

Review Article

Hypogonadism in Metabolic Syndrome: Cause or Consequence? Lesson from Genetic Hypogonadism and Disorders of Gender Identity

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Low T or True Male Hypogonadism

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Abstract

Hypogonadism is frequently associated with metabolic syndrome and testosterone levels correlate with parameters which are part of the cluster defining the syndrome itself. Different studies suggest a positive role of testosterone replacement therapy, but different aspects (including the definition of hypogonadism, especially in aging male, and the modality of treatment) still require confirmation. A model to explore the role of testosterone in influencing the beginning and course of the syndrome is early hypogonadism, due to genetic causes (both primary or secondary hypogonadism); moreover, few data are reported in transsexuals, despite the debate on biological bases of gender identity, and the influence of pharmacological treatment before and after surgical sex reversal. We present here a review of literature and some paradigmatic cases, that seem to reinforce the concept of hypogonadism as a causative factor of metabolic syndrome.

ABBREVIATIONS

MS: Metabolic Syndrome; T: Testosterone; KS: Klinefelter's Syndrome; E2: Estradiol; SHBG: Steroid Hormone Binding Globin; hrGH: Human Recombinant Growth Hormone

BACKGROUND

Metabolic syndrome (MS) is defined as a constellation of symptoms and organ involvement leading to augmented cardiovascular risk and recognizing insulin resistance as a main mechanism, even if small differences are present in different classifications [1-3]. Central obesity, hepatic steatosis and intracellular fat in muscle cells as well as lack of exercise and genetic factors precipitate the development of insulin resistance.

Hypogonadism is now recognized as a component of the

syndrome, due to the negative effects of hyperinsulinemia on testicular function and confirmed by clinical and epidemiological observations on the link between low levels of testosterone (T) and different components of MS [4-6], supported by studies in late-onset hypogonadism, as recently reviewed [7].

In vitro studies showed a stimulatory effect of insulin on testosterone production in both rat- and mouse-Leydig cells [8,9], but Leydig cells may become insulin resistant as well as other cells in hyperinsulinemic states. Moreover, young insulin resistant men produced less testosterone when stimulated with human choriogonadotropin (hCG) compared with non-obese men [10]. Lower levels of testosterone, free-testosterone and steroid hormone binding globin (SHBG) have been found in both obese [11] and diabetic men [12,13]. Hyperinsulinemic state inhibits the hepatic production of SHBG [14,26]; several

other mechanism have been hypothesized: direct inhibition of testicular production by insulin and leptin, elevation of estrogen concentrations and alterations in the secretion of gonadotropins [15-19]. It has been suggested that SHBG levels could be used as a specific marker of insulin resistance [20].

Despite all the epidemiological findings on correlation between low T and metabolic diseases, Hypogonadism has also been hypothesized to have a causative role in the development of MS: low levels of T can predict future abdominal adiposity [21], insulin resistance, metabolic syndrome and type 2 diabetes [21-34]. Testosterone influences the commitment of pluripotent stem cells and inhibits the development of preadipocytes; moreover insulin sensitivity of muscle cells is increased by augmenting mitochondrial capacity and fostering expression of oxidative phosphorylation genes [35]. A vicious circle has been therefore hypothesized [36-38], Testosterone is converted to 17- β -estradiol (E2) by the enzymatic activity of aromatase in adipose tissue. Thus, with higher adipocyte expression of aromatase comes a subsequent reduction of circulating testosterone. Falling testosterone promotes increasing adipocyte number and fat deposition, which gradually leads to a further lowering effect on testosterone levels. The excess of E2 inhibits the production of GnRH and this explain why the physiological feedback cannot compensate the T reduction in this situation; this is the so called hypogonadal-obesity-adipocytokine hypothesis [30]

Furthermore increased abdominal adiposity aggravates overall and Leydig cell insulin sensitivity and causes worse testicular function.

