Steroids and the metabolic syndrome

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A R T I C L E   I N F O

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1. Abdominal obesity, insulin resistance and the metabolic syndrome

Over the last 15 years, the concept underlying the common aggregation of major abnormalities associated with an insulin resistant state has emerged as a unique entity, the so-called metabolic syndrome. Although the concept that insulin resistance is different from the metabolic syndrome, nonetheless for many years these two conditions have often been used more or less as synonyms. This issue is, however, currently a matter of great controversy [1]. One of the reasons is certainly represented by the difficulty of measuring the insulin resistance state and the need for more reliable parameters defining the risk for cardiovascular diseases (CVD). After the first description proposed by Reaven [2], in the last decade several other definitions have been proposed, and particular attention has been paid to the National Cholesterol Education Program expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) report [3], which includes a practical definition based on clinical simple parameters, such as central obesity, high fasting glucose and triglycerides, low HDL-cholesterol and high arterial blood pressure. Regardless of the definition, a central role in the definition of the metabolic syndrome is represented by the presence of central obesity [4], easily assessed using waist circumference as a parameter. In fact, waist circumference had good predictivity on visceral fat measurement, explaining approximately 60–70% of the variance of a direct estimation performed by a computer tomography scan. Central obesity is independently associated with each of the other metabolic syndrome components, including insulin resistance.

How does the definition of the metabolic syndrome overlap that of insulin resistance? Insulin resistance and/or compensatory hyperinsulinemia are undoubtedly CVD risk factors [2]. However, there are several other considerations emphasizing why different definitions of the metabolic syndrome and of insulin resistance may in some way represent different entities and they should not therefore be used as synonyms [1]. In fact, many studies indicate that relatively new indices related to both insulin resistance and CVD, such as microalbuminuria, markers of low-grade inflammation, low adiponectin, and other factors such as fibrinogen, and plasminogen activator inhibitor (PAI-1), may also be useful predictive tools or useful additions to the definition of the metabolic syndrome [1]. Therefore, the attempt to define the metabolic syndrome as a result of a simple unifying pathophysiological process is problematic. On the other hand, insulin resistance and the metabolic syndrome can overlap, depending on how many components are used in the definition of the latter. In a study [5] performed in a large group of healthy volunteers with different anthropometric and metabolic measurements, and in which insulin resistance was defined as being in the top tertile of the steady-state plasma glucose (SSPG) during the combined octreotide–insulin–glucose test [6], it was found that, although insulin resistance and the presence of the metabolic syndrome were significantly associated \((p<0.001)\), the sensitivity and positive predictive values equaled 4 and 7%, the presence of overweight, with high triglycerides, low HDL-cholesterol or elevated blood pressure being the most common factors included in the diagnosis of the metabolic syndrome itself. However, when all five components of the metabolic syndrome were taken into account, approximately 100% of the subjects having the metabolic syndrome were insulin resistant. With some limitation, it is therefore clear that the presence of the metabolic syndrome includes a high proportion of subjects with an insulin resistance state.

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2. Pathophysiological aspects of abdominal obesity: the hypothalamic–pituitary–adrenal axis and sex hormone imbalance

Steroids play an important role in the regulation of adipose tissue metabolism, with relevant differences according to its distribution [7–10]. Alterations of the hypothalamic–pituitary–adrenal (HPA) axis and sex hormone imbalance may have profound effects on adipose tissue morphology and function. In the following sections multiple alterations of these two classic endocrine compartments in the presence of central obesity are discussed.

