Comparing Effects of a Low-energy Diet and a High-protein Low-fat Diet on Sexual and Endothelial Function, Urinary Tract Symptoms, and Inflammation in Obese Diabetic Men

Joan Khoo, MRCP,* Cynthia Piantadosi, PhD,† Rae Duncan, PhD,‡ Stephen G. Worthley, PhD,‡ Alicia Jenkins, PhD,§ Manny Noakes, PhD,¶ Matthew I. Worthley, PhD,‡ Kylie Lange, BSc,† and Gary A. Wittert, MD†

*Department of Endocrinology, Changi General Hospital, Singapore, Singapore; †Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia; ‡Cardiovascular Research Centre, School of Medicine, University of Adelaide, Adelaide, SA, Australia; §School of Medicine, University of Melbourne, Melbourne, Vic., Australia; ¶Commonwealth Scientific Industrial and Research Organisation, Adelaide, SA, Australia

DOI: 10.1111/j.1743-6109.2011.02417.x

ABSTRACT

Introduction. Abdominal obesity and type 2 diabetes mellitus are associated with sexual and endothelial dysfunction, lower urinary tract symptoms (LUTS), and chronic systemic inflammation.

Aim. To determine the effects of diet-induced weight loss and maintenance on sexual and endothelial function, LUTS, and inflammatory markers in obese diabetic men.

Main Outcome Measures. Weight, waist circumference (WC), International Index of Erectile Function (IIEF-5) score, Sexual Desire Inventory (SDI) score, International Prostate Symptom Scale (IPSS) score, plasma fasting glucose and lipids, testosterone, sex hormone binding globulin (SHBG), inflammatory markers (high-sensitivity C-reactive protein [CRP] and interleukin-6 [IL-6]) and soluble E-selectin, and brachial artery flow-mediated dilatation (FMD) were measured at baseline, 8 weeks, and 52 weeks.

Methods. Over 8 weeks, 31 abdominally obese (body mass index $\geq$ 30 kg/m^2, WC $\geq$ 102 cm), type 2 diabetic men (mean age 59.7 years) received either a meal replacement-based low-calorie diet (LCD) ~1,000 kcal/day (N = 19) or low-fat, high-protein, reduced-carbohydrate (HP) diet (N = 12) prescribed to decrease intake by ~600 kcal/day. Subjects continued on, or were switched to, the HP diet for another 44 weeks.

Results. At 8 weeks, weight and WC decreased by ~10% and ~5% with the LCD and HP diet, respectively. Both diets significantly improved plasma glucose, low-density lipoprotein (LDL), SHBG, IIEF-5, SDI and IPSS scores, and endothelial function (increased FMD, reduced soluble E-selectin). Erectile function, sexual desire, and urinary symptoms improved by a similar degree with both diets. CRP and IL-6 decreased with the HP diet. At 52 weeks, reductions in weight, WC, and CRP were maintained. IIEF-5, SDI, and IPSS scores improved further.

Conclusions. Diet-induced weight loss induces rapid improvement of sexual, urinary, and endothelial function in obese diabetic men. A high-protein, carbohydrate-reduced, low-fat diet also reduces systemic inflammation and sustains these beneficial effects to 1 year. **Khoo J, Piantadosi C, Duncan R, Worthley SG, Jenkins A, Noakes M, Worthley MI, Lange K, and Wittert GA. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms and inflammation in obese diabetic men. J Sex Med **;**:**–**.**

Key Words. Erectile Dysfunction; Urinary Tract Symptoms; Obesity; Diabetes Mellitus; Sexual Function; Endothelial Function

Introduction

Abdominal obesity and type 2 diabetes mellitus increase the risk of erectile dysfunction (ED) [1] and lower urinary tract symptoms (LUTS) [2], which are associated with each other [3,4] and also with systemic inflammation [5,6] and endothelial dysfunction [7–10]. Obesity and insulin resistance are associated with elevated plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) [5,6,10] and endothelial dysfunction as evidenced by reduced flow-mediated arterial dilatation [8,10] and increased circulating soluble cellular adhesion molecules such as soluble E-selectin [11]. Hence, interventions which reduce inflammation and/or improve endothelial function may ameliorate ED and LUTS [10].

Rapid diet-induced weight loss has been shown to improve ED and LUTS. A modified low-calorie diet (LCD) using nutritionally complete liquid meal replacements (~900 kcal/day) induced ~10% weight loss with improvement of erectile function and LUTS after 8 weeks in obese nondiabetic and diabetic men [12]. Significant improvements in endothelial function [13,14] and inflammation [5] occurred mainly in studies reporting at least 10% reduction induced by short-term use of LCD [5,13], although a few studies found that low-fat diet significantly improved brachial artery flow-mediated dilatation (FMD) despite weight loss of only ~5% [15], and reduced CRP with 2–7% weight loss [5]. The importance of macronutrient composition, and the magnitude of weight loss required, to achieve significant benefits in endothelial function and systemic inflammation, and their relation to improvement of sexual function and LUTS in obese men, thus remains to be established. Reduced weight and CRP were associated with improved erectile function in obese nondiabetic men after 2 years on a low-fat Mediterranean diet [16]. In obese type 2 diabetic subjects, a high-protein diet was as effective as a conventional diet in reducing weight and CRP, with similar long-term compliance [17]. Our study therefore aimed to compare, in obese men with type 2 diabetes, the effects of rapid weight loss induced by either LCD or a low-fat diet with an increased ratio of protein to carbohydrate on systemic inflammation, endothelial, erectile and urinary function, and the sustainability of changes in these parameters on the latter diet.

