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Mechanistic insights into the aetiology of post-prandial decline in testosterone in reproductive-aged men

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Abstract

Obesity is known to be associated with impaired testicular function potentially resulting in androgen deficiency and subfertility. While the underlying cause of obesity-related male hypogonadism is multi-factorial, here, we investigated the impact of dietary fat on testicular endocrine function. Ingestion of a high-fat "fast food" mixed meal, a common practice for obese men, produced a 25% fall in serum testosterone within an hour of eating, with levels remaining suppressed below fasting baseline for up to 4 hr. These changes in serum testosterone were not associated with any significant changes in serum gonadotrophins. The nadir in serum testosterone preceded the post-prandial increase in serum IL-6/IL-17 by several hours, suggesting that inflammation was unlikely the cause. Furthermore, intravenous administration of fat (Intralipid) had no impact on testosterone levels, while an identical oral dose of fat did suppress testosterone. These results suggest that fat does not directly impair Leydig cell function, but rather the passage of fat through the intestinal tract elicits a response that indirectly elicits a post-prandial fall in testosterone.

KEYWORDS

fat, food, inflammation, post-prandial, testosterone

1 | INTRODUCTION

Obesity is known to be one of the key drivers of androgen deficiency and impaired fertility (hypogonadism; Carrageta, Oliveira, Alves, & Monteiro, 2019; Corona, Vignozzi, Sforza, Mannucci, & Maggi, 2015). Low testosterone is also associated with an adverse lipid profile and impaired glucose homeostasis, both resulting in an increased risk of cardiovascular disease (Araujo et al., 2011). With two-thirds of adult men now being classified as overweight or obese, adiposity related male hypogonadism is becoming a major public health challenge (Corona et al., 2015).

The causal link between obesity and hypogonadism is believed to be multi-factorial (Carrageta et al., 2019). Firstly, adipose tissue contains significant amounts of aromatase activity, an enzyme capable of converting testosterone into oestrogen, with oestrogen then negatively feeding back on the hypothalamic-pituitary (HP) axis, reducing LH drive for testosterone production. Similarly, adipose tissue-derived leptin suppresses pituitary LH release and testosterone production. Secondly, obesity is associated with chronic low-grade inflammation, with multiple large epidemiological studies linking this inflammation with impaired testosterone production (Bobjer, Katrinaki, Tsatsanis, Lundberg Giwercman, & Giwercman, 2013; Tsilidis et al., 2013). Pro-inflammatory cytokines such as IL-6, IL-17, TNFα and IL-1β, frequently elevated in the serum of obese men (Ahmed & Gaffen, 2010; Tremellen, McPhee, & Pearce, 2017), impair testosterone production by activating inflammation and reactive oxygen species (ROS) production by interstitial macrophages residing adjacent to Leydig cells (Carrageta et al., 2019; Tremellen et al., 2018). Furthermore, our own work has shown that administration of the powerful immune stimulant LPS (endotoxin) to healthy men results in a rapid and profound fall in serum testosterone levels independent of changes in the hypothalamic-pituitary axis (Tremellen et al., 2017, 2018). As such, it is clear that systemic inflammation does have the potential to negatively impact Leydig cell function.

While the presence of excess adipose tissue is a clear cause of obesity-related hypogonadism, it is also possible that the type of food that obese men consume may play a significant role independent of their adiposity. Several studies have shown that high-fat meals produce an average 25% fall in serum testosterone from fasting baseline, with levels remaining suppressed for between 3 and 8 hr post-prandial (Habito & Ball, 2001; Lehtihet, Arver, Bartuseviciene, & Pousette, 2012; Meikle, Stringham, Woodward, & McMurry, 1990; Volek et al., 2001). As many obese men frequently consume these types of high-fat meals and snacks throughout waking hours, it is possible that repeated post-prandial suppression of testicular function is a major driver for hypogonadism in this group. As such, a better understanding of the underlying mechanism of this post-prandial fall in testosterone in high BMI men may help develop new therapies to combat obesity-related hypogonadism independent of the elusive goal of weight loss.

Two potential mechanisms have been suggested to mediate the post-prandial fall in testosterone. Firstly, free fatty acids (FFA) may directly impair Leydig cell function, as the addition of FFA to testicular cultures reduces LH-stimulated testosterone production (Meikle, Benson, Liu, Boam, & Stringham, 1989). Secondly, consumption of fatty meals is reported to produce a rapid post-prandial inflammatory/oxidative stress (OS) response (Emerson et al., 2017; Herieka & Erridge, 2014; Laugerette, Vors, Peretti, & Michalski, 2011), with inflammation and OS known to impair testosterone production (Bobjer et al., 2013; Tremellen et al., 2017, 2018; Tsilidis et al., 2013).