2.1. The hypothalamic–pituitary–adrenal axis

Cushing's syndrome is characterized by a redistribution of adipose tissue from peripheral to the truncal region and visceral depots. This may occur as a result of the dual effect of glucocorticoids which on the one hand down regulate hormone sensitive lipase (HSL) and increase lipolysis, and on the other favour pre-adipocyte differentiation and stimulate substrates to gluconeogenesis and free fatty acids (FFA) to central fat [79]. In addition, glucocorticoid excess inhibits glucose uptake by peripheral tissues, stimulates gluconeogenesis and causes an increase in post-absorptive glucose and insulin. In the insulin sensitive tissues, glucocorticoids also impair the post-receptor insulin function by mechanisms that involve interaction with glucose transporters [75,10]. After surgical treatment, centralization of visceral fat depots tends to be markedly reduced, a process which can be successfully completed within 1–2 years [10]. Even exogenous glucocorticoid treatment in experimental animals and humans leads to the development of the central obesity phenotype [9,10]. Moreover, animal models of obesity invariably have increased levels of corticosterone (the equivalent of cortisol in humans), and adrenalectomy leads to its reversal [9].

The central obesity phenotype and syndromes of endogenous or exogenous hypercortisolism share several similarities, including all features of the metabolic syndrome; a hypothetical role of glucocorticoid excess in the pathophysiology of the central obesity phenotype has therefore been hypothesized. These effects, however, may require the concerted action of many other hormones, including increased insulin levels, altered catecholamine regulation, growth hormone (GH) reduction and particularly decreased (in males) or increased (in females) free androgen availability [9]. Although research in this area is complicated, many studies performed so far have documented that in central obesity a subtle dysregulation of the HPA axis may exist [10], being characterized by a high secretion of cortisol after laboratory stress test, ACTH and cortisol over-responsiveness to neuropeptides and secretagogues, and increased free cortisol values in both urine or saliva [11]. This suggests a central neuroendocrine dysregulation resulting, in turn, in slightly abnormal net cortisol production, either continuous or episodic. Unfortunately, no single available marker, particularly in the basal state, has the power to detect subtle alterations of the HPA axis in these conditions, although evaluation of urinary free cortisol (HFC), particularly during night-time, and salivary free cortisol appear to be promising for these purposes [12].

Increased cortisol production in obesity may also depend on peripheral mechanisms. Higher numbers of glucocorticoid receptors have been demonstrated in visceral than in subcutaneous adipocytes, which favours an increase in intracellular cortisol action in the visceral fat [13]. In addition, alterations of the activity of two enzyme systems, such as impaired activity of the 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1), which reactivates cortisol from inactive cortisone in the liver and the adipose tissue, and enhanced activity of the 5α-reductase, which metabolizes cortisol to its tetrahydroderivates, have been described in patients with central adiposity [14,15]. The potential importance of this system has been emphasized by studies demonstrating that transgenic mice overexpressing 11βHSD-1 selectively in the adipose tissue have increased levels of corticosterone and develop visceral obesity and all features of the metabolic syndrome and insulin resistance [16], whereas those lacking 11βHSD-1 appear to be protected from these alterations [17,18].

Therefore, both neuroendocrine hyperactivity of the HPA axis as well as peripheral cortisol production can be associated with central obesity and may therefore may have some relevance in the pathophysiology of this disorder.

2.2. Sex hormone imbalance

The increase in body weight and fat tissue is associated with several abnormalities of sex steroid balance in both sexes. Such alterations involve both androgens and estrogens and, as a whole, their carrier protein, sex hormone binding globulin (SHBG). Changes in SHBG concentrations lead to an alteration of androgen and estrogen delivery to target tissues. By inhibiting its synthesis in the liver insulin has the main responsibility in decreasing SHBG blood levels, which however are regulated by a series of factors, including estrogens, iodothyronines and GH as stimulating agents, and androgens as inhibiting factors [19].

