

Gender in endocrinological diseases: biological and clinical differences

Rosa Lauretta¹, Massimiliano Sansone², Francesco Romanelli², Marialuisa Appetecchia¹

1. Endocrinology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy; 2. Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza Università di Roma, Rome, Italy. Received 17 January 2018; accepted 13 February 2018.

Summary. In the last decade, increasing attention has been paid to understanding the influence that gender can have on both human physiology and the pathogenesis of diseases. What makes women different from men is essentially represented by sex hormones and, in fact, the attention of scientific literature has been, and continues to be, an understanding of the biological mechanisms activated by sex hormones that underlie the pathophysiological diversity between men and women. Our attention has been focused on the effects that these hormones, and above all estrogens, can have in explaining gender differences in the endocrine field. Diseases such as thyroid disease, diabetes mellitus, osteoporosis, acromegaly clearly present gender differences, mainly due to the different sexual hormone structure. Energy metabolism is also gender-specific, being greatly influenced by estrogen, both at rest and during exercise. These hormones also have a significant effect on the pathogenesis of autoimmune endocrine diseases, as suggested by their different prevalence, often significantly higher in women than in men. Ultimately, there are gender differences due to sexual hormones also in response to therapies, in terms of dose/response, efficacy and adverse events, although this aspect needs to be further explored.

Key words: gender, sex hormones, endocrine system disease, estrogens.

Malattie endocrinologiche e genere: differenze biologiche e cliniche

Riassunto. Nell'ultimo decennio una sempre maggiore attenzione è stata rivolta alla comprensione dell'influenza che il sesso può avere sulla fisiologia umana e sulla patogenesi delle malattie. Ciò che rende diverse le donne dagli uomini è rappresentato essenzialmente dagli ormoni sessuali e, infatti, l'attenzione della letteratura scientifica è stata rivolta, e continua ad esserlo, alla comprensione dei meccanismi biologici attivati dagli ormoni sessuali che sottendono alla diversità fisiopatologica tra la donna e l'uomo. La nostra attenzione si è concentrata sugli effetti che tali ormoni, in primis gli estrogeni, possano avere nello spiegare le differenze di genere in ambito endocrinologico. Patologie quali le malattie della tiroide, il diabete mellito, l'osteoporosi, l'acromegalia presentano chiaramente diversità di genere, dovute principalmente al diverso assetto ormonale sessuale. Anche il metabolismo basale risulta essere genere-specifico, essendo notevolmente influenzato dagli estrogeni, sia

a riposo che durante esercizio fisico. Tali ormoni hanno un effetto non trascurabile anche sulla patogenesi delle malattie endocrine autoimmuni, come suggerito dalla loro diversa prevalenza, spesso significativamente maggiore nelle donne rispetto agli uomini. In ultima analisi, vi sono differenze tra i generi dovute agli ormoni sessuali anche nella risposta alle terapie, in termini di dose/risposta, efficacia e comparsa di eventi avversi, anche se tale aspetto deve essere ancora lungamente approfondito.

Parole chiave: genere, ormoni sessuali, malattie endocrinologiche, estrogeni.

Gender-related differences in the endocrine system

Gender-specific medicine is a complex and intriguing challenge for the future of all medical specialties. However, endocrinology can be considered the most involved in explaining the pathophysiological mechanisms underlying gender differences. In fact, hormones represent what makes a woman different from a man. Generally, women and men have the same hormones but the production of sex steroids (estrogens, progesterone and testosterone [T]) and the way they interact with various organ systems is what makes the sexes so different. Men produce predominantly T from the testes in a relatively constant daily amount according to a circadian profile. A small amount of estrogens and progesterone is produced by the testes and the adrenal glands or is produced in the peripheral tissues, such as adipose tissue or liver, by the conversion of other precursor hormones. In contrast, women produce mainly estrogens and progesterone from the ovaries in a cyclical pattern while a small amount of T is produced by the ovaries and adrenal glands. The levels of female sexual steroids follow a specific and oscillating profile, due to a complex interaction between the pituitary gland and the ovary. Keeping these basic physiological aspects in mind, it seems clear that epidemiology, clinical aspects, signs and symptoms of many diseases including the response to therapy and drug interaction can be very different between the sexes. For example, the most common endocrine diseases, such as thyroid diseases and diabetes mellitus, show marked differences between the sexes.