Methods

Thirty-one abdominally obese (body mass index >30 kg/m^2, waist circumference [WC] ≥ 102 cm) Caucasian men with type 2 diabetes mellitus, recruited by advertisement from a community in Adelaide, South Australia, were enrolled into a parallel-design weight loss trial between June 2007 and May 2008. The sample size was calculated to detect an improvement of 20% in erectile function (five-item version of the International Index of Erectile Function [IIEF-5]) score after weight loss as seen in the study of Esposito et al. [16], and a difference of 5 points between diet groups, with 80% power at 5% significance. Subjects were randomly assigned to one of two different diets: modified LCD (N = 19) or a high-protein low-fat diet (HP diet) (N = 12) based on the Commonwealth Scientific Industrial and Research Organisation (CSIRO) Total Wellbeing Diet developed by the Commonwealth Scientific Industrial and Research Organisation of Australia [17,18].

All subjects had glycated haemoglobin (GHb) ≤7% on diet control (N = 16) or oral hypoglycemic medication, i.e., metformin with (N = 1) or without (N = 14) sulfonylurea. Doses of medications were stable for 3 months prior to the study. None had a history of cardiovascular or peripheral vascular disease. Exclusion criteria included smoking, previous or current treatment for sexual problems or LUTS, glomerular filtration rate <60 mL/min, and alcohol intake exceeding 500 g/week in the previous 12 months. The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital. Informed consent was obtained from all subjects.

Subjects in the LCD group consumed two sachets daily (one at breakfast and lunch or dinner) of a liquid meal replacement (Kicstart, Pharmacy Health Solutions, Sydney, Australia), providing a maximum of 450 kcal of energy, 0.8 g/kg ideal body weight of protein, and the recommended daily allowances of minerals, vitamins, and omega-3 and omega-6 essential fatty acids, plus one other small meal, for a total of ~900 kcal/day. The HP diet was prescribed to reduce daily energy intake by ~600 kcal, including 300 g of lean meat/poultry/fish, and three servings/day of cereals/bread and low-fat dairy foods and two fruit and five vegetable serves per day [18]. Participants were permitted to consume water, tea, coffee, and diet soft drinks, and were instructed to consume at least 2 L of fluids/day. All subjects received a written plan with detailed diet information, menu

plan, recipes, and advice on cooking and eating out. Diet compliance was monitored at 2- to 4-weekly intervals using food diaries. All subjects maintained their usual daily activity. After 8 weeks, participants were switched to or continued on the HP diet for another 44 weeks.

Main Outcome Measures

Height (wall-mounted stadiometer) and weight were measured unshod. We used the mean of three measurements of WC at mid-axillary level, midway between the lower costal border and the top of the iliac crest. Plasma total cholesterol, triglyceride, high-density lipoprotein (HDL), LDL, glucose, insulin, total testosterone (TT), and sex hormone binding globulin (SHBG) were measured, and Quantitative Insulin Sensitivity Check Index (QUICKI) and free testosterone (FT) were calculated, as previously described [12]. High-sensitivity CRP was measured by a nephelometry assay (Siemens Healthcare Diagnostics Inc, Newark, DE, USA) with lower limit of detection (LLD) 0.1 mg/L, intra-assay coefficient of variation (CV_{intra}) 1.3%, and inter-assay coefficient of variation (CV_{inter}) 3.3%. ELISA kits (R & D Systems, Minneapolis, MN, USA) were used to measure IL-6 (LLD 0.039 pg/mL, CV_{intra} 5.5%, CV_{inter} 8.7%) and soluble E-selectin (sE-selectin) (LLD 0.09 ng/dL, CV_{intra} 3.8%, CV_{inter} 10.3%). Brachial artery FMD was measured using magnetic resonance imaging (MRI) as previously described [18]. The interstudy coefficient of variation (CV) was 0.3 for FMD, and CV was 0.1 for brachial artery area, similar to ultrasound measurement, with good agreement between MRI and ultrasound for measures of endothelial function and arterial structure in the same subjects [19]. The abridged IIEF-5, Sexual Desire Inventory (SDI), and International Prostate Symptom Scale (IPSS) were used to assess erectile function, interest in sexual activity, and severity of LUTS, respectively, as previously described [12]. Weight and WC were measured at baseline, 2-weekly for 8 weeks, and 4-weekly thereafter. Plasma biochemistry, FMD, and IIEF-5, SDI, and IPSS scores were measured before starting diet intervention and at 8 and 52 weeks after.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Baseline measures were compared with independent samples *t*-tests. Changes in weight, WC, measures of erectile function, sexual desire and LUTS, sex hormones, CRP, IL-6, sE-selectin, FMD, and metabolic parameters after 8 weeks and 52 weeks of dietary intervention were investigated with maximum likelihood repeated measures mixed models. Use of mixed models included all three time points in the same model, allowing for simultaneous assessment of differences between multiple pairs of time points and accounting for dropout of subjects after 8 weeks. Interactions between initial diet and time were included to test for differential effects of the weight loss and weight maintenance phases on the outcome parameters across groups. Post hoc pairwise tests with Bonferroni adjustment of 8 weeks and 52 weeks against baseline were performed following a significant interaction between the initial diet and effect of time (within each group) or a significant time effect (pooled across groups). When interactions were nonsignificant, the simpler model excluding the interactions was reported. Relationships between changes in these parameters were investigated with bivariate correlations. A P value < 0.05 was considered significant.