The primary aim of our study was to analyse temporal relationship between consumption of a high-fat mixed meal and the onset of systemic inflammation (serum IL-6 and IL-17) and oxidative stress (serum 8 OHdG), with changes in testicular endocrine function in overweight/obese men. In addition, several studies have linked consumption of a fatty meal with the passage of gut bacterial endotoxin across the intestinal epithelium where it initiates a systemic inflammatory "metabolic endotoxemia" response (Deopurkar et al., 2010; Laugerette et al., 2011). As such, a secondary aim was to investigate if the mode of delivery of fat (oral intestinal transit or direct intravenous administration) influenced changes in testicular endocrine function.

2 | MATERIALS AND METHODS

2.1 | Study cohort

Overweight or obese men aged from 18 to 50 years were recruited between July 2017 and November 2018 via advertisements and social media. Exclusion criteria were documented inflammatory or infectious disease, primary hypogonadism (Klinefelter's Syndrome, cryptorchidism or testicular injury), the consumption of immunosuppressive medication (e.g., nonsteroidal anti-inflammatory drugs [NSAID], corticosteroids or fish oil) or antibiotics, supplements that may alter intestinal function (e.g., probiotics, antibiotics in the last 1 month) or any male hormonal therapy (i.e., aromatase inhibitors, clomiphene citrate, human chorionic gonadotropin [hCG] or testosterone). Evidence of hypogonadism or infertility was not inclusion criteria for involvement in the study. This project was approved by the University of South Australia Ethics Committee (approval number 00000200913), with informed written consent being obtained from all participants. The trial was also prospectively registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR, Australia; ACTRN12617001034325).

2.2 | Habitual lifestyle behaviour assessment

Baseline dietary intake was assessed using a food frequency questionnaire (FFQ). Following individual instructions from a registered nutritionist, participants weighed their dietary intake for seven consecutive days and recorded the weight, type, brand and amount of foods and beverages consumed. This dietary data were entered into Foodworks 8 software (Xyris Software Australia Pty Ltd) to enable calculation of average daily energy and macro-nutrient content. To ensure participants did not underestimate their actual food intake, basal metabolic rate (BMR) was determined for all participants using the Scholfield equation, with results outside of the 95% CI for plausible energy requirements (based on the energy intake to BMR ratio) being excluded from the analysis (Black, 2000).

Participants completed the Pittsburgh Sleep Quality Index questionnaire (FF) to determine their sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), while average physical activity levels were quantified using the Baecke Physical Activity Questionnaire (Baecke, Burema, & Frijters, 1982).

2.3 | Meal intervention protocol

After an overnight fast, baseline blood samples were collected from all participants between 7:30 a.m. and 9 a.m. on the day of testing. Anthropometric measures (height and weight) were assessed on the day of the study meal administration. In the fasting arm of the study, participants remained fasted for the 5-hr period of blood collection, with the exception of water. In the feeding arms (high-fat mixed meal and the Intralipid fat liquid meal), participants were asked to consume the meal within 15 min of the initial blood draw over a maximum period of 5 min. The participants continued to have their blood collected hourly over a total of 5 hr from baseline. The access to water was unrestricted with no other food provided over the 5-hr period.

The high-fat mixed meal consisted of an English muffin containing sausage, egg and cheese plus two potato hash browns (McDonald's Australia). The polyunsaturated vegetable fat liquid meal consisted of a 125 ml oral dose of Intralipid 20% (Fresenius Kabi). Their detailed nutritional content is outlined in Table 1.

2.4 | Intravenous Intralipid 20% infusion (25 g fat) protocol

Following an overnight fast, identical to the conditions outlined in the meal study arms, 125 ml of Intralipid 20% was diluted in 875 ml

TABLE 1 Nutritional composition of the trial meal interventions

	McDonalds "high fat" breakfast meal	Liquid fat meal (125 ml of Intralipid 20%)
Total energy (Kj)	3,958	965
Total fat (g)	51	26
Saturated fat (g)	16	4
Polyunsaturated fat (g)	9	16
Monounsaturated fat (g)	26	5
Trans fatty acids (g)	1	1
Omega 3 fatty acid (g)	0	2
Omega 6 (g)	7	14
Protein (g)	41	1
Total carbohydrate (g)	76	3
Sugar (g)	3	0
Fibre (g)	7	0
Sodium (mg)	2,122	3

Note: Feeding Study arms: *McDonalds meal* one English muffin (sausage, egg and cheese), 2 hash browns; *liquid fat meal* 125 ml 20% Intralipid solution. *IV study arm*; Intralipid 20% Intralipid 20% (Baxter) diluted in 875 ml of saline.

of saline and administered via a peripheral vein in the arm at a rate of 0.1 g fat/min for the first 15–30 min of infusion. This was increased to approximately 0.2 g fat/min in the absence of any adverse reaction, with the total infusion taking 2 hr—the maximal permitted safe rate of administration.