In obese women, SHBG levels are inversely related to the increase in body weight [20]. This decrease of circulating SHBG determines an increase in the production rates and the metabolic clearance rate of circulating SHBG-bound steroids, specifically testosterone, dihydrotestosterone, and androstenediol, the principal active metabolite of dihydrotestosterone [21,22], but also increases the free fraction of androgens available for target tissues. Notably, obesity in women also affects androgens not bound to SHBG, production rates and metabolic clearance rates of dehydroepiandrosterenedione (DHEA) and androstenedione being equally increased in this condition [23]. Body fat distribution has an additional effect on SHBG concentrations in obese women, and the central abdominal phenotype tends to be characterized by lower SHBG levels than the peripheral phenotype, due to increased circulating insulin [24,25]. Moreover, women with the central phenotype are characterized by a significantly higher production rate of androgens bound to SHBG [22], which is only partly compensated by an increased metabolic clearance rate, therefore a condition of “mild relative hyperandrogenic state” may develop [26]. Due to the greater reduction of SHBG concentrations, the percentage of free testosterone fraction tends to be higher in women with central obesity than in those with peripheral obesity [25]. An inverse correlation exists between waist-to-hip ratio (WHR) (or other indices of body fat distribution) and testosterone or SHBG concentrations, regardless of body mass index (BMI) values [25].

In the obese male, total and free testosterone blood concentrations progressively decrease with increasing body weight, and this reduction is associated with a progressive decrease of SHBG concentrations [27]. Spermatogenesis and fertility are, however, not impaired in the majority of obese men, except in those with massive obesity [28]. Androstenedione and dihydrotestosterone circulating levels are usually normal or slightly reduced [29]. Changes in testosterone metabolism through 5α-reductase activity may also occur in male obesity. However, although reduced levels of the principal metabolites, such as androstosterone glucuronide and 5α-androstane-3α,17β-diolglucuronide, have been reported, particularly in the presence of very high BMI values, calculation of conversion rates from precursors, chiefly testosterone and DHEAS, was found to depend uniquely on decreased precursor levels, rather than on altered 5α-reductase activity [30]. Different pat-
terms of fat distribution may have a specific effect on testosterone levels in men, although contrasting data have been reported. Some studies [7,31] found an association between testosterone and WHR values, whereas others showed no correlation [32,33]. This suggests that the relationship between sex steroids and WHR may be the result of the shared covariance of WHR and total adiposity, rather than a direct relationship. Other studies confirmed that the reduction of C19 steroid precursors is predominantly associated with body fatness rather than with excess visceral fat accumulation. Glucuronic acid is able to conjugate steroids, influencing their biological activity. Notably, 3-androstenediol glucuronide levels were found, however, to be significantly higher in obese men having a central phenotype [29]. This association between 3-androstenediol glucuronide and visceral fatness suggests that an increased visceral adipose tissue corresponds to a state in which the steroid metabolism is altered. Glucuronide conjugate levels therefore appear to be more appropriate markers of peripheral androgen metabolism than circulating free steroids in obese men. Both SHBG and testosterone are negatively correlated with insulin levels, even after adjusting for BMI and WHR values [7].

Fig. 1 summarizes main sex differences and similarities in the alterations of the HPA axis and androgen balance in obese men and women.

### 3. Visceral obesity as a part of the “general maladaptation syndrome”

Life exists by maintaining a complex dynamic equilibrium or homeostasis that is constantly challenged by intrinsic and extrinsic adverse forces, the stressors. When faced with excessive stress, whether physical or emotional, a subject’s adaptive responses acquire a relatively stereotypic nonspecific nature, referred to by Selye as “the general adaptation syndrome” [34]. Stress activates the HPA axis and sympathetic nervous and the sympathoadrenal systems [35]. Defence reactions involve release of cortisol and catecholamines, and activate other endocrine systems, such as the renin-angiotension system [36]. In conditions of continuous stress exposure and poor coping, this endocrine activity may be altered, the response to stress is inadequate and compensatory mechanisms are activated, therefore the allostatic load (see below) may become overwhelming and the adaptive processes may be maladaptive [37].