Results

Subjects in the LCD and HP groups did not differ significantly in mean age, weight, WC, scores of sexual function and LUTS, insulin sensitivity, and TT, SHBG, and lipids (Table 1). The HP group had lower mean insulin levels and FMD and higher CRP, IL-6, and sE-selectin. No subjects reported hypoglycemia or required changes in oral hypoglycemic medications during the study. Four subjects in the LCD group experienced constipation in the first week which was resolved with Metamucil. All subjects completed the initial 8-week weight-loss phase. Ten subjects in the LCD group and five subjects in the HP group declined further follow-up.

At 8 weeks (Table 2), mean weight loss and decrease in WC were greater in the LCD group (~10%) than in the HP group (~5%). Plasma glucose and LDL decreased significantly in both groups. QUICKI improved in the LCD group. At 52 weeks, weight loss was maintained in both groups (Table 2). WC decreased further in the HP group, and was maintained in the LCD group.

Androgen Levels, Erectile Function, Sexual Desire, and LUTS

At 8 weeks, there was a significant increase in SHBG in both groups (Table 2), main effect of time $F(2, 21.8) = 5.38$, $P = 0.01$. Improvements in SHBG were comparable in both diet groups. The

Table 1 Baseline measures of anthropometry, sex hormones, sexual function, LUTS, inflammatory markers, endothelial function, and metabolic parameters, in subjects on LCD and the HP diet

	LCD (N = 19)	HP (N = 12)
Age (years)	58.1 ± 11.4	62.3 ± 5.9
Duration of diabetes	4.0 ± 1.0	5.3 ± 1.3
Body mass index (kg/m^2)	35.1 ± 4.3	35.6 ± 4.8
Weight (kg)	112.7 ± 19.2	109.6 ± 14.9
Waist circumference (cm)	124.6 ± 12.7	123.1 ± 10.2
Plasma TT (nmol/L)	11.70 ± 3.59	13.88 ± 3.26
Plasma SHBG (nmol/L)	22.47 ± 9.34	30.42 ± 13.88
Calculated FT (pmol/L)	285 ± 87	296 ± 47
IIEF-5 score	7.95 ± 6.23	11.75 ± 7.74
SDI score	43.68 ± 23.58	51.92 ± 21.68
IPSS score	6.26 ± 5.49	9.00 ± 6.19
Plasma CRP (mg/L)	3.82 ± 3.21*	8.32 ± 5.66*
Plasma IL-6 (pg/ml)	1.59 ± 0.55*	3.28 ± 0.92*
Plasma sE-selectin (ng/dl)	53.6 ± 11.9*	72.1 ± 4.5*
FMD (%)	5.64 ± 1.71*	3.27 ± 1.88*
Plasma glucose (mmol/L)	7.42 ± 2.40	8.65 ± 2.85
Plasma insulin (μU/mL)	21.38 ± 9.59*	14.28 ± 5.53*
Insulin sensitivity (QUICKI)	0.30 ± 0.03	0.31 ± 0.02
Plasma TG (mmol/L)	2.09 ± 0.92	2.18 ± 0.95
Plasma HDL (mmol/L)	1.17 ± 0.24	1.20 ± 0.15
Plasma LDL (mmol/L)	2.65 ± 0.96	2.50 ± 0.86

All values are given as mean ± SD.
*Significant baseline difference between the LCD and HP groups. The level of significance is set at $P < 0.05$.
LUTS = lower urinary tract symptoms; LCD = low-calorie diet; HP = high-protein low-fat; SD = standard deviation; TT = total testosterone; SHBG = sex hormone binding globulin; IIEF-5 = five-item version of the International Index of Erectile Function; SDI = Sexual Desire Inventory; IPSS = International Prostate Symptom Scale; CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; sE-selectin = soluble E-selectin; FMD = brachial artery flow-mediated dilatation; TG = triglyceride.

magnitude of weight reduction was significantly correlated with the increase in SHBG ($r = -0.63$, $P < 0.01$). Changes in TT and FT were not statistically significant in either group.