2.5 | Biochemical analysis

2.5.1 | Hormone analysis

Serum was analysed for testosterone, estradiol, follicle-stimulating hormone (FSH) and luteinising hormone (LH) using an automated chemiluminescence immunoassay (Cobas 6000 e 601, Roche Diagnostics), with the detectable ranges for each hormone being 18.4–110.10 pmol/L, 0.087–52.0 nmol/L, 0.1–200 mIU/ml and 0.2–100 mIU/ml respectively.

2.5.2 | Assessment of inflammatory and oxidative stress status

Baseline fasting exposure to endotoxin (metabolic endotoxemia) was quantified by assessment of lipopolysaccaride binding protein (LBP) using an ELISA according to the manufacturer's guidelines (Hycult), as previously published by our group (Tremellen et al., 2017, 2018). Quantification of the post-prandial inflammatory response to the high-fat mixed meal was assessed using serum IL-6 and IL-17 assessed by an ELISA assay platform (Cusabio). Oxidative stress status was assessed by quantification of oxidative damage to DNA using a serum 8 hydroxy-2′-deoxyguanosine ELISA (Crux). Cytokines and 8 OHdG levels were only quantified in the McDonalds feeding arm, not fasting controls or the Intralipid study arms.

2.6 | Statistical analysis

All demographic and biochemical variables were expressed as a range and mean ± standard deviation. All variables were tested for normality and log-transformed where appropriate. Correlation analysis was performed with SPSS using the Pearson method for normally distributed data and the Spearman method for non-parametric data (IBM Corporation). Adjustments were made for age, BMI, sleep, physical activity, total energy intake and total fat intake. A Wilcoxon matched pairs signed-rank test was used to determine differences between the baseline and treatment arm of the study at the various time points across the monitoring period. Statistical significance was set at <0.05. No formal power analysis was conducted to determine sample size.

3 | RESULTS

The baseline characteristics of the study group are outlined in Table 2. A total of 18 participants were enrolled in the study (10 participating in both the high saturated fat "fast food" mixed meal and fasting control, eight in the intravenous Intralipid arm and five in the oral Intralipid arm). While all subjects in the high-fat mixed meal also participated in the fasting control arm, participant drop out mandated replacement subjects to complete the Intralipid arms. These changes in study participants did produce some significant differences in hormonal profiles between the McDonalds/fast group and the other treatment arms, which are outlined in Table 2.

The high-fat "fast food" mixed meal produced a significant fall in serum testosterone levels within 1 hr of food ingestion, reaching a nadir of 25% of baseline by 2–3 hr post-prandial. By comparison, serum testosterone concentrations were maintained at or

TABLE 2 Baseline demographic and nutrition parameters for the study groups

	Fasting	McDonalds	Intravenous Intralipid	Oral Intralipid	*p*-value
n	10	10	8	5	
Age (years)	29.4 ± 11.1	29.4 ± 11.1	30.7 ± 10.7	32.6 ± 11.1	.843
BMI kg/m^2	37.3 ± 8.3	37.23 ± 8.3	30.6 ± 5.7	30.3 ± 5.8	.137
Sleep	6.2 ± 3.6	6.2 ± 3.6	10.1 ± 7.1	12.6 ± 5.2	.168
Physical activity	7.8 ± 1.6	7.8 ± 1.6	7.1 ± 4.7	5.2 ± 1.9	.639
Hormonal status					
Testosterone (nmol/L)	12.3 ± 3.9	11.4 ± 3.6	15.1 ± 3.9	14.7 ± 5.1	<.001
LH (mIU/ml)	4.8 ± 1.2	6.3 ± 1.6	6.6 ± 6.0	5.3 ± 2.0	.089
FSH (mIU/ml)	4.0 ± 3.1	4.7 ± 1.8	7.4 ± 11.5	4.6 ± 2.2	.082
Dietary intake					
Energy (MJ)	10.7 ± 3.2	10.7 ± 3.2	106 ± 2.8	10.1 ± 2.9	.947
Total fat (g)	104 ± 42	104 ± 42	91 ± 24	95 ± 34	.642
Saturated fat (g)	38 ± 17	38 ± 17	32 ± 11	32 ± 11	.438
Total protein (g)	114 ± 43	114 ± 43	98 ± 19	115 ± 36	.659
Total carbohydrates (g)	279 ± 77	279 ± 77	325 ± 130	313 ± 134	.755
Sugar (g)	113 ± 55	113 ± 55	154 ± 129	143 ± 128	.659
Fibre (g)	25 ± 13	25 ± 13	26 ± 14	23 ± 14	.896