Several studies performed in animal models clearly demonstrate that by means of these endocrine alterations metabolic derangements may occur and susceptibility to develop CVDs may increase. An excellent example of these studies is represented by the cynomolgus macaques model extensively investigated by Shively and Clarkson [38], who clearly described the sequence of events following a long-term exposure to chronic physical and psychological stress, that included enlarged visceral fat, insulin resistance, hyperinsulinemia, impaired glucose tolerance or type 2 diabetes mellitus T2DM, adrenal hypertrophy, enhanced cortisol response to ACTH stimulation, hypogonadism, altered lipid profiles and higher than expected incidence of coronary artery atherosclerosis and cardiac events. Increased HPA axis activity together with activation of the sympathetic system have been related to the individual inability to cope with long-term adverse stressful events during the lifespan [39–40]. This has been indirectly supported by a long series of epidemiological and clinical studies documenting that central obesity is strongly associated with stress-related or adverse life events and psychosocial conditions, low occupational and educational status, smoking habits, alcohol and/or drug abuse, fat overfeeding, psychiatric disorders, negative personality traits and subjective abnormally perceived stress [41–43].

Allostatic load has been proposed as a new conceptualization of cumulative biological burden exacted on the body through attempts to adapt to life’s demands [37]. Allostatic load therefore refers to the price the body pays for being forced to adapt to adverse environmental stressors. The distinction between protection and damage is related to the dynamics of the hormonal response, with specific reference to the activities of the HPA axis and the sympathetic nervous system (SNS). There are studies clearly demonstrating that hormonal mediators are associated with both adaptation and pathophysiology of the metabolic syndrome, including central obesity, hypertension and atherosclerosis. Using a multisystem summary measure of allostatic load (including systolic and diastolic blood pressure, WHR, total and HDL-cholesterol, glycosilated hemoglobin, DHEA-S, overnight UFC, overnight urinary nor-epinephrine and epinephrine), Seeman et al. [44] evaluated its capacity to predict health outcomes in a 7-year follow-up survey of 1189 elderly men and women. Higher baseline allostatic load scores were associated with significantly increased risk for 7-year mortality as well as with declines in cognitive and physical functioning, and were marginally associated with incident CVD events, independent of standard socio-demographic characteristics and baseline health status. Collectively, allostatic load was a better predictor of mortality and decline in physical functioning than either the metabolic syndrome or primary mediator components alone. These findings have been extended to other biomarkers, including C-reactive protein, fibrinogen, IL-6, and albumin [45]. Overall, these data support the concept that long-term maladaptation to chronic environmental stressors may have an important impact on health, being mediated by the development of central obesity and associated metabolic co-morbidities.

Interestingly, response to stress is part of the biology of human sex difference. Therefore, it follows that sex hormones are impor-
tant regulators of individual responses to stress according to sex. Chronic HPA drive and glucocorticoid hypersecretion have been implicated in the pathogenesis of several forms of systemic, neurodegenerative and affective disorders. The HPA axis is subject to gonadal influence, indicated by sex differences in basal and stress HPA function and neuropathologies associated with HPA dysfunction [46]. In view of the mutual interaction with which the hypothalamic–pituitary–gonadal (HPG) and HPA systems operate, it is difficult to construct a model of how these hormones act in the brain. Manipulation of one endocrine system is not without effects on the other, but their simultaneous manipulation can overcome this problem. Experiments performed using this dual approach in the male rat have revealed that testosterone can act and interact on different aspects of basal and stress HPA function. Basal ACTH release is regulated by testosterone-dependent effects on arginine vasopressin synthesis, and corticosterone-dependent effects on corticotropin-releasing hormone (CRH) synthesis in the paraventricular nucleus (PVN) of the hypothalamus [47]. In contrast, testosterone and corticosterone interact on stress-induced ACTH release and drive to the PVN motor neurones, and medial preoptic area, central and medial amygdala and bed nuclei of the stria terminalis are candidate structures mediating this interaction [46].