At 8 weeks, there was a significant increase in the mean IIEF-5 score in both LCD and HP groups, with no difference between the groups (Table 2). Of the 17 men (54.8%) with severe ED (IIEF-5 score <8) at baseline, seven demonstrated improvement of IIEF-5 scores (Figure 1). At 52 weeks, further significant improvements in IIEF-5 score were seen in both groups (Table 2), main effect of time $F(2, 28.1) = 41.55$, $P < 0.001$. Normal IIEF-5 score (>21) was achieved in four men (25.0%) at 12 months, compared to none at the start of the study and one in the LCD group at 8 weeks (Figure 1). SDI scores increased significantly and comparably in the LCD and HP groups at 8 weeks (Figure 1). At 52 weeks, further significant improvements in SDI scores were seen in the LCD and HP groups (Table 2), main effect of time $F(2,21.7) = 63.86$, $P < 0.001$.

LUTS of at least moderate severity (IPSS score ≥8) was reported by 35.5% (11/31) of our subjects. IPSS scores decreased significantly in both groups at 8 weeks (Figure 1) and were comparable in both groups (Table 2). The magnitude of reduction in IPSS score was significantly correlated with

Table 2 Changes in anthropometry, sex hormone, sexual function, LUTS, inflammatory markers, endothelial function, and metabolic parameters after 8 and 52 weeks of dietary modification

	LCD (N = 19) Baseline	LCD (N = 19) 8 weeks	LCD* (N = 9) 52 weeks	HP (N = 12) Baseline	HP (N = 12) 8 weeks	HP (N = 7) 52 weeks
Weight (kg)	112.7 ± 4.1	103.2 ± 4.2§¶	103.1 ± 4.2§¶	109.6 ± 5.1	104.8 ± 5.3§¶	100.6 ± 5.2§¶
Waist circumference (cm)	124.6 ± 2.7	112.5 ± 2.6§¶	112.1 ± 3.2§¶	123.1 ± 3.4	117.7 ± 3.5§¶	114.0 ± 3.9§¶
Plasma TT (nmol/L)	11.70 ± 0.78	14.81 ± 1.98	13.39 ± 1.44	13.88 ± 1.00	14.17 ± 2.49	13.65 ± 1.65
Plasma SHBG (nmol/L)	22.47 ± 2.59	31.16 ± 3.36‡	24.44 ± 3.10	30.42 ± 3.26	34.17 ± 4.23‡	35.87 ± 3.73
Calculated FT (pmol/L)	285 ± 17	282 ± 22	305 ± 21	296 ± 21	276 ± 28	259 ± 24
IIEF-5 score	7.95 ± 1.58	10.12 ± 1.71‡	14.74 ± 1.16‡	11.75 ± 1.99	14.50 ± 2.15‡	18.44 ± 1.44‡
SDI score	43.68 ± 5.25	54.05 ± 6.46‡	60.19 ± 6.12‡	51.92 ± 6.61	63.42 ± 8.15‡	72.93 ± 7.68‡
IPSS score	6.26 ± 1.26	4.58 ± 1.10‡	3.30 ± 0.73‡	9.00 ± 1.58	6.50 ± 1.38‡	4.00 ± 0.91‡
Plasma CRP (mg/L)	3.82 ± 1.00†	5.04 ± 1.13	3.79 ± 0.82	8.32 ± 1.29†	3.68 ± 1.43§¶	2.85 ± 1.01§¶
Plasma IL-6 (pg/ml)	1.59 ± 0.29†	2.23 ± 0.35	1.70 ± 0.42	3.28 ± 0.37†	1.80 ± 0.44§¶	2.40 ± 0.52¶
Plasma sE-selectin (ng/dl)	53.6 ± 3.5†	41.8 ± 4.1§¶	38.3 ± 3.8§¶	72.1 ± 4.5†	53.2 ± 5.2§¶	43.1 ± 4.6§¶
FMD (%)	5.64 ± 0.37†	10.16 ± 0.5§¶	12.46 ± 0.5§¶	3.27 ± 0.50†	5.82 ± 0.71‡¶	9.77 ± 0.76§¶
Plasma glucose (mmol/L)	7.42 ± 0.59	6.54 ± 0.46‡	7.18 ± 0.63	8.65 ± 0.75	7.32 ± 0.58‡	7.39 ± 0.76
Plasma insulin (μU/mL)	21.38 ± 1.90†	17.70 ± 3.83	17.25 ± 3.20	14.28 ± 2.39†	13.20 ± 4.82	21.24 ± 3.83
Insulin sensitivity (QUICKI)	0.30 ± 0.01	0.32 ± 0.01§¶	0.32 ± 0.01§¶	0.31 ± 0.01	0.31 ± 0.01¶	0.30 ± 0.01¶
Plasma TG (mmol/L)	2.09 ± 0.21	1.52 ± 0.20	1.54 ± 0.17‡	2.18 ± 0.27	2.15 ± 0.25	1.55 ± 0.20‡
Plasma HDL (mmol/L)	1.17 ± 0.05	1.11 ± 0.04	1.24 ± 0.07	1.20 ± 0.06	1.13 ± 0.05	1.14 ± 0.08
Plasma LDL (mmol/L)	2.65 ± 0.21	2.26 ± 0.17‡	2.35 ± 0.17‡	2.50 ± 0.27	2.22 ± 0.21‡	1.96 ± 0.21‡

All values are given as mean ± standard error.
*Subjects on LCD for the 8-week weight-loss phase were switched to the HP diet for weight maintenance.
†Significant baseline difference between the LCD and HP diet groups.
‡Significant time effect difference from baseline across groups, $P < 0.05$.
§Significant intra-group difference from baseline, $P < 0.01$.
¶Significant interaction of group and time effect. The level of significance is set at $P < 0.05$.
LUTS = lower urinary tract symptoms; LCD = low-calorie diet; HP = high-protein low-fat; TT = total testosterone; SHBG = sex hormone binding globulin; IIEF-5 = five-item version of the International Index of Erectile Function; SDI = Sexual Desire Inventory; IPSS = International Prostate Symptom Scale; CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; sE-selectin = soluble E-selectin; FMD = brachial artery flow-mediated dilatation; TG = triglyceride.