Also experimental models suggest that GnRH analog-induced hypogonadotropic hypogonadism induce a dramatic increase in visceral adiposity [39]. This phenomenon could be of fundamental relevance in the population of prostatic carcinoma, who can have increased risk for MS due to age and pharmacological treatment [40], in fact complete T deprivation, as seen in androgen deprivation therapy (ADT), has adverse impact on risk factors for cardiovascular disease defining MS [41]

This topic is also particularly relevant, when considering the morbidity and mortality related to hypogonadism. From cross-sectional studies in healthy men, lower plasma total testosterone levels seem to be associated with hyperinsulinemia, decreased glucose tolerance, and a higher level of cardiovascular risk factors [42-43]. A relatively low blood concentration of testosterone in older men might have adverse effects promoting atherosclerosis and explain the higher incidence of coronary heart disease in the male [44]. Therefore, male hypogonadism can be associated with a metabolic syndrome as well as increased risk for cardiovascular disease, despite discrepant effects of testosterone on cardiovascular system have been described [45,46].

A possible link is related to oxidative stress, since reduced antioxidant defences have been demonstrated in acquired male hypogonadism and beneficial effects of testosterone replacement therapy have been showed [47].

To explore the role of Low Testosterone in determining Metabolic Syndrome, an interesting model could be represented by hypogonadism on genetic basis, in which the effects of low testosterone are apparent in pubertal period (i.e. not influencing

sexual differentiation but the testicular function in following periods); moreover, the topic has been inadequately assessed in patients with alterations in gender identity. It has been speculated that in this patients an hypogonadism during sexual differentiation could have a causative role on the alteration of gender identity.

The question is really complex; in the first case for the rarity of syndromes, making difficult to perform longitudinal studies, both at the moment of the diagnosis and during testosterone replacement therapy; in the second group, for the usual confounding factor of steroid assumption, both before and after sex reversal surgical procedure, but especially for the discussed interaction between biological and psychological factors in psychosexual differentiation process.

PATIENTS

Case 1

A young 20-ys old male affected by hypogonadotropic hypogonadism, with pubertal delay with small testes and low grade virilization. His karyotype was 46 XY, but a point mutation of codon 260 [Thyr 260 Met] in exon 2 of PROKR2 gene was discovered in the proband and his father [48]. He had a III grade obesity, coupled with hypogonadism; the repeated GnRH test showed an absent gonadotropin response; moreover, the testis was scarcely responsive to hCG administration (basal 0.1, after 72 h 1.03 ng/ml). In the investigation of the pituitary function a GH deficiency was also observed (peak after GHRH plus arginine administration 3.04 ng/ml, less than the cut-off for obese subjects) [49]; in fact a virilization was observed with a combination of gonadotropin and hrGH administration.

Case 2

A 41-year-old man, already known by our genetics center for a 45,X chromosome constitution and a normal male differentiation [50] came back with requests on his sexual and fertility potential. At the first observation (at 20 ys), high-resolution analysis of prometaphase chromosomes revealed additional euchromatic material on a 15-p chromosome, and in situ hybridization with Y-specific probe pDP105 gave positive signal on 15p11.2, suggesting at (Yp; 15p) translocation. This case was re-examined at clinical, genetic, hormonal, and metabolic level. The new Fluorescence in situ hybridization analyses on metaphase chromosomes showed that the derivative chromosome 15 was characterized as der (15) (Ypter-->q11.21::15p11.2-->qter) [51]. Hypergonadotropinemic hypotestosteronemia was diagnosed, coupled with azoospermia; he had a I grade obesity with android characteristic.

Case 3

A 40ys old was hospitalized for liver disease of unknown origin and arterial hypertension. Hypergonadotropic hypogonadism was present, together a clinical metabolic syndrome. Genetic studies showed mosaicism 47,XXY(17)/46,XX(83). Metformin therapy was started with good clinical and metabolic response.

Case 4

A 30 ys old male, with classical Klinefelter's Syndrome (KS) phenotype, was hospitalized for osteopenia and multinodular

goiter; karyotype confirmed the diagnosis; he showed also psychological characteristics of mental retardation. On request of his wife, he gave consent to heterologous insemination and is actually father of 4 children. He is under replacement therapy with enantate testosterone with good response at clinical level and no complications.

Case 5

A 32-ys old men, with a surgical sex reversal from female to male at the age of 26 ys (in two times, first bilateral mastectomy and then hysterioansectomy, followed by the complication of an ileal volvulus) came to our observation for the monitoring of replacement therapy, due to some problems, such as headache. At this time he had good testosterone levels, with excess of aromatization (T 4.48 ng/ml and E2 60 pg/ml). He performed intense physical activity and had a normal body weight with good presence of lean body mass. No familiar history for diabetes mellitus was present.

