Have you ever smoked regularly (that is, at least once a day)? *(tick one box only)***

❑ 1 Yes
❑ 2 No

**20. How many cigarettes did you usually smoke a day?**

❑ 1 Enter number of cigarettes

_____

❑ 2 Less than one
❑ 3 Only smoke cigars or pipes

**21. How old were you when you last gave up smoking?**

❑ 1 Enter age _____
❑ 2 Can't remember

**22. At what age did you first start smoking daily?**

❑ 1 Enter age _____
❑ 2 Can't remember

**MEDICATION USE**

**23. Please list ALL medications you are currently using and the reason for using them. Please include all prescription medicines, medicine you get from the chemist and herbal remedies or supplements that you get from health food shops or supermarkets. *(Please check your medicine cabinet to make sure you don't miss any) - attach an additional page if necessary.***

| **Medication** | **Reason for taking** |
|---|---|
| _____ | _____ |
| _____ | _____ |

❑ No medications

**HEALTH CONDITIONS**

**24. Have you ever been told by a doctor that you have any of the following conditions? *(please tick all that apply)*.**

- ❑ 1 Angina
- ❑ 2 Anxiety
- ❑ 3 Asthma
- ❑ 4 Depression
- ❑ 5 Diabetes (high blood sugar)
- ❑ 6 Enlarged Prostate
- ❑ 7 High Blood Cholesterol
- ❑ 8 High Blood Pressure
- ❑ 9 Insomnia (trouble sleeping)
- ❑ 10 Osteoarthritis
- ❑ 11 Rheumatoid Arthritis
- ❑ 12 Thyroid problems
- ❑ 13 Prostate Cancer
- ❑ 14 Other cancers (please specify)

- ❑ 15 Any other health conditions (please specify)

- ❑ 16 None of the above conditions

**SURGERY**

**25. Have you had any of the following surgical procedures? *(please tick all that apply)***

- ❑ 1 Prostate removal
- ❑ 2 Trans-urethral resection of prostate (TURP)
- ❑ 3 Vasectomy
- ❑ 4 Bilateral orchidectomy (both testes removed)
- ❑ 5 Unilateral orchidectomy (one testis removed)
- ❑ 6 Penile surgery (excluding circumcision)
- ❑ 7 Bladder surgery
- ❑ 8 Other pelvic surgery (please specify)

- ❑ 9 None of the above surgery

**BONE FRACTURES**

**26. Please list ALL broken bones that you have had, the year in which they occurred and the reason for the break.**

*For example:*

| *Bone* | *Year* | *Reason for break* |
|---|---|---|
| *Hip* | *2001* | *fall* |

| Bone | Year | Reason for break |
|---|---|---|
| | | |

**DEMOGRAPHICS**

**27. What is your country of birth? *(tick one box only)***

- ❑ 1 Australia
- ❑ 2 Austria
- ❑ 3 Bosnia-Herzegovina
- ❑ 4 Canada
- ❑ 5 China
- ❑ 6 Croatia
- ❑ 7 France
- ❑ 8 Germany
- ❑ 9 Greece
- ❑ 10 Holland / Netherlands
- ❑ 11 Hong Kong
- ❑ 12 Iran
- ❑ 13 Italy

- ❑ 14 Japan
- ❑ 15 Malaysia
- ❑ 16 New Zealand
- ❑ 17 Philippines
- ❑ 18 Poland
- ❑ 19 Slovenia
- ❑ 20 Spain
- ❑ 21 U.K. and Ireland
- ❑ 22 USA
- ❑ 23 Vietnam
- ❑ 24 Former Yugoslav Republic of Macedonia
- ❑ 25 Former Yugoslav Republics of Serbia & Montenegro
- ❑ 26 Other *(please specify)* _____

**28. What year did you arrive in Australia?**

- ❑ 1 Enter year _____
- ❑ 2 Don't know

**29. Are you of Aboriginal or Torres Strait Islander origin? (For persons of both Aboriginal and Torres Strait Islander origin, tick both 'Yes' boxes)**

- ❑ 1 No
- ❑ 2 Yes, Aboriginal
- ❑ 3 Yes, Torres Strait Islander

**30. What is your marital status? *(tick one box only)***

- ❑ 1 Married or living with a partner
- ❑ 2 Separated / Divorced
- ❑ 3 Widowed
- ❑ 4 Never married

**31. What is your work status? *(tick one box only)***

- ❑ 1 Full time employed
- ❑ 2 Part time / casual employment
- ❑ 3 Unemployed
- ❑ 4 Home duties
- ❑ 5 Retired
- ❑ 6 Student
- ❑ 7 Other *(please specify)*_____

**32. What is your date of birth?**

What is your postcode?