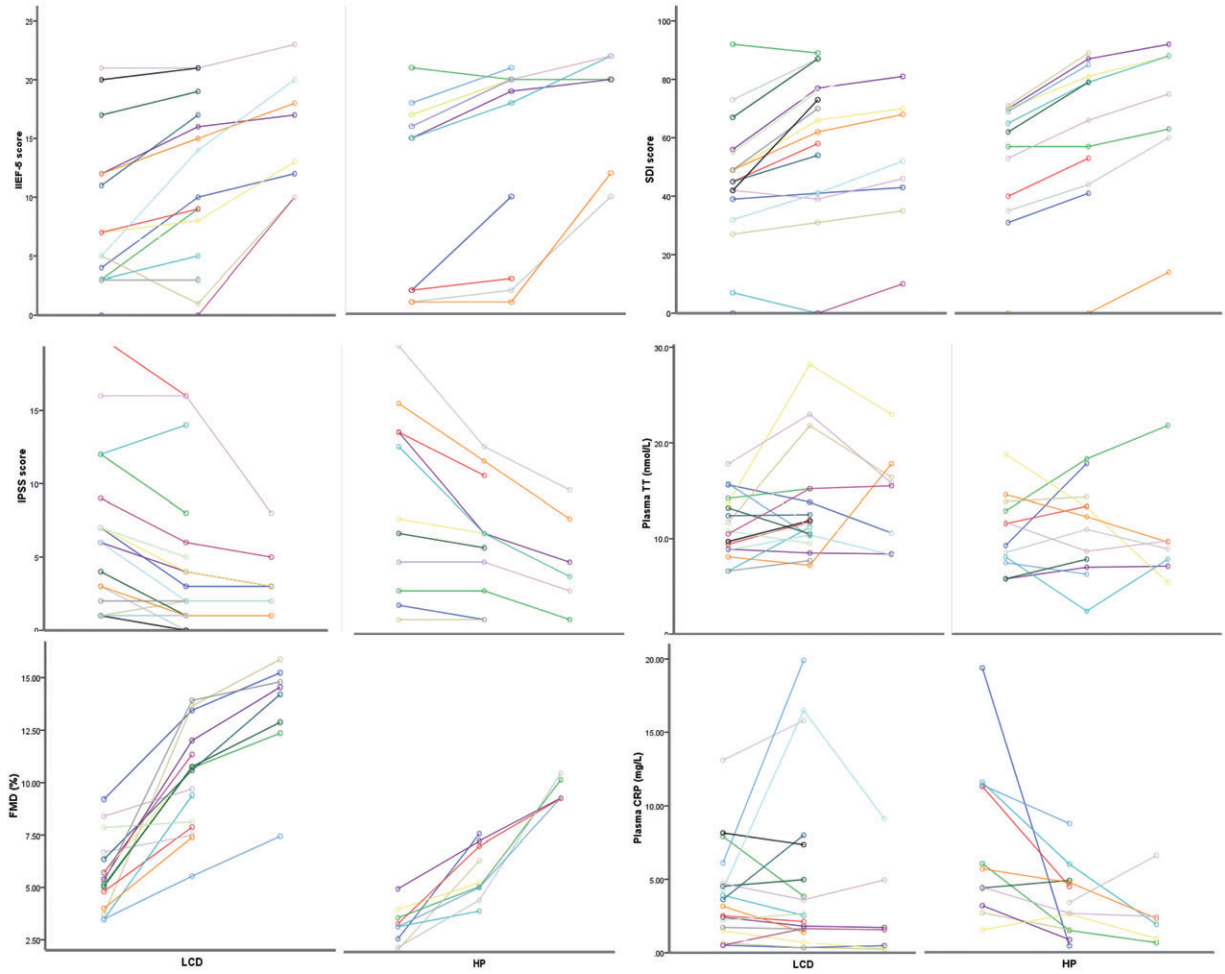

Figure 1 Comparison of individual changes in sexual function, lower urinary tract symptoms, endothelial function, and inflammatory markers in obese type 2 diabetic men at baseline, 8 and 52 weeks in the low-calorie diet (LCD) and high-protein low-fat (HP) diet groups. CRP = high-sensitivity C-reactive protein; FMD = brachial artery flow-mediated dilatation; IIEF-5 = five-item version of the International Index of Erectile Function; IPSS = International Prostate Symptom Scale; SDI = Sexual Desire Inventory; TT = total testosterone.

that of weight ($r = 0.69$, $P < 0.01$) and WC ($r = 0.66$, $P < 0.01$). At 52 weeks, mean IPSS score decreased further in both groups (Table 2), main effect of time $F(2,27.8) = 29.44$, $P < 0.001$.