Case 6

A 31-ys old woman, with a surgical sex reversal from male to female (in two times, at the age of 26 and 28), came to our observation for the suspicion of a pituitary adenoma. She could not perform estrogen replacement therapy due to a venous thrombosis in inferior leg but had been treated with cyproterone acetate. Repeated MRI showed pituitary hyperplasia, without evidence of focal lesions: PRL levels were normal both as basal levels (14 ng/ml) and in dynamic studies (peak after TRH 200 ug iv 112.2 ng/ml). She had grade I obesity and underwent metabolic evaluation in our center.

The Table 1 shows the glycemic and insulinemic values after standard oral glucose tolerance test (75 g) showing in all cases an elevated peak insulin response, with normal glucose values; a marked insulin-resistance was present in case 3.

DISCUSSION AND CONCLUSION

No statistic conclusion can be drawn from this presentation and it is not our aim to do so, but to strengthen the hypothesis that long-term hypogonadism, even if mild, can contribute to the development of MS.

Epidemiological observations suggest a relationship between hypogonadism and cardiovascular diseases. Recent studies have shown that men with Coronary Artery Disease (CAD) have significantly lower concentrations of bioavailable testosterone than men with normal angiograms [52]. The prevalence of

hypogonadism in a population of men with CAD is about twice that observed in the general population [53]. Hypotestosteronemia is associated with an atherogenic lipid profile (elevated low-density lipoproteins and triglycerides, decreased high-density lipoprotein), high fibrinogen with a hypercoagulable state, an increase in insulin resistance and hyperinsulinemia, and higher systolic and diastolic blood pressure [54]. Experimental data also reinforce the concept of a positive effect of exogenous testosterone administration. In an animal model, castration increased aortic atheroma formation, and testosterone replacement ameliorated this effect [55]. In addition, testosterone has direct vasoactive properties, which directly affect the vascular smooth muscle, not mediated by the nuclear androgen receptor, in that the effect is too rapid and is not reduced by flutamide, a nuclear androgen receptor blocker [56-58]. When testosterone is instilled into the left coronary artery, vasodilatation ensues and coronary flow increases [59]. More importantly, acute administration of intravenous testosterone improves exercise tolerance and reduces the angina threshold in men with CAD [60,61]. These positive effects seem to be related to the nongenomic action of testosterone on vascular smooth muscle cells [62,63]. Oxidative stress can underlie the above-mentioned clinical conditions. As demonstrated by statistical metaanalysis, low testosterone and androgen deficiency were associated with an increased risk of developing a metabolic syndrome over time [64]. However, the pathophysiological details of these changes in atherosclerosis [65] and implications in testosterone replacement therapy [66] are still under investigation.

Moreover, the role of gonadal steroids in the regulation of systemic antioxidants is not known. We therefore investigated the role of CoQ10, a lipidic antioxidant [67], and the total antioxidant capacity (TAC) of blood plasma in secondary male hypogonadism [47]. Conflicting results do not allow unequivocal conclusions on the role of androgens in coronary artery disease, as in important reviews [44,68]. Many confounding factors contribute in making this question very complex. Endogenous androgen levels depend on different mechanisms, such as gender-specific gene expression, distribution of body fat, vascular factors, and adaptation to aging. Similarly, studies on exogenous androgen administration are influenced by dose, route of administration, duration of treatment, and again patients variables such as gender, age, and condition of recipients. The knowledge about the role of androgens in CV system is continuously growing and there is still not a clear overview on it. Therefore, data on antioxidant regulation by steroids can be useful to clarify molecular mechanisms of testosterone action.

Table 1: Metabolic parameters in our patients.

		Glucose (mg/dl)			Insulin (μU/ml)			METFORMIN
		0'	60'	120'	0'	60'	120'	
Case 1	Secondary hypogonadism	89	152	76	20.7	148.6	107.5	Yes
Case 2	45 X, male	89	171	128	14.3	104.7	89.9	Yes
Case 3	Mosaic Klinefelter	84	174	142	52.5	733.7	791.1	Yes
Case 4	Klinefelter's syndrome	90	150	135	18	135	90	No
Case 5	F to M transsexual	71	195	115	2.7	90.9	25.8	No
Case 6	M to F transsexual	81	136	75	16.3	82.7	12.0	No

Testosterone therapy reported values toward the same levels observed in normogonadic patients, with a significant increase in CoQ10 concentrations. TAC, expressed as LAG (latency phase before the appearance of radicals in a tested sample after induced oxidative stress) [68,69], which exhibited a trend toward lower values in hypogonadal subjects, also increased significantly with testosterone treatment [47].