As stated above, the activity of the HPA axis, in both basal and stimulated condition, is different according to sex. In rodents basal ACTH and corticosterone levels, as well as their response to various stimuli, have been found uniformly greater in females than in males [48,49]. Accordingly, it has been shown that healthy women may be more responsive to CRH [50] or to a combination of CRH and arginine-vasopressin (AVP) with respect to ACTH secretion [51–53]. It is of interest for the purpose of this review that cortisol responses to acute stress challenges have been found to be higher in abdominally obese women [54] and that stress-related cortisol positively correlated with central fatness in middle-aged men [55]. We have recently shown that both normalweight but even obese men had significantly higher ACTH and cortisol concentrations than normalweight and obese women [56], by contrast, hormone response to CRH plus AVP stimulation was significantly higher in the latter compared to the former. Therefore, a sex difference in the activity of the HPA axis still persists even in the presence of obesity. Interestingly, however, in the presence of obesity, differences between sexes in the HPA axis hyperresponsiveness are significantly amplified. At variance, one study [57] performed in male and female healthy volunteers undergoing CRH stimulation test after 3–5 months gonadal suppression injections showed that leuprolide stimulated hormone values were unexpectedly higher in men than in women. This may be consistent with the concept that, when sex hormones are suppressed, the relationship is completely overturned, which implies a different role of androgens and estrogens in the regulation of HPA axis activity. In rats it has been shown that ovariectomy leads to attenuated HPA axis response, whereas estradiol substitution induced HPA axis stimulation [58,59]. In healthy young men short-term estradiol treatment leads to an enhanced ACTH and cortisol stress response [60]. Androgens, conversely, act on the HPA axis by inhibitory effects. Experiments performed in rats have suggested that basal ACTH release is regulated by a testosterone-dependent effect on AVP and a corticosterone-dependent effect on CRH synthesis at the hypothalamic level [47]. In addition, ACTH and corticosterone responses to acute stress in the male rat are increased by gonadectomy, whereas this effect is reversed with testosterone replacement, probably occurs via an androgen receptor-mediated mechanism [47].

The functional cross-talk between the HPA axis and sex steroids is however bidirectional, and may be different according to sex. Several years ago, Per Bjorntorp proposed the hypothesis that the combined alteration of the glucocorticoid pathway and sex hormone balance, particularly androgens, associated with central obesity, may have a role in the pathophysiology of the metabolic syndrome and insulin resistance [11,41]. According to his conceptual view, a primary event in the development of this general steroid imbalance should be represented by a mild but persistent activation of the HPA axis, via central neuroendocrine disturbances, as a consequence of a chronic maladaptation to environmental stressors. This hypothesis, that needs to be confirmed by experimental data, does however have a well-defined physiological and pathophysiological basis [39]. In fact, several interactions between CRH and the gonadotropin-releasing hormone (GnRH) peripheral axes have been described in Ref. [61]. Moreover, there is considerable evidence to suggest that an increased CRH secretion may inhibit GnRH secretion [62]. According to this theory, the association between increased HPA axis activity and low testosterone levels in obese men makes sense, although many other factors are involved in determining hypotestosteronemia in male obesity [26]. There are in fact difficulties in applying this mechanism in central obesity females, who are relatively hyperandrogenic. As occurs in those with the polycystic ovary syndrome (PCOS), there are theoretical bases to suggest that an insulin-mediated overstimulation of ovarian steroidogenesis may occur in these women, since insulin acts as a true gonadotropic hormone, synergizing LH activity [63]. However, there are no consistent in vitro or in vivo data supporting a clear responsibility of insulin [or other factors mimicking insulin action, such as the insulin growth factor 1 (IGF–1)] in women with central obesity. Conditions of hypercortisolism such as Cushing’s syndrome are good examples of how the HPA axis may differently regulate gonadal function according to sex. Cushing’s syndrome is in fact associated, in men, with reduced gonadotropin levels and pulsatility and low testosterone concentrations, regardless of the extent of the hypercortisolism [64]. On the contrary, women with Cushing’s syndrome and mild hypercortisolism may present with androgen excess of both adrenal and ovarian origin, reduced gonadotropins, and with polycystic ovaries, whereas when severe hypercortisolism is present the HPG axis may be inhibited, sharing a similar condition to Cushing’s syndrome in men [65]. In a recent study we found that ACTH response to a combined stimulation of the HPA axis with CRH plus AVP was negatively correlated with LH concentrations in both obese men and women, whereas cortisol response tended to be negatively correlated with the free testosterone index (FAI) in obese men, but positively in obese women [56]. These findings may therefore provide additional explanatory clues to the mechanisms leading to the disparate behaviour of androgen levels in obesity according to sex. In addition, they suggest disparate effects of overactive HPA axis in obesity, according to sex. Much more data are however needed to support this hypothesis.