Endothelial Function and Inflammatory Markers

Mean sE-selectin levels decreased in both groups after 8 weeks (Table 2). At 52 weeks, reduction in sE-selectin was maintained in the LCD group, and further reduction occurred in the HP group (Table 2). Mean brachial FMD increased significantly in both LCD and HP groups after 8 weeks (Table 2), and showed a tendency ($P = 0.05$) to correlate with the magnitude of weight loss. At 52 weeks, improvements in mean FMD were maintained (Table 2). Group–time interaction effects were significant for sE-selectin, $F(2,18.0) = 3.74$, $P = 0.04$, and FMD, $F(2,15.6) = 4.33$, $P = 0.03$.

At 8 weeks, mean CRP and IL-6 levels decreased significantly in the HP, but not in the LCD group (Table 2). Reduction in IL-6 was associated with decrease in CRP ($r = 0.68$, $P < 0.01$) and sE-selectin ($r = 0.37$, $P = 0.04$) and increase in FMD ($r = -0.86$, $P < 0.01$). At 52 weeks, CRP was maintained (Table 2). Group–time interaction effects were significant for CRP, $F(2,17.4) = 8.10$, $P < 0.01$, and IL-6, $F(2,16.3) = 6.44$, $P < 0.01$.

Discussion

Our study shows that a modified meal replacement program (LCD) and a diet of whole foods of high

nutritional quality (HP) are both effective in inducing rapid and significant weight loss and improvement in dyslipidemia, sexual and endothelial function, and LUTS in obese men with type 2 diabetes. The HP diet was effective for maintenance or further improvement. Our findings are concordant with results of studies showing that LCDs safely and rapidly induce ~10% weight loss and improve insulin resistance and other cardiovascular risk factors [5,12,20], and that low-fat, high-protein diets are effective for short-term weight loss and long-term maintenance of weight and cardiometabolic benefits [5,16,17].

More than half of our subjects had previously undiagnosed severe impairment of erectile function (IIEF-5 score <8), supporting the observation that significant sexual dysfunction is frequently undiagnosed in diabetic men, as in the Quality of Care and Outcomes in Type 2 Diabetes Study [21]. In our study, erectile function and sexual desire increased after 5–10% weight loss in 8 weeks, in contrast with failure of LCD to improve sexual function in men with no history of ED [22], and similar to the improvement in IIEF-5 scores 2 years after surgical weight loss of ~30% [23]. As in the Look AHEAD study where ~10% weight loss induced by diet modification and increased activity maintained or improved IIEF scores in a majority of obese type 2 diabetic men after 1 year [24], erectile function improved or normalized completely in a significant proportion of our subjects. Although our study may be underpowered to detect a significant difference between the two diet groups, and these differences may not be apparent beyond a "threshold" of weight loss, nutritional quality may contribute as much as caloric restriction to rapid improvement and maintenance of sexual function.

Short-term weight loss induced by caloric restriction was shown to increase testosterone and SHBG levels in abdominally obese nondiabetic [12] and diabetic [22,25] men, which is concordant with rapid increment in SHBG and correlation with the magnitude of weight loss in our study. Abdominal obesity is associated with reduced SHBG due to hyperinsulinemia [26], and thus, SHBG is expected to increase after reduction in weight, WC, and insulin resistance, as was seen in our subjects, particularly the LCD group. As visceral adiposity and insulin resistance are associated with production of inflammatory cytokines and increased aromatization of testosterone to estradiol in adipose tissue, leading to decreased pituitary gonadotropin release and testicular androgen production [27,28], weight loss and improvement in insulin sensitivity may increase testicular testosterone production and thus sexual function. Moreover, marked caloric restriction and consequent rapid weight loss may inhibit the activity of the hypothalamic-pituitary-gonadal axis, thereby causing a smaller increase in testosterone production than expected, and increasing SHBG. Our study may have been underpowered to detect statistically significant changes in TT, while the increase in SHBG contributed to the lack of change in FT.

The age-standardized prevalence of moderate and severe LUTS in Australian men aged 40 years and above is half (~16%) of that in our study [29], suggesting that LUTS remains undiagnosed in a significant proportion of obese diabetic men. Abdominal obesity is associated with ~2-fold increase in LUTS [2], and accordingly, decrease in IPSS score was related to reduction in weight and WC. Obesity-associated genitourinary dysfunction is attributed to atherosclerosis, endothelial dysfunction, and autonomic system overactivity leading to impaired penile rigidity and voiding [4]. We reported improvement of LUTS in obese men after ~10% weight loss with LCD [12], but significant reductions in IPSS scores even with ~5% weight loss on HP diet indicate the importance of a diet of high nutritional quality for improving and maintaining urinary tract health in obese diabetic men.