**33. Are you currently a shift-worker? *(tick one box only)***

- ❑ 1 Yes

If Yes, please indicate for how many years:_____

- ❑ 2 No

**34. Have you ever been a shift-worker? *(tick one box only)***

- ❑ 1 Yes

If Yes, please indicate for how many years:_____

- ❑ 2 No

**SLEEP**
The next questions are common symptoms in people with Sleep Apnoea.

***1.Do you snore?***
- ❑ a. Yes
- ❑ b. No
- ❑ c. Don't know

**If you snore:**
***2.Your snoring is:***
- ❑ a. Slightly louder than breathing
- ❑ b. As loud as talking
- ❑ c. Louder than talking
- ❑ d. Very loud – can be heard in adjacent rooms

**3.How often do you snore?**
- ❑ a. Nearly every day
- ❑ b. 3-4 times a week
- ❑ c. 1-2 times a weeks
- ❑ d. 1-2 times a month
- ❑ e. Never or nearly never

**4. Has your snoring ever bothered other people?**
- ❑ a. Yes
- ❑ b. No
- ❑ c. Don't know

**5. Has anyone noticed that you quit breathing during your sleep?**
- ❑ a. Nearly every day
- ❑ b. 3-4 times a week
- ❑ c. 1-2 times a weeks
- ❑ d. 1-2 times a month
- ❑ e. Never or nearly never

**6. How often do you feel tired or fatigued after your sleep?**
- ❑ a. Nearly every day
- ❑ b. 3-4 times a week
- ❑ c. 1-2 times a weeks
- ❑ d. 1-2 times a month
- ❑ e. Never or nearly never

**7. During your waking time, do you feel tired, fatigued or not up to par?**
- ❑ a. Nearly every day
- ❑ b. 3-4 times a week
- ❑ c. 1-2 times a weeks
- ❑ d. 1-2 times a month
- ❑ e. Never or nearly never

**8. Have you ever nodded off or fallen asleep while driving a vehicle?**
- ❑ a. Yes
- ❑ b. No

***If Yes:***
**9. How often does this occur?**
- ❑ a. Nearly every day
- ❑ b. 3-4 times a week
- ❑ c. 1-2 times a weeks
- ❑ d. 1-2 times a month
- ❑ e. Never or nearly never

**10. Do you have high blood pressure?**
- ❑ a. Yes
- ❑ b. No
- ❑ c. Don't know

**PROSTATE IPSS**

**1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you have finished urinating?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**3. Over the past month, how often have you found you stopped and started again several times when you urinated?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**4. Over the past month, how often have you found it difficult to postpone urination?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**5. Over the past month, how often have you had a weak urinary stream?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**6. Over the past month, how often have you had to push or strain to begin urination?**

- ❑ 0 Not at all
- ❑ 1 Less than 1 time in 5
- ❑ 2 Less than half the time
- ❑ 3 About half the time
- ❑ 4 More than half the time
- ❑ 5 Almost always

**7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?**

- ❑ 0 None
- ❑ 1 1 time
- ❑ 2 2 times
- ❑ 3 3 times
- ❑ 4 4 times
- ❑ 5 5 times

**8. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about it?**

- ❑ 0 Delighted
- ❑ 1 Pleased
- ❑ 2 Mostly satisfied
- ❑ 3 Mixed
- ❑ 4 Mostly dissatisfied
- ❑ 5 Unhappy
- ❑ 6 Terrible

**SEXUAL HEALTH AND WELL BEING**

The first 14 questions ask about your level of sexual desire. By desire, we mean INTEREST IN or WISH FOR sexual activity. For each item, please tick the box that best shows your thoughts and feelings. Please answer each question and be as honest as possible. Your answers will be private.

