Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Medical intelligence | Published 21 March 2016, doi:10.4414/smw.2016.14283

Cite this as: Swiss Med Wkly. 2016;146:w14283

Metabolic syndrome and hypogonadism – two peas in a pod

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Summary

Testosterone deficiency is highly prevalent in up to 50% of men with the metabolic syndrome and type 2 diabetes mellitus. Low testosterone levels in men appear to be an independent cardiovascular risk factor and predictor of subsequent development of the metabolic syndrome. Reciprocally, the metabolic syndrome leads to a decrease in testosterone levels. This review provides an account of the pathophysiological mechanisms in the bidirectional relationship between hypogonadism and body composition, inflammation and insulin sensitivity as well as the effects of testosterone replacement on diverse metabolic parameters.

Key words: *metabolic syndrome; obesity; diabetes mellitus; hypogonadism; testosterone*

Introduction

Obesity and the metabolic syndrome are worldwide pandemics that cause a multitude of comorbid conditions and are associated with an increased risk of cardiovascular disease, which is the leading cause of death and disability worldwide [1]. A large number of studies in men have demonstrated a close association between central obesity, the metabolic syndrome and hypogonadism. Reciprocally, men with hypogonadism share an increased life-time risk for the development of the metabolic syndrome, which suggests a bidirectional relationship between states of insulin resistance and low levels of testosterone [2–6]. Notably, there are substantial data suggesting that low serum testosterone levels are associated with increased risk of atherosclerosis, and cardiovascular morbidity and mortality and that testosterone replacement therapy has beneficial effects on various surrogate parameters for these pathological conditions [7–10]. In epidemiological models testosterone deficiency has been projected to be involved in the development of approximately 1.3 million new cases of cardiovascular disease and 1.1 million of diabetes mellitus, accounting for approximately $190 to $525 billion in inflation-adjusted USA healthcare expenditures over a 20-year period [11]. However, to date there is no large-scale randomised interventional study on testosterone supplementation and cardiovascular outcomes. Against the background of scarce outcome data, testosterone replacement therapy remains controversial in patient populations with a high cardiovascular risk profile and/or history of coronary artery disease.

Testosterone deficiency as a consequence of metabolic syndrome

The metabolic syndrome is a clustering of several cardiovascular risk factors consisting of an accumulation of visceral adipose tissue, dyslipidaemia, insulin resistance and hypertension. Epidemiological studies reveal a fast increase in the prevalence of the metabolic syndrome and obesity globally, reaching pandemic scale [12, 13]. There have been various attempts to define standardised criteria for the diagnosis of the metabolic syndrome. In 1998 the World Health Organization (WHO) developed a definition emphasising the evidence of insulin resistance and at least two of the following four additional factors: hypertension, hyperlipidaemia, obesity, and microalbuminuria [14]. In recent years, there has been harmonisation of the diagnostic criteria, as proposed by the USA National Cholesterol Education Program (NCEP) and the International Diabetes Federation (IDF), in which the need for demonstration of insulin resistance was replaced by increased waist circumference as indicator for abdominal obesity [15, 16].

Testosterone deficiency is a clinical syndrome characterised by low serum testosterone concentrations in combination with a set of symptoms and clinical signs [17]. Clinical symptoms include fatigue, decreased libido, erectile dysfunction, decreased energy, depressed mood and decreased sense of well-being [18, 19]. Objective signs include, among others, changes in body composition, in the form of decreased lean body mass and increased body fat mass (both visceral and total), weight gain, decreased bone density and anaemia [18–21].