Note: Sleep was measured using the Pittsburgh Sleep Quality Index; Physical activity was measured using the Baecke Physical Activity Questionnaire; Dietary data represent 7 days of dietary intake analysed using Foodworks 8 software (Xyris Software Australia Pty Ltd).

above fasting levels for 5 hr in the control group consuming water only (Figure 1a). There were no significant changes in post-prandial gonadotrophin levels (LH and FSH) or estradiol in any of the study arms. However, a small non-significant increase in serum LH levels 5 hr after a meal was observed in the high-fat mixed meal challenge (Figure 1b), a change that most likely representing a mild compensatory increase in pituitary LH drive to correct for falling testosterone levels. However, there was certainly no obvious post-prandial fall in LH to suggest suppression of the HP axis is the primary driver of the post-meal drop in testosterone.

Ingestion of the high-fat mixed meal resulted in a minor post-prandial inflammatory response, with both serum IL-6 and IL-17 levels becoming significantly elevated above fasting baseline from 4 hr post-meal (Figure 2a). However, no significant interaction was observed between serum IL-17 and testosterone levels, or any of the remaining reproductive hormones (FSH, estradiol). Furthermore, it should be noted that the nadir in serum testosterone preceded these inflammatory changes by at least 3 hr (Figures 1 and 2).

Post-prandial levels of 8 OHdG declined post-mixed-meal, with this fall from baseline becoming significant between 2 and 5 hr post-prandial (Figure 2b). No significant relationship was observed between serum 8 OHdG and testosterone levels.

Baseline measures of metabolic endotoxemia exposure (LBP) negatively correlated with serum testosterone (r = −.579 and p = .009), as previously reported (Tremellen et al., 2017, 2018). However, LBP levels did not correlate with any other reproductive hormone, nor fasting IL-6 and IL-17 levels. Furthermore, the magnitude of the post-prandial drop in testosterone was unrelated to baseline inflammatory status.

Oral administration of 25 g of Intralipid fat did result in a statistically significant fall in serum testosterone levels at 1 hr compared with baseline, but the magnitude of this decline was smaller and of a shorter duration than that seen with a high-fat mixed meal (Figure 3). Interestingly, the direct intravenous administration of an identical dose of Intralipid fat had absolutely no impact on testosterone (Figure 3), or any other hormones reproductive hormones (data not shown).

4 | DISCUSSION

While a post-prandial fall in testosterone levels is well established, especially following high-fat (Habito & Ball, 2001; Lehtihet et al., 2012; Meikle et al., 1990; Volek et al., 2001) and liquid glucose meal (Caronia et al., 2013; Iranmanesh, Lawson, & Veldhuis, 2012), this paper has identified several novel potentially clinically important findings.

Firstly, the results of this study show for that fat and its metabolites do not directly suppress Leydig cell function, as had earlier been reported by in vitro studies (Meikle et al., 1989). We observed absolutely no change in serum testosterone following intravenous Intralipid administration, despite visible lipidaemia being present in the 1- and 2-hr study samples. However, an identical oral dose of Intralipid did produce a significant post-prandial fall in testosterone, thereby suggesting that fat must traverse the intestine in order to impair testosterone production. Earlier we had postulated that the transfer of gut bacterial endotoxin across the small intestinal mucosal barrier, facilitated by fat laden chylomicron particles,