Improvements in endothelial function were concordant with studies of nonpharmacological weight loss in the short [13] and long term [14]. The HP diet induced significant increase in FMD after only ~5% weight reduction, in contrast with studies where less than 10% weight loss over 3–9 months failed to induce increase in FMD [30,31]. Rapid reductions in inflammatory markers on HP diet contrast with failure of low-fat diets (also ~5% weight loss) to reduce CRP and IL-6 after 6–14 months [5]. It is possible that the low-fat content and high-protein quality of the HP diet may have contributed to improvements in endothelial function and inflammation despite less weight loss than LCD. Interactions between the group and time effects on sE-selectin, FMD, CRP, and IL-6 suggest that these benefits are more evident with greater degrees of endothelial dysfunction and systemic inflammation.

The strengths of our study are comprehensive assessments, parallel dietary approaches, and relatively long duration of follow-up. Our main limitation is the small cohort, causing imbalance in baseline characteristics between diet groups, and the study to be underpowered to detect associations between reduction in weight and waist

circumference, and improvements in sexual, urinary, and endothelial function. No control group was used, as we felt it was unethical to withhold intervention in men with high cardiovascular risk. A similar magnitude of diet-induced weight loss may not be sustainable in the community, but awareness of sexual dysfunction and perceptible improvement are likely to motivate obese men to improve compliance with lifestyle modification.

Conclusions

We conclude that rapid diet-induced weight loss improves sexual, urinary, and endothelial function, and reduces systemic inflammation, in a population comprised exclusively of obese diabetic men. Further improvements during weight maintenance, using a high-protein low-fat diet, suggest that both nutrient quality and caloric restriction contribute to these benefits. Larger studies of different types of diets may be useful to explain the contribution of macronutrient composition.

Acknowledgments

Funding for this study was provided by the National Heart Foundation and the Medical Benefits Foundation of Australia. Kicstart was supplied by Pharmacy Health Solutions Pty Ltd, who had no role in the design, implementation, or analysis of the study.

Corresponding Author: Joan Khoo, MRCP, Department of Endocrinology, Changi General Hospital, Singapore, Singapore 529889. Tel: +65-68503807; Fax: +65-67816202; E-mail: furrina_2000@yahoo.com

Conflict of Interest: G.A.W. has received payment as a consultant to Pharmacy Health Solutions. M.N. developed, and published several books about, the HP diet. None of the other authors has any conflicts of interest to declare.

Statement of Authorship

Category 1

(a) Conception and Design
Gary A. Wittert; Stephen G. Worthley; Manny Noakes; Alicia Jenkins

(b) Acquisition of Data
Cynthia Piantadosi; Matthew I. Worthley; Rae Duncan; Stephen G. Worthley; Joan Khoo

(c) Analysis and Interpretation of Data
Joan Khoo; Gary A. Wittert; Kylie Lange; Alicia Jenkins; Cynthia Piantadosi

Category 2

(a) Drafting the Article
Joan Khoo; Gary A. Wittert; Kylie Lange

(b) Revising It for Intellectual Content
Joan Khoo; Cynthia Piantadosi; Rae Duncan; Stephen G. Worthley; Alicia Jenkins; Manny Noakes; Matthew I. Worthley; Kylie Lange; Gary A. Wittert

Category 3

(a) Final Approval of the Completed Article
Joan Khoo; Cynthia Piantadosi; Rae Duncan; Stephen G. Worthley; Alicia Jenkins; Manny Noakes; Matthew I. Worthley; Kylie Lange; Gary A. Wittert

References

1 Esposito K, Giugliano F, Martedi E, Feola G, Marfella R, D'Armiento M. High proportions of erectile dysfunction in men with the metabolic syndrome. Diabetes Care 2005;28: 1201–3.
2 Kupelian V, McVary KT, Kaplan SA, Hall SA, Link CL, Aiyer LP, Mollon P, Tamimi N, Rosen RC, McKinlay JB. Association of lower urinary tract symptoms and the metabolic syndrome: Results from the Boston Area Community Health Survey. J Urol 2009;182:616–24.
3 Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E. Lower urinary tract symptoms and male sexual dysfunction: The multinational survey of the aging male (MSAM-7). Eur Urol 2003;44:637–49.
4 McVary K. Lower urinary tract symptoms and sexual dysfunction: Epidemiology and pathophysiology. BJU Int 2006;97(2 suppl):23–8.
5 Forsythe LK, Wallace JMW, Livingstone MBE. Obesity and inflammation: The effects of weight loss. Nutr Res Rev 2008;21:117–33.
6 St Sauver JL, Sarma AV, Jacobson DJ, McGree ME, Lieber MM, Girman CJ, Nehra A, Jacobsen SJ. Associations between C-reactive protein and benign prostatic hyperplasia/lower urinary tract symptom outcomes in a population-based cohort. Am J Epidemiol 2009;169:1281–90.
7 Esposito K, Ciotola M, Maiorino MI, Giugliano F, Autorino R, De Sio M, Jannini E, Lenzi A, Giugliano D. Circulating CD34+ KDR+ endothelial progenitor cells correlate with erectile function and endothelial function in overweight men. J Sex Med 2009;6:107–14.
8 Costa C, Virag R. The endothelial-erectile dysfunction connection: An essential update. J Sex Med 2009;6:2390–404.
9 Angulo J, González-Corrochano R, Cuevas P, Fernández A, La Fuente JM, Rolo F, Allona A, Sáenz de Tejada I. Diabetes exacerbates the functional deficiency of NO/cGMP pathway associated with erectile dysfunction in human corpus cavernosum and penile arteries. J Sex Med 2010;7:758–68.
10 Hannan JL, Maio MT, Komolova M, Adams MA. Beneficial impact of exercise and obesity interventions on erectile function and its risk factors. J Sex Med 2009;6:254–61.
11 Leinonen E, Hurt-Camejo E, Wiklund O, Hultén LM, Hiukka A, Taskinen MR. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis 2003;166:387–94.
12 Khoo J, Piantadosi C, Worthley S, Wittert GA. Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. Int J Obes (Lond) 2010;34: 1396–403.
13 Raitakari M, Ilvonen T, Ahotupa M, Lehtimäki T, Harmoinen A, Suominen P, Elo J, Hartiala J, Raitakari OT. Weight reduc-