Numerous epidemiological studies over the past decades have shown a high prevalence of low testosterone levels in men with the metabolic syndrome [22–24]. Evidence suggests that there is a close inverse relationship between the degree of obesity and serum concentrations of testosterone in men [25, 26]. Since total testosterone depends on sex

hormone-binding globulin (SHBG) levels, one could argue that levels of total testosterone were reduced solely owing to decreased serum levels of SHBG. In fact, the production of SHBG is significantly reduced in insulin resistance states such as the metabolic syndrome, confounding the diagnosis of concomitant hypogonadism [27, 28]. However, Dhindsa et al. demonstrated that, independently from SHBG, free testosterone levels measured by equilibrium dialysis were lower in men with metabolic syndrome and type 2 diabetes mellitus (T2DM) than in men without T2DM [24]. Further cross-sectional studies confirmed the association of low total as well as calculated free testosterone levels in men with the metabolic syndrome compared with healthy control individuals. Indeed, hypogonadism was highly prevalent at up to 50% in men with metabolic syndrome and insulin resistance states [22, 29–33].

As a consequence, weight loss improves levels of both free and total testosterone proportional to the amount of weight lost. Losing 10% of the starting body weight leads to a rise in total testosterone of approximately 2–4 nmol/l, whereas bariatric surgery may even increase levels of total testosterone by up to 10 nmol/l [34–39].

Metabolic syndrome in consequence of testosterone deficiency

Longitudinal population studies have shown that low levels of total and free testosterone, as well as SHBG, are associated with an increased risk for the development of the metabolic syndrome [2–6]. Laaksonen et al. conducted a population-based cohort study of 702 middle-aged men who at baseline had neither diabetes nor the metabolic syndrome. After 11 years of follow-up, men with total testosterone, calculated free testosterone and SHBG levels in the lower quartile had a twofold to threefold increased risk of developing the metabolic syndrome when compared with men with higher testosterone levels (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.5–3.4; 1.7, 1.2–2.5; and 2.8, 1.9–4.1, respectively), even after adjustment for potential confounders such as cardiovascular disease, smoking, alcohol intake and socioeconomic status [40]. The Massachusetts Male Aging study (15-year follow-up) of 950 healthy, aging men revealed that lower concentrations of total testosterone and SHBG were predictive of the development of the metabolic syndrome [3]. Likewise, the NHANES III study has found an increased risk of the metabolic syndrome and T2DM in men with low levels of testosterone, even in men who were not obese at the beginning of the study [5]. In view of that, low levels of testosterone seem to be an independent risk factor and biomarker for the future onset of the metabolic syndrome.

Furthermore, recent studies have revealed that men with inherited pathologies of hypogonadism, such as Klinefelter's syndrome, share a fourfold increased prevalence of developing metabolic syndrome, obesity and insulin resistance compared with that of age-matched controls [41, 42]. In contrast, men with Klinefelter's syndrome have traditionally been described as tall, slim, narrow shouldered and with small testes, which may be one explanation why approximately 75% of the expected numbers of men with Klinefelter's syndrome remain undiagnosed [43]. An age-matched Danish epidemiological study on 781 men bearing Klinefelter's syndrome showed that patients with Klinefelter's syndrome were prone to develop T2DM, and had a 40% increase in risk of mortality with an average loss of 2 years of life expectancy in comparison with age-matched controls [44].

In a study conducted by Yialamas and colleagues in men with idiopathic hypogonadotropic hypogonadism, testosterone substitution was acutely discontinued and the patients returned to initial androgen deficiency status. Thereafter, they exhibited an acute reduction in insulin sensitivity within 2 weeks as serum testosterone levels decreased from 18.36 ± 2.26 to 0.97 ± 0.28 nmol/l and fasting insulin levels, as well as the values of the homeostatic model assessment of insulin resistance (HOMA-IR), significantly increased [45]. This may suggest acute effects of testosterone on insulin secretion and resistance, as the findings were not confounded by changes in body composition.

In addition, several studies have revealed that androgen-deprivation therapy, which causes profound testosterone deficiency, in patients with advanced prostate cancer leads to an increase in BMI and a decline in lean body mass when compared with prostate cancer patients who underwent local surgery and/or radiation therapy but had not received androgen-deprivation therapy [46].

In summary, the above described evidence supports the hypothesis of a bidirectional relationship between the metabolic syndrome and low levels of testosterone.