**SDI**

**1. During the past month, how often would you have liked to engage in sexual activity with a partner (for example, touching each other's genitals, giving or receiving oral stimulation, intercourse etc.)?**

- ❑ 0 Not at all
- ❑ 1 Once a month
- ❑ 2 Once every 2 weeks
- ❑ 3 Once a week
- ❑ 4 Twice a week
- ❑ 5 3 to 4 times a week
- ❑ 6 Once a day
- ❑ 7 More than once a day

**2. During the past month, how often have you had sexual thoughts involving a partner?**

- ❑ 0 Not at all
- ❑ 1 Once or twice a month
- ❑ 2 Once a week
- ❑ 3 Twice a week
- ❑ 4 3 to 4 times a week
- ❑ 5 Once a day
- ❑ 6 A couple of times a day
- ❑ 7 Many times a day

***The next 7 questions ask you to indicate your level of sexual desire on a scale of 0 to 8, with 0 being "no desire" and 8 being "strong desire". Please** circle **the number that best corresponds to your level of desire.***

**3. When you have sexual thoughts, how strong is your desire to engage in sexual behaviour with a partner?**

(No desire) 0 1 2 3 4 5 6 7 8 (Strong desire)

**4. When you first see an attractive person, how strong is your sexual desire?**

(No desire) 0 1 2 3 4 5 6 7 8 (Strong desire)

**5. When you spend time with an attractive person (for example at work or school), how strong is your sexual desire?**

(No desire) 0 1 2 3 4 5 6 7 8 (Strong desire)

**6. When you are in romantic situations (such as candle lit dinner, a walk on the beach, etc.) how strong is your sexual desire?**

(No desire) 0 1 2 3 4 5 6 7 8 (Strong desire)

**7. How strong is your desire to engage in sexual activity with a partner?**

(No desire) 0 1 2 3 4 5 6 7 8 (Strong desire)

**8. How important is it for you to fulfil your sexual desire through activity with a partner?**

0 1 2 3 4 5 6 7 8

(Not at all important) (Extremely important)

**9. Compared to other people of your age and sex, how would you rate your desire to behave sexually with a partner?**

0 1 2 3 4 5 6 7 8

(Much less desire) (Much more desire)

The next 4 questions ask about your level of desire to behave sexually by yourself.

**10. During the last month, how often would you have liked to behave sexually by yourself (for example, masturbating, touching your genitals etc.)?**

- ❑ 0 Not at all
- ❑ 1 Once a month
- ❑ 2 Once every 2 weeks
- ❑ 3 Once a week
- ❑ 4 Twice a week
- ❑ 5 3 to 4 times a week
- ❑ 6 Once a day
- ❑ 7 More than once a day

**11. How strong is your desire to engage in sexual behaviour by yourself?**

0 1 2 3 4 5 6 7 8

(No desire) (Strong desire)

**12. How important is it for you to fulfil your desires to behave sexually by yourself?**

0 1 2 3 4 5 6 7 8

(Not at all important) (Extremely important)

**13. Compared to other people of your age and sex, how would you rate your desire to behave sexually by yourself?**

0 1 2 3 4 5 6 7 8

(Much less desire) (Much more desire)

**14. How long could you go comfortably without having sexual activity of some kind?**

- ❑ 0 Forever
- ❑ 1 A year or two
- ❑ 2 Several months
- ❑ 3 A month
- ❑ 4 A few weeks
- ❑ 5 A week
- ❑ 6 A few days
- ❑ 7 One day
- ❑ 8 Less than one day

The following questions ask about your ability to get and maintain erections.