Gender-related differences and thyroid disease

Thyroid diseases are 5-8 times more common in women than men. Such data can be considered not only for clinical and/or subclinical hypothyroidism and hyperthyroidism and for nodular thyroid diseases, but also for autoimmune conditions, such as Hashimoto's thyroiditis and Graves' disease. It can be hypothesized that female sex hormones (estrogens and progesterone) and their particular pattern may be involved in the higher prevalence of thyroid diseases in females. Differentiated thyroid carcinoma (DTC), the most common endocrine neoplasm, is also more common in women than in men, but evidence regarding gender-related differences is poor¹. According to data published by the Italian Association for Cancer Registries (AIRTUM) 2014, 78% of patients with thyroid cancer are females; however, females have a better survival rate than males of the same age. Therefore, thyroid cancer is more common in women, but is more aggressive in men. Pathophysiological reasons that may explain this difference are unknown, but it has been proposed that estrogens may play a fundamental role. This hypothesis is supported by evidence that thyroid cancer has a higher incidence in fertile women. A causal role for the number of children has also been suggested. According to a recent meta-analysis, women with children have an increased risk of thyroid cancer compared to men, but a linear relationship between the number of children and increased risk has not been demonstrated. Nevertheless, the recent guidelines published by the American Association of Clinical Endocrinologists and the American College of Endocrinology in 2015 suggest that clinical trials do not support the role of estrogens as a risk factor for the development of thyroid cancer at present². Female sex, together with the absence of lymph node metastasis, and the American Thyroid Association (ATA) pediatric risk stratification system continue to be factors related to better outcomes in pediatric DTC, even in longer periods of observation (i.e., 32 years). Furthermore, girls with no lymph node metastasis at diagnosis, and those classified as low risk by the ATA pediatric risk stratification system were more likely to have no evidence of disease within the first year compared to boys³. Regarding the therapeutic aspects, gender does not affect the function of salivary glands in patients affected by thyroid cancer undergoing first radioactive iodine therapy⁴.

Gender-related differences and diabetes mellitus

Recently, it has been observed that diabetes mellitus also may have some gender-specific peculiarities; some data highlight that women have a longer-term illness and present a higher body mass index (BMI). In women, diabetes

mellitus appears to be less controlled considering each metabolic parameter. Italian data from annals published by *Associazione Medici Diabetologi* (AMD), the Italian association of diabetologists, showed that diabetic women have a 14% higher chance of having glycated hemoglobin (HbA1c) >9% regardless of insulin therapy, are 42% more likely to have low density lipoprotein (LDL) cholesterol >130 mg/dL regardless of statin therapy and have a 50% greater chance of having BMI >30 kg/m². These data seem to be partially confirmed in type 1 diabetic patients, in whom women show worse metabolic control and men have worse blood pressure⁵. Furthermore, diabetic women, regardless of menopausal state, present a significantly higher risk of ischemic cardiomyopathy than diabetic men; diabetic women also have a worse prognosis after myocardial infarction and a higher mortality rate from cardiovascular disease than diabetic men^{6,7}. A Canadian study showed that long-term statin therapy reduces total and cardiovascular mortality after myocardial infarction and this effect is more pronounced over time in both sexes. However, this risk reduction is lower in women than in men suggesting a gender-specific model of therapy response⁸. Regarding the metabolic aspect, women show a different behavior in their insulin response compared to men. In fact, the susceptibility to develop insulin resistance and insulin response to stimuli that physiologically improve or compromise insulin sensitivity is different in the two sexes⁹. Women tend to have lower insulin sensitivity than their male counterparts, but increase their insulin response to maintain normoglycemia (Table 1)^{10,11}. It can be suggested that these differences in insulin action may explain that in the pre-diabetic state, women are more prone to develop impaired glucose tolerance whereas their male counterparts are more susceptible to develop impaired fasting glycemia¹². This gender-related physiology may underline the different effects showed by a combined therapy with exenatide and metformin which induced better therapeutic results in women compared with men¹³. Interestingly, the difference in sex affects the prevalence of diabetes that is reversed according to the stage of reproductive life; there are more diabetic men before the age of puberty, while there are more diabetic women after the age of menopause and in old age¹². The role of menopausal estrogen (E2) deficiency in the increased risk of type 2 diabetes in women has been extensively studied; it should be considered that estrogens affect positively glucose homeostasis within a physiological window and any change outside the physiological range, such as menopause or oral contraceptives, represents a risk factor for insulin resistance¹². In diabetes mellitus, women are at higher risk of experiencing hypoglycemia using insulin and for urinary tract and genital infection using gliflozin drugs; as a result of the use of thiazolidinediones, the risk of bone fractures in postmenopausal women increases¹⁴.

Table 1. Pathophysiological effects of sex hormones.