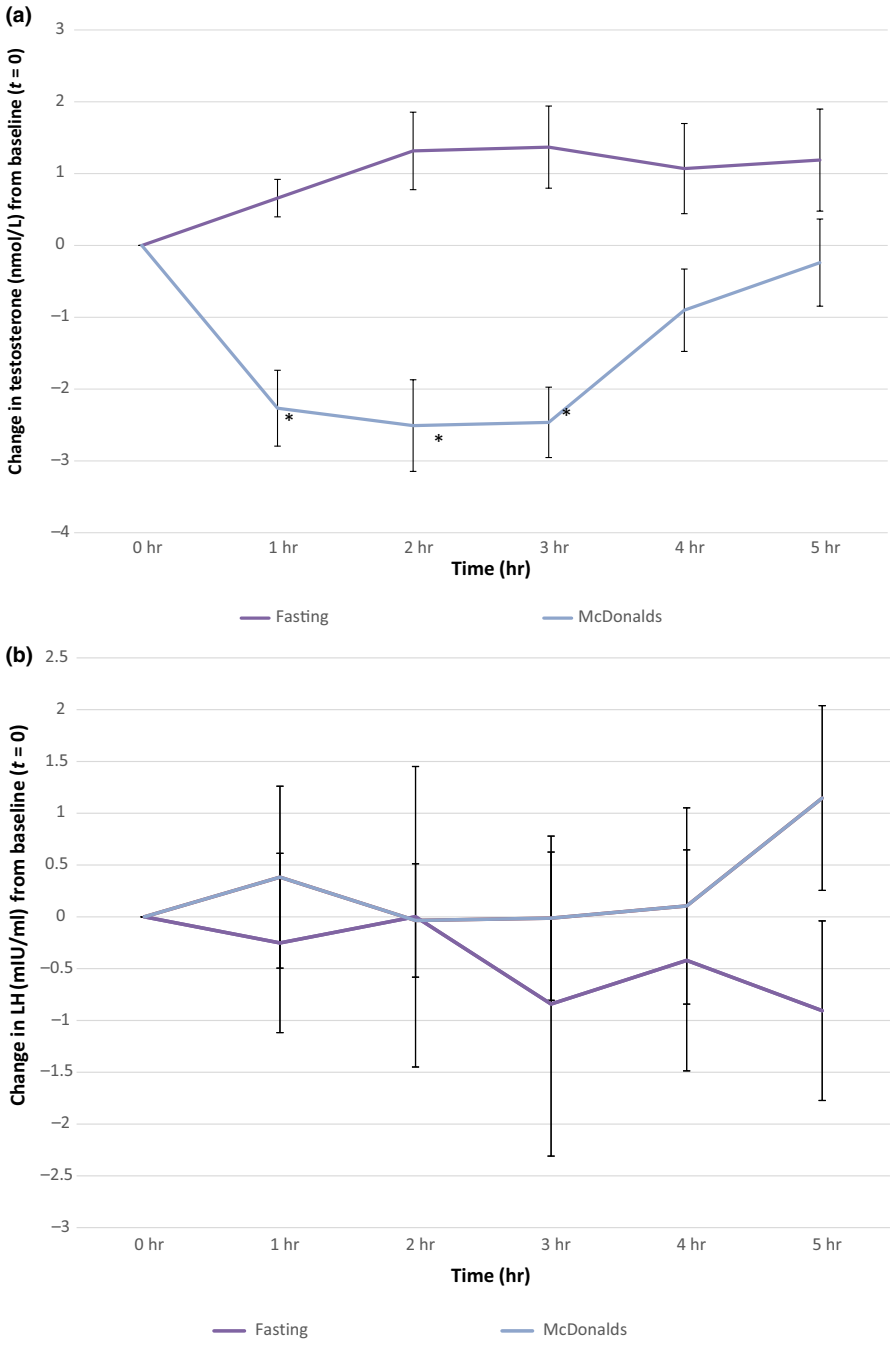

FIGURE 1 Changes in serum testosterone and LH from fasting baseline following a high-fat mixed meal (McDonalds breakfast). Data expressed as mean ± *SEM*. Statistical significance ($p < .05$) recorded as *

may be the underlying inflammatory trigger for this post-prandial drop in testosterone. This hypothesis was plausible given that ingestion of fatty food has been reported to trigger a transient increase in circulatory endotoxin levels (Deopurkar et al., 2010; Laugerette et al., 2011) and increase in the two pro-inflammatory cytokines IL-6 and IL-17 (Emerson et al., 2017; Herieka & Erridge, 2014; Peluso et al., 2012), both known to interfere with testosterone production (Poutahidis et al., 2014; Tremellen et al., 2017, 2018). Furthermore, we had earlier shown that direct intravenous administration of endotoxin to healthy men resulted in a decline in serum testosterone levels (Tremellen et al., 2018). However, our current observations do not support this "metabolic endotoxemia" inflammatory mechanism for post-prandial fall in testosterone as the observed nadir in testosterone occurred 2–3 hr before the increase in IL-6 and IL-17. Furthermore, earlier work has suggested that serum testosterone levels fall within 15–30 min of a meal (Iranmanesh et al., 2012; Lehtihet et al., 2012), a very rapid response more likely to be mediated by neuronal (autonomic) or endocrine (incretins, insulin) responses to food rather than the observed quite delayed inflammatory response. Given that we observed a fall in serum 8 OHdG after the high-fat mixed meal, consistent with antioxidants in the food reducing oxidative damage to DNA, it is also unlikely that oxidative stress is the underlying cause for post-prandial drop in testosterone.