**Impotence means being unable to get and keep an erection that is rigid enough for satisfactory sexual activity. How would you describe yourself? *(tick one box only)***

- ❑ 0 Always able to get an keep an erection good enough for sexual intercourse
- ❑ 1 Usually able to get and keep an erection good enough for sexual intercourse
- ❑ 2 Sometimes able to get and keep an erection good enough for sexual intercourse
- ❑ 3 Never able to get and keep an erection good enough for sexual intercourse

***In answering the remaining questions, the following definitions apply:***

***Sexual Intercourse** is defined as vaginal penetration (entry) of the partner

****Sexual Activity** includes intercourse, caressing, foreplay and masturbation

*****Ejaculate** is the ejection of semen from the penis (or the sensation of this)

******Sexual Stimulation** includes situations such as love-play with a partner, looking at erotic pictures, etc.

**IIEF**

**1. Over the past 4 weeks, how often were you able to get an erection during sexual activity**?**

- ❑ 0 No sexual activity
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**2. Over the past 4 weeks, when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?**

- ❑ 0 No sexual stimulation
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

The next 3 questions ask about the erections you may have had during sexual intercourse*

**3. Over the past 4 weeks, when you attempted sexual intercourse*, how often were you able to penetrate (enter) your partner?**

- ❑ 0 Did not attempt intercourse
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**4. Over the past 4 weeks, during sexual intercourse*, how often were you able to maintain your erection after you had penetrated (entered) your partner?**

- ❑ 0 Did not attempt intercourse
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**5. Over the past 4 weeks, during sexual intercourse*, how difficult was it to maintain your erection to completion of intercourse?**

- ❑ 0 Did not attempt intercourse
- ❑ 5 Extremely difficult
- ❑ 4 Very difficult
- ❑ 3 Difficult
- ❑ 2 Slightly difficult
- ❑ 1 Not difficult

**6. Over the past 4 weeks, how many times have you attempted sexual intercourse*?**

- ❑ 0 No attempts
- ❑ 1 1-2 attempts
- ❑ 2 3-4 attempts
- ❑ 3 5-6 attempts
- ❑ 4 7-10 attempts
- ❑ 5 11+ attempts

**7. Over the past 4 weeks, when you attempted sexual intercourse*, how often was it satisfactory for you?**

- ❑ 0 Did not attempt intercourse
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**8. Over the past 4 weeks, how much have you enjoyed sexual intercourse*?**

- ❑ 0 No intercourse
- ❑ 5 Very highly enjoyable
- ❑ 4 Highly enjoyable
- ❑ 3 Fairly enjoyable
- ❑ 2 Not very enjoyable
- ❑ 1 Not enjoyable

**9. Over the past 4 weeks, when you had sexual stimulation**** or intercourse*, how often did you ejaculate?**

- ❑ 0 No intercourse
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**10. Over the past 4 weeks, when you had sexual stimulation**** or intercourse*how often did you have the feeling of orgasm or climax?**

- ❑ 0 No intercourse
- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

***The next 2 questions ask about sexual desire. Sexual desire is defined as a feeling that may include wanting to have a sexual experience (eg, masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.***

**11. Over the past 4 weeks, how often have you felt sexual desire?**

- ❑ 5 Almost always or always
- ❑ 4 Most times (much more than half the time)
- ❑ 3 Sometimes (about half the time)
- ❑ 2 A few times (much less than half the time)
- ❑ 1 Almost never or never

**12. Over the past 4 weeks, how would you rate your level of sexual desire?**

- ❑ 5 Very high
- ❑ 4 High
- ❑ 3 Moderate
- ❑ 2 Low
- ❑ 1 Very low or none at all

**13. Over the past 4 weeks, how satisfied have you been with your overall sex life?**

- ❑ 5 Very satisfied
- ❑ 4 Moderately satisfied
- ❑ 3 About equally satisfied and dissatisfied
- ❑ 2 Moderately dissatisfied
- ❑ 1 Very dissatisfied

**14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?**

- ❑ 5 Very satisfied
- ❑ 4 Moderately satisfied
- ❑ 3 About equally satisfied and dissatisfied
- ❑ 2 Moderately dissatisfied
- ❑ 1 Very dissatisfied

**15. Over the past 4 weeks, how would you rate your confidence that you could get and keep an erection?**

- ❑ 5 Very high
- ❑ 4 High
- ❑ 3 Moderate
- ❑ 2 Low
- ❑ 1 Very Low

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