Estrogens	Thyroid	Increase thyroxine-binding globulin; decrease free fraction of thyroxine ⁶⁴ ; down-regulation of the thyroid somatostatin receptor ^{22, 64}
	Glucose metabolism	Increase insulin sensitivity; protect pancreatic β -cells ^{10,11, 65}
	Bone	Inhibit generation and activity of osteoclasts; up-regulation of osteoprotegerin; decrease T cell activation; decrease IFN- γ release by T cells; increase intestinal calcium absorption ¹⁸
	Muscle	Increase levels of pro-anabolic factors; reduce muscle inflammation; decrease muscle damage; increase post-exercise muscle satellite cell activation and proliferation; increase intrinsic contractile muscle function ^{40, 41}
	GH/IGF-1 axis	Decrease hepatic IGF-1 production; down-regulation of the thyroid somatostatin receptor ²²
	Adipose tissue	Increase gynoid fat deposition ²⁶ ; decrease postprandial fatty acid oxidation ^{31,32} ; increase fat oxidation during submaximal exercise ^{33,34} ; decrease energy intake; increase energy expenditure; reduce tissue inflammation ⁶⁵
	Immune system	Decrease proinflammatory cytokines ⁶⁵ ; inhibit production of TNF- α , IL-1 β , and IL-6; and activity of NK cells (high level) ⁵⁷
Testosterone	Adipose tissue	Suppress the adipogenic line cells and favor the myogenic line; increases lipolysis and the number of β -adrenergic receptors on the membranes of adipocytes; inhibit triglyceride uptake and lipoprotein lipase activity ²⁹
	Muscle	Muscle mass and strength ²⁹

GH, growth hormone; IFN, interferon; IGF, insulin growth factor; IL, interleukin; TNF, tumor necrosis factor.

Gender-related differences and osteoporosis

A large part of the clinical evidence is based on studies conducted on male subjects creating the so-called male-biased evidence-based medicine. Nevertheless, scientific studies on osteoporosis represent an exception to male-biased evidence-based medicine. In fact, osteoporosis has been always considered as a typical female disease while it is also common in males. As a consequence, osteoporosis is often investigated in women, especially in postmenopausal state and it is not often considered in men, also presenting significant risk factors¹⁵. Interestingly, the Epidemiologic Study On the Prevalence of Osteoporosis (ESOPO), the main Italian epidemiological study on osteoporosis, was conducted on 11,011 women and 4981 men and it showed that in women the prevalence of osteoporosis is about 18.5% while in men it is about 10%. Similarly, the prevalence of osteopenia is 44.7% in women and 36% in men. The presence of bone fracture was confirmed in 17.6% of women and in 17.5% of men. Thereafter, mortality is 2-3 times higher in men with femur fracture than in women. These data suggest that bone health and status should be carefully evaluated even in elderly men¹⁶. The pathophysiology of osteoporosis is clearly gender-specific. Men tend to have a higher density and bone content and reach it at an older age than women, while women tend to lose bone at a younger age and at a faster rate than men and also have higher bone reabsorption markers. Later, the production of sex hormones decreases earlier and more markedly in women than men; this aspect can be the basis of the presence of

fractures about 5-10 years earlier in women than in men¹⁷. Indeed, estrogens play a crucial role in bone health both in women and in men and their deficiency is believed to be the main cause of bone loss in postmenopausal women and in elderly men. Estrogens inhibit generation and activity of osteoclasts through an upregulation of osteoprotegerin, decrease T cell activation and consequently also interferon- γ release by T cells, and increase intestinal calcium absorption. In women, estrogen decline is abrupt during the menopausal period, while in men the decline in T and, consequently, estrogen is low and constant with aging, so it is easy to understand how gender differences in osteoporosis exist. In postmenopausal women compared to premenopausal women an increase both in bone formation markers and in bone resorption markers is observed suggesting an increase in the rate of bone remodeling as confirmed by histomorphometry. In elderly men, biochemical markers of bone degradation seem to increase but bone formation markers appears to be stable or decreased suggesting a low bone remodeling rate (Table 1)¹⁸. Furthermore, an alteration of the inflammatory state of the bone has been demonstrated to be more pronounced in postmenopausal women than in older men, thus negatively affecting bone health¹⁹.

According to the underlining causes, osteoporosis may be primary or secondary and in women secondary osteoporosis represents 20-40% of cases while this value rises to 65% in men²⁰. Scientific studies on osteoporosis therapy have also focused their attention on women considering their results applicable to men. However, it seems that women are more prone to suffer from side

effects associated with bisphosphonates. The higher relative cases of atypical bone fractures in women than in men are not entirely related to an increased use of bisphosphonates, but also to gender *per se*, which should be considered a risk factor for atypical fracture²¹.

Gender-related differences and the growth hormone/insulin growth factor 1 axis

Clinical evidence supports the effects of estrogens on the growth hormone/insulin growth factor 1 axis (GH/IGF-1). In fact, several studies have shown that estrogens inhibit GH-stimulated hepatic production of IGF-1. In turn, GH levels rise to overcome the inhibitory effects of estrogen. It has been observed that the levels of GH are higher in women than in men and they fluctuate according to the phase of the menstrual cycle and depend on the menopausal state. Moreover, during the first trimester of pregnancy, estrogen levels increase and consequently IGF-1 levels decrease in the absence of any change in GH levels. IGF-1 levels increase from the beginning of the second quarter due to the gradual increase in placental GH. The effect of estrogens on the GH/IGF-1 axis is also noteworthy even in those pathologies characterized by deficiency or excess of GH.