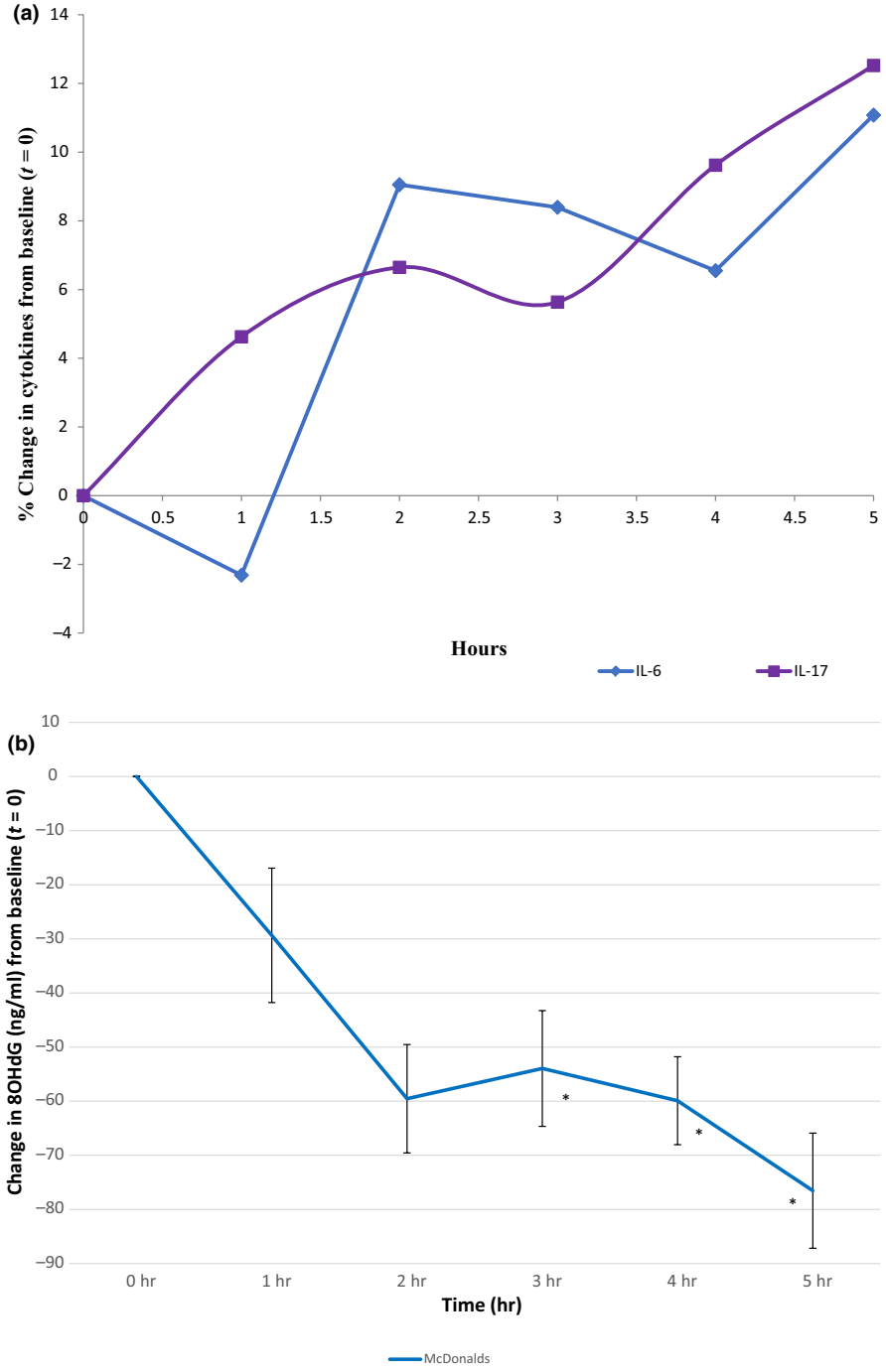

FIGURE 2 Changes in serum inflammatory cytokines (IL-6 and IL-17) and oxidative stress status (8 OHdG) following a high-fat mixed meal. Data expressed as mean ± *SEM*. Statistical significance ($p < .05$) recorded as *