Hypogonadism and cardiovascular and all-cause mortality

There is increasing evidence indicating that high endogenous testosterone concentrations in men are associated with a more favourable cardiovascular disease risk factor profile. Men with high endogenous testosterone levels have higher high-density lipoprotein (HDL) cholesterol concentrations [47, 48], increased insulin sensitivity [23], reduction of abdominal fat [49] and lower blood pressure [50]. A meta-analysis by Araujo et al., which investigated studies of 16,184 community-dwelling men with a mean follow-up of 9.7 years, found that low levels of testosterone were associated with an increased risk of cardiovascular mortality, with a hazard ratio of 1.35 (95% CI, 1.13–1.62; p <.001) [7]. Further meta-analytical studies and observational prospective studies have likewise consistently shown that low levels of testosterone predict both all-cause and cardiovascular mortality in men [8–10].

A European prospective population study (EPIC–Norfolk study) investigated levels of endogenous testosterone and all-cause and cardiovascular mortality in 11,606 healthy men aged 40–79 years over a follow-up period of 6–10 years. Endogenous testosterone concentrations at baseline were inversely related to all-cause mortality, cardiovascular mortality and cancer-related deaths (p <0.001) after correcting for other comorbidities. An increase of 6 nmol/l in serum testosterone (≈1 standard deviation) reduced the risk of mortality by 14% over the study period [51]. In a longitudinal cohort study of 930 men with coronary artery disease with a follow-up of 6.9 ± 2.1 years, mortality in patients with testosterone deficiency was 21%, compared

with 12% in patients with normal levels of testosterone [52]. Moreover, erectile dysfunction, a common symptom of hypogonadism, has been shown to be strongly predictive for subsequent cardiovascular morbidity and mortality, and has been identified as a sentinel symptom of systemic atherosclerotic disease [53]. Nevertheless, whether low concentrations of testosterone are simply an association with cardiovascular risk and severe morbidity, or depend on causal effects, awaits future large-scale endpoint trials.

Effects of testosterone replacement therapy

Established benefits of testosterone replacement therapy (TRT) in hypogonadal men include improved sexual desire and function [54, 55], improved energy, mood and vitality [56, 57]. There are numerous interventional studies that have shown beneficial effects of testosterone supplementation on various cardiovascular risk factors, surrogate markers and symptoms of the metabolic syndrome [58]. A randomised, placebo-controlled interventional trial investigated the effects of intramuscular testosterone undecanoate in 184 middle-aged men with hypogonadism and metabolic syndrome. After 30 weeks of testosterone administration there were significant decreases in HOMA-IR, waist circumference, BMI, leptin and inflammatory cytokines such as interleukin (IL)1β, tumour necrosis factor-α (TNFα) and C-reactive protein (CRP) [59]. A randomised, placebo-controlled trial was performed to investigate the effects of transdermal preparations of testosterone on abdominal fat mass in 30 obese men. In the group that received testosterone, visceral fat mass, as measured by computed tomography, decreased significantly without notable changes in other fat depots. Further effects of TRT were decreased plasma triglycerides, cholesterol and fasting blood glucose concentrations, as well as diastolic blood pressure [60]. Further interventional trials confirmed the metabolic effects of TRT, reporting increased lean mass [57, 61–64], decreased waist circumference [65–67], reduced total body fat mass [57, 62–64, 68], increased bone mineral density [66, 69, 70], improved insulin sensitivity [68, 71–73] and reduced glycated haemoglobin levels [71, 74–76] in men with metabolic syndrome and T2DM (table 1). Several studies have also reported that TRT had a beneficial anti-ischaemic effect in men suffering from coronary artery disease and angina pectoris. These effects were shown not only in hypogonadal [77], but also in eugonadal men [78–81]. In a large retrospective cohort study on 83 010 male veterans with documented low testosterone levels, those who received TRT with resulting normalisation of testosterone levels had significantly reduced risks of all-cause mortality, myocardial infarction and stroke [82]. However, a recent randomised controlled trial involving 308 old men (age >60 years) with low or low-normal testosterone levels, did not show beneficial effects of testosterone administration for 3 years versus placebo on subclinical atherosclerosis progression [83].