4. Association between steroid imbalance, insulin resistance and the metabolic syndrome

What is reported in the previous paragraphs emphasises the fact that alterations of the glucocorticoid axis combined with a sex hormone imbalance may have a coordinating role in the pathophysiology of central obesity and associated metabolic alterations. In the following part of this review, we will focus on the studies showing an association between abnormalities of the HPA axis and those of sex hormones, particularly androgens, with the metabolic syndrome, T2DM and CVDs.

4.1. With alterations of the HPA axis

As for Cushing’s syndrome, insulin resistance is frequently associated with visceral fat accumulation and increased susceptibility
for CVDs and T2DM. Although the pathophysiology of the metabolic syndrome is only partially understood, available evidence indicates that insulin resistance could underlie the association between all its features, particularly central obesity [1,2]. Although direct evidence is lacking in humans, there are epidemiologic data providing evidence for a significant positive association between cortisol levels and alterations of the glucose–insulin system and altered lipid profiles [66,67]. There are also studies showing a significant association between morning cortisol concentrations and insulin resistance, relative hypertension, glucose intolerance and hypertriglyceridemia, all features of the metabolic syndrome, with some difference according to sex [66,68,69]. There is also some evidence that increased cortisol levels may be an early feature of essential hypertension [70]. In a study performed in a South Asian cohort, it was recently found that the associations between morning cortisol concentrations and CVD risk factors were stronger than those observed in Caucasian populations, despite similar mean cortisol concentrations, and that they were amplified by adiposity, which suggests that increased glucocorticoid action may contribute to ethnic differences in the prevalence of the metabolic syndrome, particularly among men and women with a higher BMI [71]. Clinical studies performed in women with different obesity phenotypes have additionally shown a significant correlation between cortisol response to acute CRH plus AVP stimulation and fasting insulin or the homeostasis insulin resistance model (HOMA) [72] and, more recently, a positive significant correlation between nightly UFC excretion and insulin resistance indexes, which further emphasize the potential link between HPA axis alterations, insulin resistance and the metabolic syndrome [12].

A dangerous allostatic load has also been associated with metabolic disorders, and this appears to be the consequence of the failure to turn off of the HPA axis, together with the sympathetic activity, after chronic stress exposure [37]. Moreover, the reduction of the allostatic load appears to be associated with lower all-cause mortality [73], which implies a concomitant improvement of most important risk factors for CVDs. Notably, allostatic as well as allostatic load, are affected by a number of behavioural aspects, which are strictly linked to human obesity, such as diet, smoking, alcohol consumption and the amount of physical activity [37]. This can explain why the reduction of the allostatic load by lifestyle management has been found to improve the dangerous impact of the metabolic disturbances [73].

Some evidence from human studies for an association between marker of a SNS overactivity and these metabolic disorders is further proof in favour of this complex association with abnormalities of the stress hormonal systems. In fact, Brunner et al. [74] found that middle-aged men with the metabolic syndrome were characterized by significantly higher urine free cortisol and cortisol metabolites and normetanephrine, together with more prevalent alterations of inflammatory markers and worsened indices of psychosocial and behavioural parameters, which suggests that both neuroendocrine axes were overactive in the presence of the metabolic syndrome. This is in line with our own data obtained in groups of women with different obesity phenotypes showing that, by steadily increasing blood norepinephrine with yohimbine infusion to levels similar to those measured after a moderate acute stress exposure, the HPA response (measured as ACTH and cortisol blood levels) was significantly enhanced with respect to that observed in the control saline study, particularly in those with the abdominal obesity, which confirms a coordinated role of the overactive sympathetic pathways and activity of the HPA axis in the response to stress [12].