tion with very-low-calorie diet and endothelial function in overweight adults: Role of plasma glucose. Arterioscler Thromb Vasc Biol 2004;24:124–8.
14 Bigornia SJ, Mott MM, Hess DT, Apovian CM, McDonnell ME, Duess MA, Kluge MA, Fiscale AJ, Vita JA, Gokce N. Long-term successful weight loss improves vascular endothelial function in severely obese individuals. Obesity 2010;18: 754–9.
15 Phillips SA, Jurva JW, Syed AQ, Syed AQ, Kulinski JP, Pleuss J, Hoffmann RG, Gutterman DD. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. Hypertension 2008;51:376–82.
16 Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D. Effect of lifestyle changes on erectile dysfunction in obese men: A randomized controlled trial. JAMA 2004;291:2978–84.
17 Brinkworth GD, Noakes M, Parker B, Foster P, Clifton PM. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: One-year follow-up of a randomised trial. Diabetologia 2004;47:1677–86.
18 Wyld B, Harrison A, Noakes M. The CSIRO total wellbeing diet book 1: Sociodemographic differences and impact on weight loss and well-being in Australia. Public Health Nutr 2010;13:2105–10.
19 Leeson CP, Robinson M, Francis JM, Robson MD, Channon KM, Neubauer S, Wiesmann F. Cardiovascular magnetic resonance imaging for non-invasive assessment of vascular function: Validation against ultrasound. J Cardiovasc Magn Reson 2006;8:381–7.
20 Moreno O, Meoro A, Martinez A, Rodriguez C, Pardo C, Aznar S, Lopez P, Serrano J, Boix E, Martin MD, Pico Alfonso AM. Comparison of two low-calorie diets: A prospective study of effectiveness and safety. J Endocrinol Invest 2006;29:633–40.
21 De Berardis G, Pellegrini F, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, Kaplan SH, Rossi MC, Sacco M, Tognoni G, Valentini M, Nicolucci A, QuED (Quality of Care and Outcomes in Type 2 Diabetes) Study Group. Longitudinal assessment of quality of life in patients with type 2 diabetes and self-reported erectile dysfunction. Diabetes Care 2005;28: 2637–43.
22 Kaukua J, Pekkarinen T, Sane T, Mustajoki P. Sex hormones and sexual function in obese men losing weight. Obes Res 2003;11:689–94.
23 Reis LO, Favaro WJ, Barreiro GC, de Oliveira LC, Chaim EA, Fregonesi A, Ferreira U. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: A prospective randomized controlled trial. Int J Androl 2010;33:736–44.
24 Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano Iii IN, Kitabchi A, Schneider SH, Wadden TA. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med 2010; 7:156–65.
25 Niskanen L, Laaksonen DE, Punnonen K, Mustajoki P, Kaukua J, Rissanen A. Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. Diabetes Obes Metab 2004;6:208–15.
26 Abate N, Haffner SM, Garg A, Peshock RM, Grundy SM. Sex steroid hormones, upper body obesity, and insulin resistance. J Clin Endocrinol Metab 2002;87:4522–7.
27 Vermeulen A, Kaufman JM, Giagulli VA. Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. J Clin Endocrinol Metab 1996;81:1821–6.
28 Loves S, Ruinemans-Koerts J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. Eur J Endocrinol 2008;158:741–7.
29 Holden CA, Mclachlan RI, Pitts M, Cumming R, Wittert G, Agius PA. Men in Australia telephone survey (MATeS): A national survey of the reproductive health and concerns of middle-aged and older Australian men. Lancet 2005;366:218–24.
30 Brook RD, Bard RL, Glazewski L, Kehrer C, Bodary PF, Eitzman DL, Rajagopalan S. Effect of short-term weight loss on the metabolic syndrome and conduit vascular endothelial function in overweight adults. Am J Cardiol 2004;93:1012–6.
31 Skilton MR, Sieveking DP, Harmer JA, Franklin J, Loughnan G, Nakhla S, Sullivan DR, Caterson ID, Celermajer DS. The effects of obesity and non-pharmacological weight loss on vascular and ventricular function and structure. Diabetes Obes Metab 2008;10:874–84.