Despite these data on favourable metabolic outcomes of TRT, there has lately been growing concern regarding its effects on cardiovascular mortality and morbidity, in particular considering the widespread and increasing use of testosterone supplementation over past decades [84]. Two recent retrospective studies, a meta-analysis and a prematurely terminated interventional prospective trial, which reported increased cardiovascular risks in men on TRT, have contributed to the uncertainty and have gained considerable public and media attention [85–88]. However, to date there are no large, adequately powered, long-term, randomised placebo-controlled clinical trials regarding the effects of TRT with cardiovascular mortality as the primary endpoint. Though, numerous studies indicate that low testosterone concentrations are associated with increased cardiovascular risk and mortality and that TRT actually may have benefits. Nonetheless, given the large number of men potentially eligible to receive TRT, a thorough assessment of the risk-benefit ratio is crucial, as most treated men would be expected to require long-term testosterone therapy. Caution is especially required in elderly men with a high cardiovascular risk profile and/or history of coronary artery disease [87]. TRT should be very restrictively initiated in patients at high risk of prostate cancer, haematocrit above 50%, untreated severe obstructive sleep apnoea and severe prostate hyperplasia. Similarly caution is required in patients with prostate cancer. Once TRT has been initiated, with any of the approved formulations, chosen on the basis of the patient's preference, the target should be to raise testosterone levels to mid-normal range [89].

Based on available data, consensus guidelines do not recommend population screening but do recommend case detection in patients at high risk for hypogonadism (e.g. T2DM) plus symptoms suggestive for hypogonadism [89, 90].

Possible pathophysiological mechanisms

Numerous different pathophysiological mechanisms have been proposed as causative for the development of hypogonadism in individuals with metabolic syndrome and obesity.

Inactivation of testosterone in visceral adipose tissue

While women are generally characterised by gynoid fat distribution (gluteal-femoral region), men tend to accumulate adipose tissue in the abdomen (android fat distribution) [91, 92], especially in form of visceral adipose tissue (VAT) [93]. In fact, there is growing evidence that sex-related differences in the prevalence of cardiovascular disease may be explained by the amount of VAT [94]. In a prospective study conducted by Larsson and colleagues, VAT was a strong predictor of cardiovascular disease and death even in non-obese individuals [95]. It is well-established that testosterone is inactivated in the abdominal adipose tissue of men, as indicated by high expression of inactivating enzymes [96, 97]. Testosterone itself though seems to be a key modulator of body fat distribution. Woodhouse et al. have shown a dose-dependent decrease of VAT volume with increasing testosterone enanthate doses in an interventional trial on healthy young men [98]. Decreased testosterone production in obese men therefore promotes additional fat deposition, contributing to a vicious cycle of fat accumulation.

Oestrogen-mediated negative feedback

Several studies have implicated the hypothalamic-pituitary-testicular (HPT) axis, being not only regulated by direct negative feedback of testosterone on the hypothalamus and pituitary gland [99, 100], but also by inhibitory feedback of oestradiol [101, 102]. In 1979 Schneider et al. described twofold elevation of serum oestrone and 17-β-oestradiol levels in a group of morbidly obese men and the urinary excretion rates of these hormones highly correlated to the degree of obesity [103]. Consequently, treatment of obese men with an aromatase inhibitor, in order to prevent conversion of testosterone to oestradiol, resulted in sustained resolution of hypogonadotropic hypogonadism with normalisation of serum luteinising hormone and testosterone concentrations [104–106]. As a result of additional stimulatory effects on follicle-stimulating hormone secretion, aromatase inhibitors could be of benefit in the treatment of infertility in obese men [107]. However, excessive reduction of oestradiol levels by aromatase inhibition may otherwise adversely affect bone metabolism.