Taken together, these findings are consistent with a potential role of increased HPA axis activity in determining insulin resistance and in favouring the development of central obesity and the metabolic syndrome. This could also help to explain the claimed dangerous effect of chronic environmental stress exposure with poor coping, whose effects throughout life appear to be mediated by a dysregulation of the HPA axis and the sympathetic nervous system, leading, ultimately, to multiple metabolic, hemodynamic and cardiovascular perturbations. A better understanding of the HPA axis function and activity in individuals with abdominal obesity and the metabolic syndrome is therefore mandatory. This is further emphasized by the International Diabetes Federation, which highlighted a number of parameters potentially related to the metabolic syndrome, including the HPA axis, for in-depth research studies [4].

4.2. With alterations of sex hormones

Since androgens have an important impact on both glucose and lipid metabolism and on fat homeostasis, it is likely that androgen imbalance in obesity may play a role in the pathophysiology of the metabolic syndrome and increase the risk for cardiovascular diseases [75,76]. Although the few large prospective studies have not confirmed a significant association, cross-sectional studies have nonetheless provided some evidence for a linkage between low testosterone levels and CHD events, particularly in men [75]. One reason for the failure to achieve conclusive information from clinical and epidemiological studies may be partly dependent on the sex-related different behaviour of sex hormones in the presence of obesity. On the other hand, this hypothesis has attracted scientific concern since low testosterone in men and a condition of relative hyperandrogenism in women are associated with abdominal obesity and all the features of the metabolic syndrome, and with insulin resistance and compensatory hyperinsulinemia. Accordingly, it has been speculated that altered testosterone concentrations may be a surrogate of the risk represented by the presence of obesity and associated insulin resistance with T2DM and CHD in both women and men, albeit with some differences [75,77].

In men, there are studies showing that after adjusting for measurement of obesity, fat distribution and insulin resistance, the correlations of major cardiovascular risk factors with testosterone, but not with visceral fat or insulin levels, lost their statistical significance [78,79]. Other studies, however, found that, after adjustment for BMI and WHR, the negative correlation of testosterone with insulin and lipid levels remained statistically significant [80]. Moreover, it has also been reported that high testosterone and SHBG levels in males are associated with higher insulin sensitivity and reduced risk for the metabolic syndrome, independently of body weight and composition [81]. Epidemiological studies performed in diabetic men have shown that testosterone is lower in diabetics with respect to non-diabetic subjects, with a higher prevalence of a hypogonadism state [77]. Lower testosterone levels have also been found in men with impaired glucose tolerance [82]. Intriguingly, low testosterone levels in men have been proposed as a potential component of the metabolic syndrome [83]. This can however be suspected only based on indirect evidence. In fact, studies performed in both hypogonadic men and obese subjects have provided consistent evidence that a substantial decrease in testosterone blood levels may be responsible for excess visceral fat, which, in turn, represents a key event in the pathophysiology of insulin resistance, the core abnormality of the metabolic syndrome [26]. Enlarged abnormal fat depots and some degree of insulin insensitivity characterize hypogonadal men, which is partly dependent on the degree of body fat excess [84,85]. By contrast, suppression of testosterone secretion by long-term administration of a GnRH analog has been found to increase serum leptin and insulin, a marker of insulin resistance [86]. However, lowered testosterone blood levels and insulin resistance tend to recover together after substantial
weight loss [26]. In addition, long-term treatment with testosterone in obese men with high WHR values has been found to be associated with a selective decrease of visceral fat and a significant improvement of the insulin resistant state [85].