Women suffering from GH deficiency require a much higher dose of recombinant human GH (rhGH) than men. Women taking oral estrogens need a higher dose of rhGH than those taking transdermal estrogens. It can be hypothesized that the inhibitory action of oral estrogens on the metabolic effect of GH is mediated by stimulation of cytokine 2 suppressor expression (SOCS-2), which in turn inhibits the phosphorylation of Janus kinase 2 (JAK2), a key passage in the signaling path JAK2/signal transducer and activator of transcription 5 (STAT5) activated by GH; the absence of the enzymatic function JAK prevents GH from exerting its metabolic effects, including the hepatic synthesis of IGF-1. Indeed, stimulated JAK2 adds a phosphate group to specific tyrosine residues on the cytoplasmic domain of the GH receptor; therefore, using its Src homology 2 (SH2) domain, STAT5 binds to these phosphorylated tyrosine residues. The bound STAT5 is phosphorylated by JAK2 to specific tyrosine residues, and is ready to form homodimers or heterodimers to act as a transcription factor (Table 1)²². Women suffering from acromegaly show lower IGF-1 levels than men who suffer from the same condition. It is interesting to highlight that in some specific acromegalic women IGF-1 levels decrease during the first trimester of pregnancy. A possible explanation could be the physiological increase in estrogen levels and their subsequent inhibition of IGF-1 production in the liver²³. This mechanism can be considered as a possible reason for the improved clinical conditions of acromegalic women during this period.

Acromegaly has also shown some clinical differences between the sexes; it seems that some specific metabolic alterations of acromegaly are gender-specific. Acromegalic women are more prone to suffer from insulin resistance and metabolic syndrome than men, even in the absence of significant differences in blood glucose and/or HbA1c. In addition, a higher prevalence of metabolic syndrome, visceral obesity and diabetes mellitus was observed in postmenopausal women compared to premenopausal women and men²⁴. It is interesting to note that the administration of rhGH often leads to hypothyroidism through both central and peripheral mechanisms; in particular, rhGH appears to decrease the thyroid-stimulating hormone (TSH) level by increasing IGF-1²⁵. In fact, IGF-1 seems to be involved in the direct stimulation of somatostatin mRNA synthesis and, in turn, somatostatin inhibits TSH secretion. This process has not always been observed in women and it seems that gonadal hormones play a fundamental role due to their inhibition of IGF-1 secretion, as mentioned above, and their down-regulation of the thyroid somatostatin receptor (SSTR) by estrogen. SSTRs 1, 3, 4 and 5 are highly present in normal thyroid tissue and estrogen has a differential effect on distinct SSTRs, down-regulating the expression of SSTRs 1 and 5²². These data should be considered to more carefully evaluate metabolic homeostasis, obesity and nutrition in postmenopausal women in order to reduce cardiovascular events.

These data suggest a gender-specific metabolic imbalance, but many other factors may represent a possible explanation and other studies are warranted before drawing a definitive conclusion.

Gender-related differences and fat metabolism

Women and men also show marked differences in the incidence of obesity, in fat deposition patterns, and in fat metabolism; women generally have a higher percentage of fat mass, and are more likely to deposit fat subcutaneously and on their lower extremities while men are more likely to deposit visceral fat in the abdominal region²⁶. Adipose tissue increases with puberty and early pregnancy in women, suggesting gonadal steroids can influence body fat. After menopause-induced estrogen loss a shift towards visceral adiposity occurs, which is sensitive to estrogen therapy²⁷. These facts highlight the importance of estrogens in subcutaneous fat accumulation. At cellular level, estrogen function is mediated by estrogen receptor alpha (ER α) and beta (ER β) although recent research observed nongenomic and rapid effects of steroid hormones throughout cytosolic or plasma membrane-associated receptors. Both ER α and ER β are expressed in subcutaneous and visceral adipose tissues; however, it seems that ER α plays a pivotal role in sexual dimorphism