Inflammatory hypothesis

Adipose tissue, in particular VAT, is highly associated with elevated levels of inflammatory mediators, since cytokines appear to play a major role in adipose tissue metabolism [108, 109]. Cross-sectional and prospective studies have described elevated circulating levels of acute-phase proteins, such as CRP, fibrinogen, plasminogen activator inhibitor, serum amyloid A, and a variety of cytokines and chemokines (e.g. IL-6 and IL-1β), as a sign of a state of chronic inflammation in obesity and T2DM [110–112]. Plasma CRP levels reflect the amount and activity of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6,

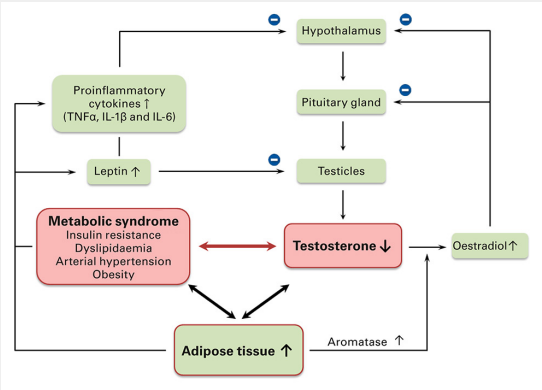

Figure 1

Pathophysiological interplay between adverse metabolic parameters, adipose tissue and testosterone deficiency. Adipose tissue as a pivotal component of the pathophysiological interplay leads to increased release of inflammatory mediators (TNF-α, IL-1β and IL-6) and leptin which cause dysfunctions of the hypothalamic-pituitary-testicular axis and result in decreased testosterone production. Increased activity of aromatase in adipose tissue enhances the conversion of testosterone to oestradiol which exerts negative feedback effects on both hypothalamus and pituitary gland. Consecutive testosterone deficiency promotes an increase in fat mass and worsening of metabolic surrogate parameters, demonstrating the bidirectional relationship.
TNF-α = tumour necrosis factor α;
IL-1β = interleukin 1β; IL-6 = interleukin 6

Table 1: Most important randomised controlled trials on metabolic outcomes of testosterone replacement therapy.

	Study								
	Wang 2000 [61]	Boyanov 2003 [130]	Kapoor 2006 [75]	Heufelder 2009 [72]	Aversa 2010 [131]	Kalinchenko 2010 [59]	Srinivas-Shankar 2010 [57]	Jones 2011 [71]	Hackett 2013 [56]
No. patients	227	48	24	32	50	184	274	220	190
Age (years)	60	57	64	57	58	52	73	60	62
Indication	Hypogonadism	T2DM	T2DM	MetS and newly diagnosed T2DM	MetS	MetS	Frailty and hypogonadism	T2DM and/or MetS	T2DM
Inclusion TT (nmol/l)	≤10.4	<12	<12	<12	≤11	<12	<12	≤11	<12
Mean baseline TT (nmol/l)	8.3	9.6	8.6	10.5	8.4	6.7	11.0	9.4	9.1
Testosterone treatment	TDT 50 / 100 mg/d / TP 5 mg/d	TU oral 120 mg/d	TE i.m. 200 mg 2 weekly	TDT 50 mg/d	TU i.m. 1 000 mg 12 weekly	TU i.m. 1 000 mg 12 weekly	TDT 50 mg/d.	TDT 60 mg/d	TU i.m. 1,000 mg 12 weekly
Duration (weeks)	26	12	12	52	52	30	26	52	30
Mean baseline BMI (kg/m^2)	28	31	33	NC	31	35	28	32	33
Mean baseline HbA_{1c} (%)	NC	7.3	7.3	7.5	5.7	NC	NC	7.3	7.6
Effect on HbA_{1c} (%)	NC	–1.8 (p <0.05)	–0.4 (p <0.05)	–0.8 (p <0.05)	–1.1 (p <0.05)	NC	NC	–0.5 (NS)	–0.4 (p <0.05)
Further outcomes	↑LBM, ↓body fat,	↓BW, ↓WHR, ↓body fat	↓IR, ↓WC, ↓WHR, ↓body fat, ↓TC	↓IR, ↓WC, ↓TG, ↑HDL-C	↓IR, ↓WC, ↓CRP, ↓body fat	↓IR, ↓WC, ↓BMI, ↓leptin, ↓CRP, ↓TNF-α, ↓IL-1β	↑LBM, ↓body fat	↓IR, ↓WC, ↓body fat	↓WC, ↓TC