Women present the opposite relationships between endogenous androgens and obesity, insulin and cardiovascular risk factors [75]. It should be recognized that the dichotomy in body fat distribution is more evident in female than male obesity, particularly after the menopause or in classic hyperandrogenic states, and that specific alterations of the responsible androgen imbalance are more typical features of the abdominal rather than the peripheral obesity phenotype. Again, the marked reduction in SHBG concentrations generally occurring in women with central obesity, a condition of moderate-to-severe insulin resistant state, has been found to be an independent risk factor for the development of T2DM [87]. There are relatively few studies investigating the relationship between endogenous levels of androgens, insulin resistance, and the metabolic syndrome.

The paradigm of PCOS is a good example supporting the association between hyperandrogenemia and the metabolic syndrome. In women with PCOS, insulin resistance and compensatory hyperinsulinemia are very common, as is the presence of obesity, particularly the abdominal phenotype [88]. In these women, excess androgens show a positive significant correlation with insulin levels and, indirectly, with indices of insulin resistance [63]. Due to its gonadotrophic action, the hyperinsulinemia, which accompanies insulin resistance, has a direct pathophysiological role on hyperandrogenism, synergizing with LH to stimulate excess ovarian androgen production [63]. Improvement of the insulin resistant state which occurs after hypocaloric diet [89] or insulin sensitizer administration [90] commonly favours a decrease of androgen levels in PCOS women, both obese and normalweight. However, androgen excess per se may be responsible for the development of insulin resistance. In rats, a moderate increase of testosterone concentrations is in fact followed by a decrease of insulin sensitivity [91]. Similar findings have been reported in rats after exposure to excess androgenic maternal environment [92]. Additional studies performed in women have shown that androgen administration may cause insulin resistance [93]. Moreover, long-term administration of antiandrogens may improve insulin sensitivity, at least in women with PCOS [94]. A vicious circle therefore takes place in which excess insulin, insulin resistance and excess androgens influence each other, leading to the development of the PCOS phenotype. Whether this mechanism may operate also in women with the abdominal obesity phenotype is however uncertain.

Women with PCOS also have a higher than expected susceptibility to develop T2DM, obesity representing a prerequisite for such an evolution [95]. Women with PCOS, obesity and impaired glucose tolerance or T2DM are more hyperandrogenic and insulin resistant compared to women with PCOS with a similar degree of obesity but normal glucose tolerance, again suggesting a coordinated role of these hormonal abnormalities in favouring states of glucose intolerance [96]. Whether women with PCOS are susceptible to develop more cardiovascular events, particularly coronary events, is however a matter of controversy, in spite of the fact that they often present with multiple cardiovascular risk factors, including lipid and hemocoagulative alterations and inflammatory factors [97]. Given the high prevalence of PCOS in the general population, this should remain a high priority target for future research.

5. Summary and conclusions

The concept that central obesity and associated metabolic and cardiovascular co-morbidities may be part of the so-called “general adaptation syndrome” proposed by Salye 60 years ago has attracted scientific attention in the last 15 years, although the pathophysiology of this relationship in humans is poorly understood. However, animal data support this concept and emphasize the role of the two main stress endocrine systems, the HPA axis and the SNS, in the cascade on events leading to end terminal diseases. As previously suggested by Per Bjorntorp (see previous paragraphs), we support the concept that sex hormone imbalance may play an additional role in this context, taking into consideration that alterations of androgen balance associated with central obesity is part of the pathobiology of sex differences.

Human studies have clearly shown that in the presence of central obesity the activity of the HPA axis is increased and the catecholaminergic system is overactivated, particularly in women. An androgen imbalance is also present, with low testosterone levels in male obesity, and a condition of functional hyperandrogenism in female obesity, particularly in the presence of the central phenotype. One major problem in clinical and epidemiological research is however represented by the lack of reliable markers of the HPA axis hyperactivity in these patients.

Recent studies clearly suggest that alterations of the endocrine system and the metabolic syndrome are associated. Moreover there are data supporting the concept that low androgen levels in men are strongly predictive of an individual susceptibility to develop T2DM. Finally, an altered androgen balance may cooperate with an overactive HPA axis and sympathetic pathways in increasing the individual risk of CVD. Further intensive research in this area should therefore be performed.

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