of fat distribution. Female and male mice that lack ER α have visceral obesity with severe insulin resistance. Estrogen seems to promote and maintain the typical female fat distribution affecting lipolysis which is controlled in humans primarily by the action of β -adrenergic receptors (lipolytic) and α 2A-adrenergic receptors (antilipolytic). Estrogen increases the number of anti-lipolytic α 2A-adrenergic receptors in subcutaneous adipocytes; in contrast, no effect of estrogen on α 2A-adrenergic receptor mRNA expression was observed in adipocytes from the intra-abdominal fat depot where a high α 2A/ β ratio is present²⁸. T exerts its anti-obesity effect by activation of the androgen receptor (AR) pathway on mesenchymal stem cells, suppressing the adipogenic line cells and favoring the myogenic line. Furthermore, T increases lipolysis and the number of β -adrenergic receptors on the membranes of adipocytes and inhibits triglyceride uptake and lipoprotein lipase activity. Nevertheless, in women hyperandrogenisms positively correlated with visceral fat, waist circumference, and insulin resistance. Androgen excess may induce these effects through both central and peripheral mechanisms. Failure to activate leptin with consequent blockage of brown adipose tissue thermogenesis and reduced expression of hypothalamic proopiomelanocortin may represent important central control mechanisms. Peripherally, the interaction with estradiol may explain the different effects of T on women metabolism²⁹. Additionally, cross-sex hormonal therapy of male-to-female transsexuals increases the amount of subcutaneous adipose tissue accrual relative to intra-abdominal adipose tissue and a more masculine body fat distribution with a lower hip circumference in transmen³⁰. Estrogen affects also fuel metabolism reducing postprandial fatty acid oxidation leading to an increase in body fat which may account for the increased fat mass observed in women compared to men and the increase in fat early in pregnancy (Table 1)³¹. Interestingly, O'Sullivan et al showed that basal lipid oxidation was reduced in pregnant and non-pregnant women compared to postmenopausal women and postprandial lipid oxidation was reduced in pregnancy compared to non-pregnant healthy women, who in turn have lower postprandial lipid oxidation than postmenopausal women³². A possible explanation for this efficient fat storage of energy in female puberty and in early pregnancy is the obvious biological advantage in preparation for fertility, fetal development and lactation³¹. Otherwise, women show a greater reliance on fat oxidation than men during submaximal exercise and it seems to be due to both genomic and not genomic estrogen actions. In particular, estrogens mainly act through ER α in skeletal muscle to stimulate the genomic expression of proteins to increase the availability of long chain fatty acids (LCFA) improving adipocyte lipolysis and increasing intra-myocellular lipid storage. Following on, estrogens affect fuel metabolism during exercise by non-ge-

nomics means to increase the activation of 5' adenosine monophosphate-activated protein kinase (AMPK)^{33,34}.

Most scientific studies on drug response have been performed on male subjects and the results have been considered valid also for women assuming that gender did not affect the outcome (Yentl syndrome). However, it should be noted that in 2005 eight out of ten prescription drugs were withdrawn from the US market because of women's health issues³⁵. Recently, the NHS and Medical Research Council evaluated the causes and effects of women's socio-demographic exclusions from clinical trials; therefore, use of statins and non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated. These drugs demonstrated a marked difference in the gender of subjects included in the trials. Studies on NSAIDs have reflected the population in which they were used, while those for statins did not and only 16% of women were included in trials compared with 45% who were using statins³⁶. The therapeutic response may be different between genders and even if evidence is far from being definitive, the existing data are to be considered and evaluated. Indeed, it is well known that cytochrome expression may be a gender-specific altering drug metabolism. As regards lipid-lowering drugs, it has been observed that women on atorvastatin have more side effects (i.e., increased liver enzymes and myalgia) than men. However, atorvastatin and rosuvastatin seem to have similar efficacy in both sexes³⁷. On the contrary, fenofibrate improves lipid profile more in women than in men, reduced cardiovascular events by 30% in women and 13% in men^{38,39}.

Gender-related differences in sarcopenia

Sarcopenia is an age-related syndrome defined by the loss of muscle mass and strength, associated with chronic diseases, sarcopenic obesity and prolonged immobilization. However, it also represents a physiological condition of aging. The etiology of sarcopenia is multifactorial but still poorly understood; a decrease of anabolic hormones plays a role in the development and in the maintenance of sarcopenia. In particular, the decrease in T appears to be crucial in elderly men and administration of T in hypogonadal men may be extremely helpful in limiting the loss of muscle mass and strength. In postmenopausal women, evidence regarding the effect of abrupt decrease of estrogens on muscle mass and strength and, eventually, the impact of hormonal replacement therapy (HRT) is scarce. During menopause, women show a marked decrease in muscle mass and strength, while in men this loss is constant and takes place more slowly; however, this is not shown in women undergoing HRT⁴⁰. A meta-analysis showed that strength was significantly greater in women on HRT. The effect sizes were calculated as the standardized mean difference and

amounted to 0.23, equating to women on HRT being ~5% stronger; nevertheless effect sizes tended to be greater (~0.45) when only randomized, controlled trials were considered or when strength was normalized for muscle size, indicating that estrogens affect positively muscle strength⁴¹. Estrogens appear to act via several mechanisms, such as increased levels of pro-anabolic factors, reduced systemic and muscle inflammation, decreased muscle damage, augmented post-exercise muscle satellite cell activation and proliferation. Furthermore, estrogens seem also to augment intrinsic contractile muscle function altering myosin functions as reported by increased strength normalized to muscle size (Table 1)^{40,42}. A recent study with monozygotic twin pairs showed that thigh muscle cross-sectional area tended to be larger, relative muscle area greater, and relative fat area smaller in HRT users than in their sisters. In particular, tibolone administration increased muscle cross-sectional area⁴³. Tibolone is a tissue-specific compound with estrogenic, progestogenic, and weak androgenic activities⁴⁴. Tibolone showed promising effects increasing significantly hand-grip strength compared to placebo in postmenopausal women and improving markedly isometric knee extension strength, adjusted for BMI⁴⁵. In a cross-sectional study, mean knee extensor strength was higher in women taking tibolone or estrogen compared to no HRT⁴⁶. Following on, tibolone seems to affect body composition, increasing the lean mass and decreasing the total body fat mass^{44,47-49}. Thus, the lower rate of falling in the tibolone group observed by Cummings et al might reflect an androgenic effect on muscular function⁵⁰.