These previously reported data reinforce the concept that hypogonadism could represent a condition of oxidative stress. Although the small number of patients studied does not allow definitive conclusions, lower levels of CoQ10 were discovered in isolated hypogonadal compared with normogonadal patients. To our knowledge, we for the first time reported of the testosterone effect on antioxidant systems in humans. Further studies can clarify the relationship of this datum with the increased cardiovascular risk in such patients.

Different studies report metabolic alterations in KS (Table 2, with references indicated in square brackets), as reviewed by Bojesen et al. [38].

The clinical impact of the physiopatology of hypogonadism and MS obviously concern the possible role of T replacement therapy and its beneficial effects, not only on sexual aspects (as originally believed) but also on anthropometric and metabolic parameters. A number of studies have been performed (Table 3), even if the heterogeneity of treatment (duration and/or doses, kind of replacement therapy, classes of patients and controls, and so on) does not allow definitive conclusions [70].

Among the reported study, the one from Jones et al. (the last one) is particularly significant, due to the number of involved patients and the methodology (prospective, randomized, double-blind, placebo-controlled; it was conducted in hypogonadal men with type 2 diabetes and/or MS, showing after 6 month period, a beneficial effect of transdermal T replacement therapy on insulin resistance, total and LDL-cholesterol, Lpa and sexual health [82]. A meta-analysis, with a comprehensive search of randomized clinical trials, was published by Isidori et al. [95]: overall, 1083 subjects were evaluated (625 randomized to T, 427 to placebo and 31 to observation; T treatment produced a reduction of total body fat, increase in fat free mass, decrease in total cholesterol, improvement of bone mineral density (BMD) at the lumbar spine;

on the contrary, an heterogenous response was observed on muscle strength, HDL-cholesterol, femoral neck BMD, depending on the dose/type of T employed. For these Authors, further interventional studies were justified by the encouraging results. However a conclusion will be drawn with long-term evaluation, since caution has been suggested following a recent study showing an increase in cardiovascular event in testosterone-treated, frail, elderly men [96]. The effects of sexual steroids on renal-vascular system are complex: conflicting data have been report. While acute T administration seems to decrease vascular tone, the long-term net effect seems to be vasoconstriction, due to upregulation of thromboxane A2 expression, norepinephrine synthesis, angiotensin II expression, endothelin action [97]. The accurate choice of candidates to this treatment and an overall consideration of anthropometric, metabolic, cardiovascular, skeletal and sexual parameters is recommended.

Also our patients 45,X male previously reported allowed different considerations on the relationship between hypogonadism and MS [52]. The presence of a male phenotype in a 45, X-chromosome constitution is a very rare condition [98-108], but no paper describes the natural history of such patients. Despite Y-material traslocation, allowing normal male differential, in our patient small testes were observed in adult age, with primary hypogonadism. The interest of this case, therefore, strongly reinforces the metabolic role of testosterone and suggests that hypogonadism could cover a role in the development of a metabolic syndrome in our patient.

Despite conflicting results do not allow unequivocal conclusions on the role of androgens in coronary artery disease, as reviewed by Wu and Liu [46,68], the reported case underlines the need of metabolic, and not only sexual, evaluation in gene-related hypogonadism.

Finally, the role of biological factor in transexualism is still far to be elucidated. Most attempts to identify biological underpinnings of gender identity and sexual orientation in humans have investigated effects of sex steroids, so pivotal in the differentiation of the genitalia, showing strong parallels between animals and the human. The information on humans is derived from the so-called 'experiments of nature', clinical entities with a lesser-than-normal androgen exposure in XY subjects and a higher than normal androgen exposure in XX subjects. Prenatal

Table 2: Metabolic alterations in patients with Klinefelter's syndrome.