BW = body weight; CRP = C-reactive protein; HbA1c = glycated haemoglobin; HDL-C = HDL cholesterol; i.m. = intramuscular; IR = insulin resistance; LBM = lean body mass; LDL-C = LDL cholesterol; MetS = the metabolic syndrome; NC = not checked; NS = not significant; T2DM = type 2 diabetes mellitus; TC = total cholesterol; TDT = transdermal testosterone; TE = testosterone esters; TG = triglycerides; TNF = tumour necrosis factor α; TP = testosterone patch; TT = total testosterone; TU = testosterone undecanoate; WC = waist circumference; WHR = waist:hip ratio.

which are known to be implicated in the process of atherosclerotic plaque formation and acute coronary syndrome [113, 114]. Obesity and the metabolic syndrome are thus considered chronic low-grade inflammatory states [115]. Accordingly, it has been shown that weight reduction, resulting from nutritional intervention and bariatric surgery significantly improves the systemic and adipose tissue inflammatory states associated with the metabolic syndrome [116–118].

Increased fat mass is associated with augmented release of adipocytokines and pro-inflammatory cytokines which in turn have been described as having an inhibitory effect on the hypothalamic-pituitary-gonadal axis, ultimately leading to hypogonadism [18, 119, 120]. The proinflammatory mediators are not only produced locally by macrophages in white adipose tissue [115, 116], but also directly in the hypothalamus [119, 121, 122], impairing hypothalamic function. Morelli et al. provided evidence of activated proinflammatory pathways within the hypothalamus and decreased gonadotrophin-releasing hormone secretion in rabbits with high fat diet-induced metabolic syndrome and consecutive hypogonadotropic hypgonadism. [119]. This complex pathophysiological interplay is termed the hypogonadal-obesity-adipocytokine hypothesis, which describes the bidirectional relationship between low levels of testosterone and the metabolic syndrome (see fig. 1) [22, 23, 123].

It has long been recognised that testosterone has immunemodulating properties. Cell cultures of human monocytes, macrophages and endothelial cells incubated with testosterone show attenuated production of proinflammatory cytokines (TNF-α, IL-1β and IL-6) [124–126]. In a placebo-controlled trial on hypogonadal men, testosterone supplementation resulted in a significant decrease of the proinflammatory mediators TNF-α and IL-1β, accompanied by an increase of the anti-inflammatory cytokine IL-10 [127]. In another randomised controlled trial (Moscow study) of 184 men suffering from both the metabolic syndrome and hypogonadism, testosterone treatment for 30 weeks with testosterone undecanoate significantly decreased the inflammatory markers IL-1β, TNF-α and CRP [59]. Besides its action on cytokines, testosterone treatment in hypogonadal men significantly decreased plasma adiponectin [128] and leptin levels [129].

Conclusion

In conclusion, low testosterone levels in men appear to be an independent cardiovascular risk factor closely associated with the metabolic syndrome. Reciprocally, the metabolic syndrome leads to a decrease in testosterone levels, suggesting a bidirectional relationship. Testosterone treatment has beneficial effects on diverse surrogate parameters of the metabolic syndrome; however, evidence concerning the effects of testosterone treatment on cardiovascular events or mortality is still lacking. From a clinical perspective, testosterone levels potentially add predictive risk information beyond obesity and may be relevant in guiding clinical risk stratification. In accordance with consensus guidelines, we do not recommend population screening, but recommend case detection in patient populations with high prevalence of hypogonadism (e.g. T2DM) and symptoms suggestive of testosterone deficiency. Future studies are required to elucidate the effects of testosterone on cardiovascular morbidity and mortality and to shed light on the pathophysiological mechanisms in the bidirectional interplay between testosterone and the metabolic syndrome.

Disclosure statement: The authors have no competing interests to disclose.