Gender-related differences in endocrine autoimmune diseases

The immune system is a host defense system, which includes many biological structures and processes within an organism that protects against disease. The immune system works differently according to gender; in fact, women are able to produce a stronger immune response than men and this applies to both humoral and cell-mediated response. In particular, women show a more efficient process of phagocytosis, antigen processing and presentation, and an increased production of cytokines and circulating antibodies in response to stimulating antigens⁵¹. At high levels, estrogens may promote inhibition of production of tumor necrosis factor- α , interleukin-1 beta, interleukin-6 and of activity of natural killer (NK) cells, whereas progesterone inhibits Th1 response, activity of NK cells, macrophagy, and T cells, nitric oxide production and promote Th2 response⁵². These sex-based differences in immune responses, affecting both the innate and adaptive immune responses, contribute to differences in the pathogenesis of infectious diseases in

males and females, the response to viral vaccines and the prevalence of autoimmune diseases⁵³. This marked activation of immune response in women may have pros and cons; on the one hand, it helps to protect against infections, but on the other it can be responsible for the development of immune mediated diseases (i.e., autoimmune diseases)⁵⁴. An autoimmune disease is a condition arising from an abnormal immune response to a normal body part. It is a chronic disease whose etiology is unknown. Many factors have been studied as possible causes explaining the onset of an autoimmune disease but there is no conclusive evidence⁵⁵. It has been observed that most autoimmune diseases are more prevalent in women than men (Table 1)^{56,57}. Endocrine autoimmune diseases, such as Graves' disease and Hashimoto's thyroiditis, are 7-10 times more common in women than in men. In Graves' disease it has been observed that men have a worse prognosis than women when treated with anti-thyroid drugs (ATD) and they present not only a larger thyroid volume at onset of disease, but also a more marked familiar autoimmune background. These aspects may underline the worse prognosis in males undergoing ATD⁵⁸. No gender difference is present in type 1 diabetes mellitus (T1DM)⁵³. In T1DM, pubertal age is associated with a decreased incidence in girls who maintain stronger residual β -cell function than boys⁵⁹⁻⁶¹. This suggests that female gonadal hormones transiently protect against T1DM. Consistent with this possibility, serum levels of estradiol are decreased in adolescents with T1DM, suggesting that they are not protected by E2⁶². Gender-related differences in autoimmune diseases are not only related to prevalence, but also involve clinical signs and symptoms, drug response, disease course and overall survival⁶³.

Key messages

- Gender-related differences are present both in human physiology and pathophysiology.
- Sex hormones play a pivotal role in explaining gender-related differences.
- The endocrine system is deeply affected by sex hormones.
- Gender-specific metabolic imbalances present in endocrine diseases, as well as many other factors, may represent a possible explanation of the prevalence and severity of the various complications caused by disease.
- Gender-related physiology may explain the different effects of a therapy which induce different therapeutic results in women compared with men.

Conclusions

Finally, gender-specific aspects can be observed in several endocrine diseases but the majority of these aspects have not been carefully assessed so far. However, evidence in the scientific literature holds that gender should always be considered in every element of the disease, from the causes to the treatment.