Author	Year	Number of patients	Metabolic alteration
Klinefelter [71]	1942		Original description of abdominal obesity
Jackson et al [72]	1966	8 KS	1/8 with mild diabetes
Becker et al [73]	1966	50 KS	5/50 with diabetes
Zuppinger et al [74]	1967	24 KS	Overt diabetes in 2 and glucose intolerance in 4
Nielsen et al. [75]	1969	31 KS	Increased prevalence of glucose intolerance (39%)
Pei et al. [76]	1988	7 KS/7 HH	Elevated fasting insulin vs controls
Yesilova et al. [77]	2005	13 KS	Increased fasting insulin, but not altered insulin sensitivity
Bojesen et al [78]	2006	70 KS	Half of the patients with ATPIII criteria of MS
Ishikawa [79]	2008	60 KS	34% prevalence of MS, in comparison with azoospermic controls
Aksklaede et al. [80]	2008	24 KS	Increased fat mass using DXA
Bojesen et al. [81]	2006	71 KS	Striking difference in body composition without difference in BMI

Table 3: Studies on testosterone treatment.

Author	Year	Number of patients	Duration of treatment	Metabolic effects
Marin et al. [82]	1992	23 obese men	8 months	Reduction in visceral obesity and increase in insulin sensitivity
Mauras et al. [83]	1998	6 healthy lean men, before and after GnRH analog	10 weeks	Induced Hypogonadism caused increase in fat mass and decrease in REE, lean body mass, muscle strength
Snyder et al. [84]	1999	108 > 65 ys men (T or placebo)	36 months	Increase in lean body mass and decrease in fat mass
Bhasin et al. [85]	2001	61 eugonadal men (GnRH plus graded T)	20 weeks	Dose-dependent increase in free-fat mass
Singh et al. [86]	2002	61 eugonadal men (GnRH plus graded T)	20 weeks	No difference in insulin resistance
Steidle et al. [87]	2003	406 hypogonadal men	3 months	Increase in lean body mass and decrease in fat mass
Wittert et al. [88]	2003	76 healthy > 60 ys	1 year	Increase in lean body mass and decrease in fat mass
Wang et al. [89]	2004	163 hypogonadal men	42 months	Increase in lean body mass and decrease in fat mass
Page et al. [90]	2005	77 hypogonadal men (T with placebo or finasteride)	36 months	Increase in lean body mass and decrease in fat mass
Kapoor et al. [91]	2006	24 hypogonadal men with type 2 diabetes	3 months	Decrease in insulin resistance and improvement of glycemic control
Bojesen et al. [81]	2006	35 KS	Treated at the moment of the study	Non significant trend in reduction in truncal fat, total cholesterol, fasting plasma glucose and leptin
Mancini et al. [48]	2008	10 secondary hypogonadism	6 months	Increase in total antioxidant capacity
Caminiti et al. [92]	2009	70 Elderly men	12 weeks	Improved muscle strength, insulin sensitivity, maximal O ₂ consumption and arterial baroreceptor cardiac reflex sensitivity
Singh et al. [93]	2011	63 MS and 32 controls	3 months	Improved HOMA-IR in MS males with hypogonadism
Jones et al. - TIMES2 Study [94]	2011	220 Hypogonadic with type 2 Diabetes or MS	6 months	Transdermal T improved insulin resistance, total and LDL-cholesterol, Lpa and sexual health

androgenization appears to predispose to a male gender identity development, but this is not mandatory, since 40-50% of 46, XY intersexed children with a history of prenatal androgen exposure do not develop a male gender identity. Male-to-female transsexuals, with a normal androgen exposure prenatally (since there is clear evidence of the contrary) develop a female gender identity, through unknown biological mechanisms apparently overriding the effects of prenatal androgens. The latest studies in 46, XX subjects exposed to prenatal androgens show that prenatal androgenization of 46, XX fetuses leads to marked masculinization of later gender-related behavior but does not lead to gender confusion/dysphoria. The example of female-to-male transsexuals, without evidence of prenatal androgen exposure, indicates that a male gender identity can develop without a significant androgen stimulus. So the role of hormonal imprinting on gender identity formation is still far away to be comprehended. [109,110]. However, also in this case, a metabolic evaluation, due to possible precocious alteration in hormonal milieu and/or pharmacological modification of steroid levels, should be performed.

In conclusion, hypogonadism is surely associated with MS, with a possible causative role or, at least, as a worsening factor. Most studies confirm a possible usefulness of T replacement therapy, but still need definitive and personalized confirmation.

CONFLICT OF INTEREST

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