A potential candidate for initiating a post-prandial drop in testosterone is GLP-1. This incretin peptide is produced by the L cells of the small intestine following exposure to food, with its principal role being to slow gastric transit and initiate satiety—thereby preventing overeating. Serum GLP-1 levels are known to increase within 15 min of a meal (Lindgren et al., 2011), proceeding the observed post-prandial decline in testosterone. Importantly, intravenous administration of GLP-1 has been reported to result in a decline in testosterone production within 30 min of injection (Jeibmann, Zahedi, Simoni, Nieschlag, & Byrne, 2005), making GLP-1 a scientifically plausible mediator of our observations. Finally, intravenous administration of Intralipid fat, thereby bypassing intestinal L cell detection, does not alter serum GLP-1 levels, while administration of an identical oral dose of Intralipid is reported to produce a large increase in serum GLP-1 (Lindgren et al., 2011). This observation may help explain why identical doses of oral Intralipid inhibited testosterone production but intravenous Intralipid had no impact. However, as we did not measure GLP-1 levels in this study, and only a single paper has previously suggested a link between GLP-1 and impaired testicular function, we acknowledge that this proposed mechanism is only speculative.

While insulin levels increase rapidly following a meal, we believe that insulin is unlikely responsible for the observed post-prandial reduction in testosterone levels for three reasons. Firstly, infusion of insulin during euglycaemic insulin clamp experiments results in

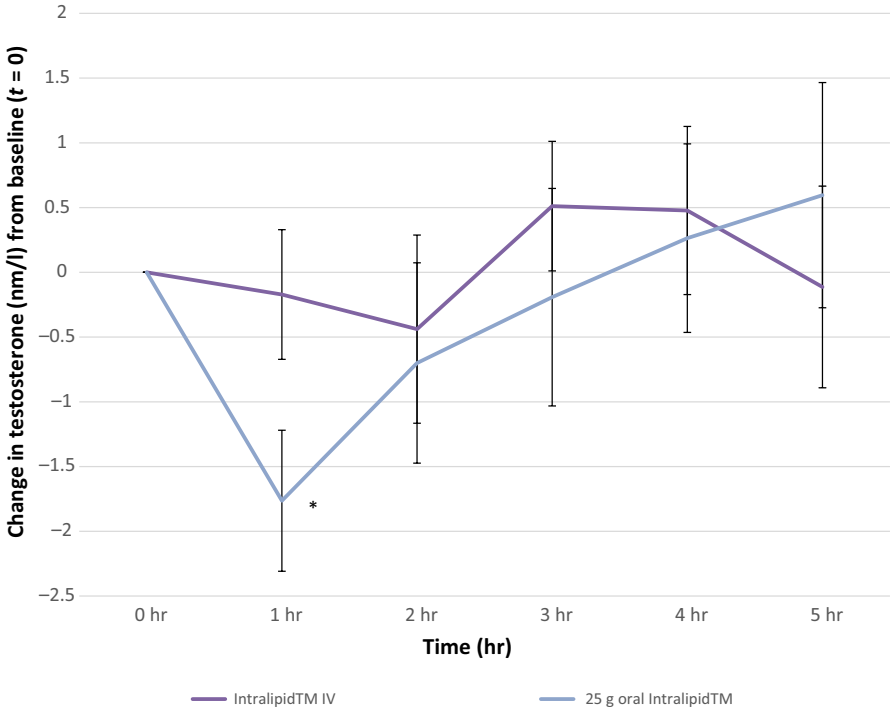

FIGURE 3 Comparison of changes in testosterone following administration of 125 ml Intralipid (25 g fat) administered either intravenously or orally. Data expressed as mean ± *SEM*. Statistical significance ($p < .05$) recorded as *

either no change (lean controls) or an actual increase (obese men) in serum testosterone (Pasquali et al., 1997), not a decline. Secondly, earlier post-prandial studies reported no significant association between post-prandial changes in insulin and testosterone levels (Volek et al., 2001). Finally, suppression of insulin production using long-term diazoxide treatment is known to reduce serum testosterone levels (Pasquali et al., 1995), implying that insulin is more likely to boost than reduce testosterone production.

The existing literature surrounding the influence of habitual dietary fat intake on testicular endocrine function is contradictory and confusing. The Murcia Young Men's Study from Spain analysed average food intake in 215 young men using food frequency questionnaires and reported that dietary intake of fat impaired Leydig cell function, signified as either a reduction in serum testosterone or a rise in LH with no change in testosterone (compensated hypogonadism), depending upon the sub-type of fat analysed (trans fat, PUVA or MUFA; Mínguez-Alarcón et al., 2017). Conversely, an Australian study of 269 young men observed no relationship between the type of diet, assessed binomially as either a "Western" high fat/sugar diet or a "healthy" diet low in saturated fat and high in fruit and vegetables, and serum testosterone and LH levels (Ognjenovic et al., 2019). However, both of these studies measured male reproductive hormones in the non-fasting state, making direct comparisons with our work impossible. Our work highlights the need to assess testosterone in the fasting state in order to avoid this important post-prandial suppression confounder.