References

- Zhu J, Zhu X, Tu C, et al. Parity and thyroid cancer risk: a meta-analysis of epidemiological studies. *Cancer Med* 2016; 5: 739-52.
- Davies L, Morris LG, Haymart M, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: The increasing incidence of thyroid cancer. *Endocr Pract* 2015; 21: 686-96.
- Pires BP, Alves PA Jr, Bordallo MA, et al. Prognostic factors for early and long-term remission in pediatric differentiated thyroid carcinoma: the role of sex, age, clinical presentation, and the newly proposed American Thyroid Association Risk Stratification System. *Thyroid* 2016; 26: 1480-7.
- Upadhyaya A, Meng Z, Wang P, et al. Effects of first radioiodine ablation on functions of salivary glands in patients with differentiated thyroid cancer. *Medicine* 2017; 96: e7164.
- Manicardi V, Russo G, Napoli A, et al. Gender-disparities in adults with type 1 diabetes: more than a quality of care issue. A cross-sectional observational study from the AMD Annals Initiative. *PLoS One* 2016; 11: e0162960.
- Rossi MC, Cristofaro MR, Gentile S, et al. Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD Annals initiative. *Diabetes Care* 2013; 36: 3162-8.
- Manicardi V, Rossi MC, Romeo EL, et al. Gender differences in type 2 diabetes (Italy). *Ital J Gender-Specific Med* 2016; 2: 60-8.
- Karp I, Chen SF, Pilote L. Sex differences in the effectiveness of statins after myocardial infarction. *CMAJ* 2007; 176: 333-8.
- Mittendorfer B. Insulin resistance: sex matters. *Curr Opin Clin Nutr Metab Care* 2005; 8: 367-72.
- Goedecke JH, George C, Veras K, et al. Sex differences in insulin sensitivity and insulin response with increasing age in black South African men and women. *Diabetes Res Clin Pract* 2016; 122: 207-14.
- Basu A, Dube S, Basu R. Men are from Mars, women are from Venus: sex differences in insulin action and secretion. *Adv Exp Med Biol* 2017; 1043: 53-64.
- Mauvais-Jarvis F. Gender differences in glucose homeostasis and diabetes. *Physiol Behav* 2017 Aug 24 [Epub ahead of print].
- Quan H, Zhang H, Wei W, et al. Gender-related different effects of a combined therapy of exenatide and metformin on overweight or obesity patients with type 2 diabetes mellitus. *J Diabetes Complications* 2016; 30: 686-92.
- Kautzky-Willer A, Harreiter J. Sex and gender differences in therapy of type 2 diabetes. *Diabetes Res Clin Pract* 2017; 131: 230-41.
- D'Amelio P, Isaia GC. Male osteoporosis in the elderly. *Int J Endocrinol* 2015; 2015: 907689.
- Maggi S, Noale M, Giannini S, et al. Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOP study. *Osteoporos Int* 2006; 17: 237-44.
- Alswat KA. Gender disparities in osteoporosis. *J Clin Med Res* 2017; 9: 382-7.
- Pietschmann P, Rauner M, Sipos W, et al. Osteoporosis: an age-related and gender-specific disease--a mini-review. *Gerontology* 2009; 55: 3-12.
- Pietschmann P, Gollob E, Brosch S, et al. The effect of age and gender on cytokine production by human peripheral blood mononuclear cells and markers of bone metabolism. *Exp Gerontol* 2003; 38: 1119-27.
- South-Paul JE. Osteoporosis: part I. Evaluation and assessment. *Am Fam Physician* 2001; 63: 897-904, 908.
- Kharazmi M, Hallberg P, Michaelsson K. Gender related difference in the risk of bisphosphonate associated atypical femoral fracture and osteonecrosis of the jaw. *Ann Rheum Dis* 2014; 73: 1594.
- Sgro P, Sansone M, Parisi A, et al. Supra-physiological rhGH administration induces gender-related differences in the hypothalamus-pituitary-thyroid (HPT) axis in healthy individuals. *J Endocrinol Invest* 2016; 39: 1383-90.
- Leung KC, Johannsson G, Leong GM, et al. Estrogen regulation of growth hormone action. *Endocr Rev* 2004; 25: 693-721.
- Ciresi A, Amato MC, Pivonello R, et al. The metabolic profile in active acromegaly is gender-specific. *J Clin Endocrinol Metab* 2013; 98: E51-9.
- Sgro P, Guidetti L, Crescioli C, et al. Effect of supra-physiological dose administration of rhGH on pituitary-thyroid axis in healthy male athletes. *Regul Pept* 2010; 165: 163-7.
- Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr* 2008; 99: 931-40.
- Meyer MR, Clegg DJ, Prossnitz ER, et al. Obesity, insulin resistance and diabetes: sex differences and role of oestrogen receptors. *Acta Physiol (Oxf)* 2011; 203: 259-69.
- Lizcano F, Guzman G. Estrogen deficiency and the origin of obesity during menopause. *Biomed Res Int* 2014; 2014: 757461.
- Bianchi VE, Locatelli V. Testosterone a key factor in gender related metabolic syndrome. *Obes Rev* 2018 Jan 21 [Epub ahead of print].
- Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol* 2018; 178: 165-73.
- O'Sullivan AJ. Does oestrogen allow women to store fat more efficiently? A biological advantage for fertility and gestation. *Obes Rev* 2009; 10: 168-77.
- O'Sullivan AJ, Martin A, Brown MA. Efficient fat storage in premenopausal women and in early pregnancy: a role for estrogen. *J Clin Endocrinol Metab* 2001; 86: 4951-6.
- Oosthuyse T, Bosch AN. Oestrogen's regulation of fat metabolism during exercise and gender specific effects. *Curr Opin Pharmacol* 2012; 12: 363-71.
- Sarafian D, Schutz Y, Montani JP, et al. Sex difference in substrate oxidation during low-intensity isometric exercise in young adults. *Appl Physiol Nutr Metab* 2016; 41: 977-84.