Contributions: FE and MCC wrote the manuscript and approved the final version of this manuscript.

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Figures (large format)

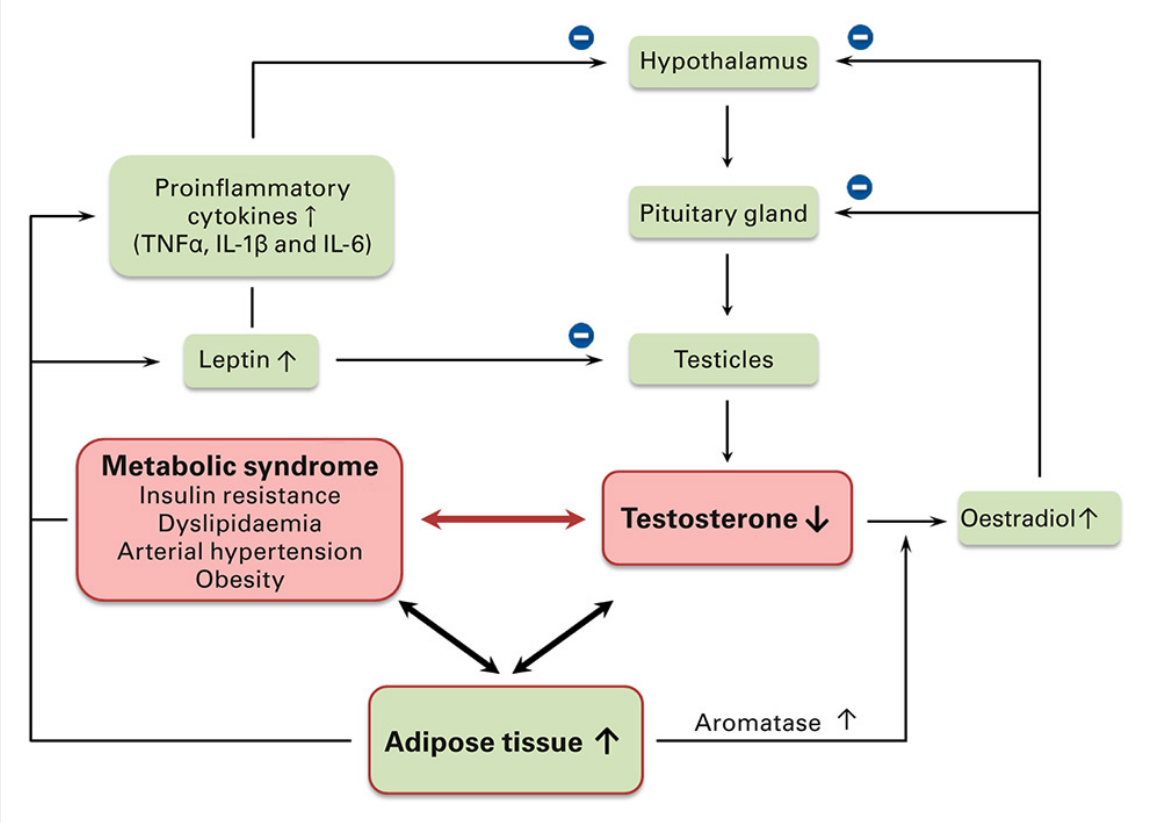

Figure 1

Pathophysiological interplay between adverse metabolic parameters, adipose tissue and testosterone deficiency. Adipose tissue as a pivotal component of the pathophysiological interplay leads to increased release of inflammatory mediators (TNF-α, IL-1β and IL-6) and leptin which cause dysfunctions of the hypothalamic-pituitary-testicular axis and result in decreased testosterone production. Increased activity of aromatase in adipose tissue enhances the conversion of testosterone to oestradiol which exerts negative feedback effects on both hypothalamus and pituitary gland. Consecutive testosterone deficiency promotes an increase in fat mass and worsening of metabolic surrogate parameters, demonstrating the bidirectional relationship.
TNF-α = tumour necrosis factor α; IL-1β = interleukin 1β; IL-6 = interleukin 6