The Effect of Diet and Exercise Interventions for the Treatment of Male Obesity Induced Sub Fertility

Nicole Olivia McPherson

B.Hlth.S.(Hons.)

Discipline of Obstetrics and Gynaecology

School of Paediatrics and Reproductive Health

Faculty of Health Science

The University of Adelaide

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Nicole McPherson

Wednesday, 10th September 2014

Abstract

Male overweight/obesity effects 70% of the adult Australian population with this rate 10% higher (80%) in men attending a South Australian fertility clinic, suggesting a link between male overweight/obesity and sub fertility. Male obesity alters the molecular structure of sperm, increasing sperm DNA damage and reactive oxygen species (ROS) and altering mitochondrial function. This perturbed sperm function leads to altered embryo quality (reduced blastocyst development, blastocyst cell numbers and blastocyst mitochondrial function) which subsequently reduces implantation and live birth rates. Rodent models of male obesity have further implicated male obesity in the development of adult chronic diseases, increasing the susceptibility of obesity, diabetes and sub fertility in offspring across two generations.

Limited published research has assessed the reversibility of male obesity induced sub fertility. Due to limitations inherited in human studies, the aim of this thesis was to establish if obesity induced sub fertility could be reversed utilising a rodent model of male obesity with short term diet and/or exercise interventions for proof of concept. Male mice were fed a high fat diet (HFD) containing 21% fat or a control diet (CD) containing 6% fat for a period of 8-10 weeks to increase adiposity, following HFD exposure mice were allocated to one of four treatment groups 1) diet intervention (HC, change to CD), 2) exercise intervention (HE, continuation of a HFD with 3 x 30 min swimming sessions a week), 3) combined diet/exercise intervention (HCE, change to a CD with swimming exercise) or 4) continuation of a HFD (HH) for a further 8-10 weeks. Mice allocated to the CD continued on the CD (CC) for intervention period.

Diet intervention with (HCE) or without (HC) exercise reduced bodyweight, adiposity, and serum cholesterol while exercise intervention alone (HE) maintained their original level of adiposity. All interventions had improvements to serum glucose and leptin regulation while exercise subsequently improved serum free fatty acids and C - reactive protein. All interventions restored sperm function (motility, morphology, mitochondrial function, ROS and DNA damage levels). Males were subsequently mated with super ovulated normal weight females for assessment of embryo quality. All interventions restored blastocyst cell numbers and day 18 fetal weights while, exercise with (HCE) or without (HE) as CD further restored embryo development. As early embryo and fetal health are predictors of subsequent offspring health, males were also mated with naturally cycling normal weight females to produce offspring. Diet intervention alone (HC) showed the biggest restorations to male offspring sperm function (motility, sperm binding, capacitation and mitochondrial function). In contrast, exercise intervention alone (HE) showed the biggest restoration to female offspring metabolic health (glucose and insulin sensitivity and adipose accumulation) while the remaining interventions (HC and HCE) had minimal impact. The improvements to female offspring metabolic health from exercise interventions in their fathers may be related to their partial restoration of sperm X-linked microRNA abundance (i.e. mir-503 and mir-465b-5p), with these microRNAs specifically targeting pathways important for early embryo development including cell cycle control and apoptosis.

Together these studies provided some of the first evidence for the reversibility of obesity related fertility issues in males, highlighting that it may be more about restoring systematic metabolic health rather than a reduction in adiposity, with the deciphering an epigenetic mechanism in sperm for transmission of effects to the embryo and offspring phenotypes. These studies will undoubtedly stimulate further research into other related molecular mechanisms and the independent associations between obesity related metabolic changes and their relationships with male fertility.

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Publications arising from this Thesis

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‘**N. O. Palmer**, H.W. Bakos, J.A. Owens, B.P. Setchell and M.Lane (2012) ‘Diet and exercise in an obese mouse fed a high fat diet improves metabolic health and reverses perturbed sperm function’, **American Journal of Physiology Endocrinology and Metabolism**, Apr 1; 302 (7): E768-80

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Abstracts arising from this Thesis

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Oozoa Student Award Finalist, SRB Student Travel Grant, Robinson Institute Travel Grant

N. O. Palmer, H. W. Bakos, J. A. Owens, B. P. Setchell and M. Lane (2012) 'Exercise and to a lesser extent a low fat diet in obese fathers restores metabolic health of subsequent offspring', Adelaide Post Graduate Research day, Wine Centre Adelaide

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Prize Poster - Student

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