35. Holdcroft A. Gender bias in research: how does it affect evidence based medicine? *J R Soc Med* 2007; 100: 2-3.
36. Bartlett C, Doyal L, Ebrahim S, et al. The causes and effects of socio-demographic exclusions from clinical trials. *Health Technol Assess* 2005; 9: iii-iv, ix-x, 1-152.
37. Goldstein LB, Amarenco P, Lamonte M, et al. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *Stroke* 2008; 39: 2444-8.
38. d'Emden MC, Jenkins AJ, Li L, et al. Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* 2014; 57: 2296-303.
39. Benz V, Kintscher U, Foryst-Ludwig A. Sex-specific differences in type 2 diabetes mellitus and dyslipidemia therapy: PPAR agonists. *Handb Exp Pharmacol* 2012: 387-410.
40. Tiidus PM, Lowe DA, Brown M. Estrogen replacement and skeletal muscle: mechanisms and population health. *J Appl Physiol* (1985) 2013; 115: 569-78.
41. Greising SM, Baltgalvis KA, Lowe DA, et al. Hormone therapy and skeletal muscle strength: a meta-analysis. *J Gerontol A Biol Sci Med Sci* 2009; 64: 1071-81.
42. Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. *Exerc Sport Sci Rev* 2010; 38: 61-7.
43. Ronkainen PH, Kovanen V, Alen M, et al. Postmenopausal hormone replacement therapy modifies skeletal muscle composition and function: a study with monozygotic twin pairs. *J Appl Physiol* (1985) 2009; 107: 25-33.
44. Jacobsen DE, Samson MM, Kezic S, et al. Postmenopausal HRT and tibolone in relation to muscle strength and body composition. *Maturitas* 2007; 58: 7-18.
45. Meeuwswen IB, Samson MM, Duursma SA, et al. Muscle strength and tibolone: a randomised, double-blind, placebo-controlled trial. *BJOG* 2002; 109: 77-84.
46. Brooke-Wavell K, Prelevic GM, Bakridan C, et al. Effects of physical activity and menopausal hormone replacement therapy on postural stability in postmenopausal women--a cross-sectional study. *Maturitas* 2001; 37: 167-72.
47. Boyanov MA, Shinkov AD. Effects of tibolone on body composition in postmenopausal women: a 1-year follow up study. *Maturitas* 2005; 51: 363-9.
48. Meeuwswen IB, Samson MM, Duursma SA, et al. The effect of tibolone on fat mass, fat-free mass, and total body water in postmenopausal women. *Endocrinology* 2001; 142: 4813-7.
49. Arabi A, Garnero P, Porcher R, et al. Changes in body composition during post-menopausal hormone therapy: a 2 year prospective study. *Human Reprod* 2003; 18: 1747-52.
50. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008; 359: 697-708.
51. Markle JG, Fish EN. Sex matters in immunity. *Trends Immunol* 2014; 35: 97-104.
52. Ortona E, Delunardo F, Maselli A, et al. Sex hormones and gender disparity in immunity and autoimmunity. *Ital J Gender-Specific Med* 2015; 1: 45-50.
53. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. *J Autoimmun* 2012; 38: J282-91.
54. Zandman-Goddard G, Peeva E, Shoenfeld Y. Gender and autoimmunity. *Autoimmun Rev* 2007; 6: 366-72.
55. Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* 2010; 34: J168-77.
56. Brandt JE, Priori R, Valesini G, et al. Sex differences in Sjogren's syndrome: a comprehensive review of immune mechanisms. *Biol Sex Differ* 2015; 6: 19.
57. Ortona E, Pierdominici M, Maselli A, et al. Sex-based differences in autoimmune diseases. *Ann Ist Sup Sanità* 2016; 52: 205-12.
58. Magri F, Zerbini F, Gaiti M, et al. Gender influences the clinical presentation and long-term outcome of Graves disease. *Endocr Pract* 2016; 22: 1336-42.
59. Blohme G, Nystrom L, Arnqvist HJ, et al. Male predominance of type 1 (insulin-dependent) diabetes mellitus in young adults: results from a 5-year prospective nationwide study of the 15-34-year age group in Sweden. *Diabetologia* 1992; 35: 56-62.
60. Nystrom L, Dahlquist G, Ostman J, et al. Risk of developing insulin-dependent diabetes mellitus (IDDM) before 35 years of age: indications of climatological determinants for age at onset. *Int J Epidemiol* 1992; 21: 352-8.
61. Samuelsson U, Lindblad B, Carlsson A, et al. Residual beta cell function at diagnosis of type 1 diabetes in children and adolescents varies with gender and season. *Diabetes Metab Res Rev* 2013; 29: 85-9.
62. Martinez D, Castro A, Merino PM, et al. Oestrogen activity of the serum in adolescents with type 1 diabetes. *Diabet Med* 2016; 33: 1366-73.
63. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. *Front Neuroendocrinol* 2014; 35: 347-69.
64. Mazer NA. Interaction of estrogen therapy and thyroid hormone replacement in postmenopausal women. *Thyroid* 2004; 14 Suppl 1: S27-34.
65. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 2013; 34: 309-38.

Conflict of interest statement: the Authors declare no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Correspondence to:
Marialuisa Appetecchia
Endocrinology Unit, IRCCS Regina Elena National Cancer Institute
Via Elio Chianesi, 53
00144 Rome, Italy
email marialuisa.appetecchia@ifog.gov.it