We acknowledge some significant weaknesses in this study. Firstly, our study sample size is small, an unavoidable restriction placed on us by the significant cost of reimbursement of volunteers for an invasive in-patient interventional study. However, as we did observe several clear and consistent statistically significant differences in the various treatment arms, and as such we do not see the size of our small pilot study as a major weakness. In terms of helping determine mechanism of action, we would have liked to have measurements of GLP-1 and plasma endotoxin. We spent considerable time attempting to validate an assay for measuring acute changes in plasma endotoxin using the LAL assay, but were unable to obtain robust results as has also been reported by others (Gnauck, Lentle, & Kruger, 2016). As such, we needed to rely on the indirect markers of metabolic endotoxemia inflammatory response (serum IL-6 and IL-17), rather than direct measurement of endotoxin. However, since we observed a rapid fall in testosterone level within an hour of eating, several hours before a modest increase in IL-6 and IL-17, or reported post-prandial endotoxin exposure (Emerson et al., 2017; Laugerette et al., 2011), we are confident that endotoxin and inflammation is unlikely to be the principal trigger for the post-prandial drop in testosterone.

Since our study only targeted overweight and obese men, we acknowledge that our results may not be applicable to lean men. However, we focused our work on overweight men for three reasons. Firstly, this group is known to have a more exaggerated inflammatory response to a meal (metabolic endotoxaemia) because of increased intestinal permeability, plus they are more likely to consume a diet high in fat content. Furthermore, as many overweight men are borderline hypogonadal, we felt that any post-prandial fall in testosterone is more likely to be clinically meaningful compared with lean eugonadal men, giving our results more significance. Importantly, previous studies of healthy lean to mildly overweight men (Lehtihet et al., 2012; Volek et al., 2001) have also reported a 2.5–4 nmol drop in serum testosterone shortly following a meal—a change of similar magnitude and time pattern to what we observed in our overweight/obese cohort. As such, it would appear that post-prandial changes in testosterone appear to be universal to men of all BMI classifications.

We acknowledge that the biological activity of testosterone is confined to the relatively small proportion of testosterone unbound to sex hormone-binding globulin (SHBG), yet we have not reported free (bioactive) testosterone levels. We omitted SHBG measurements primarily because it is well documented by several studies that there is no significant change in SHBG levels after a high-fat meal (Habito et al., 2001; Volek et al., 2001), mixed meal (Lehtihet et al., 2012) or pure 75 g oral glucose load (Caronia et al., 2013), making SHBG measurement unnecessary.

Finally, while we did not observe any significant fall in serum LH levels to suggest a reduction in pituitary drive as a cause of the post-prandial fall in testosterone, we cannot exclude this possibility. LH levels fluctuate rapidly, and small changes may have been missed by our relatively infrequent sampling (hourly). Previous studies sampling LH levels every 5 min have reported a reduction in LH pulsatility following an OGTT glucose challenge (Iranmanesh et al., 2012). As such, we cannot be certain if the observed drop in testosterone after meals is related to pituitary suppression or a direct inhibitory effect on the Leydig cell.

Future experiments investigating the impact of other macro-nutrients (carbohydrate and protein) and various types of fats (saturated, MUFA, PUFA) on post-prandial testosterone levels are still required. Furthermore, if our suggestion that GLP-1 is responsible for the post-prandial reduction in testosterone is indeed correct, this link may have important implications for both the endocrine and the fertility management of overweight men, as many of these men are hypogonadal and on GLP-1 agonist therapy (exenatide, litaglutide). While acknowledging this GLP-1/testosterone link is not yet conclusively proven, the recent publication of a case report detailing reversible impairment of spermatogenesis while on litaglutide therapy certain supports this concern (Fontoura et al., 2014).

5 | CONCLUSION

While the observed falls in serum testosterone (25% decline from baseline, 2–3 nmol in absolute terms) are unlikely to be of major clinical significance for the average eugonadal man, these declines are likely to be clinically significant for the obese or older man with low baseline levels of testosterone. These men are likely to be placed into a continuous hypogonadal state during waking hours if they frequently consume meals and snacks high in fat. This will clearly have an adverse impact on both their mental and physical wellbeing, plus possibly their fertility potential. Our results suggest that these men should minimise their fat intake and avoid inter-meal snacking in order to optimise testicular function.

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