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Thyroid diseases and gender

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Summary. Gender has been always cited among the relevant epidemiological variables to consider when studying thyroid diseases, but the relatively new approach of modern gender medicine contributes to adding new perspectives to the subject. The relevance and frequency of both functional and neoplastic thyroid disorders has prompted us to review the available findings in the literature and clinical practice, with no ambition to cover the entire breadth of the matter but to give a few hints to start a fresh and stimulating debate. For sure, further research is needed to establish better diagnostic and therapeutic strategies and implement them in daily clinical work-up, as a result of an effective mindset shift in our practice.

Key words. Thyroid diseases, women's health, prognostic factors.

Patologie della tiroide e genere

Riassunto. Tra le variabili che condizionano l'espressione e l'andamento delle patologie funzionali e neoplastiche della tiroide, il genere è sempre stato citato, ma l'approccio relativamente nuovo della medicina di genere ha dato un ulteriore impulso a considerare attentamente questo fattore nella diagnosi e nella gestione clinica di queste patologie. Dato che, dopo il diabete mellito, le tireopatie sono il motivo endocrino-metabolico più frequente che porta i pazienti all'attenzione dell'endocrinologo e del medico di medicina generale, si è pensato potesse essere utile passare brevemente in rassegna gli aspetti meglio conosciuti e i punti ancora da indagare in questo campo.

Parole chiave. Tireopatie funzionali e neoplastiche, salute della donna, fattori prognostici.

Introduction

Gender differences are firmly established as significant clinical variables to be looked at in the diagnosis, prognosis and management of most diseases[1-5]. Endocrine diseases are no exception. The definition of 'gender' is broader than that of 'sex': the latter stands for the biological differences in females and men induced by both hormones and genetic array, where the former also includes a bundle of cultural, psychological and environmental factors. Data shows that women are more often than men affected by a number of metabolic and endocrine alterations, with different clinical courses and outcomes. It comes as no surprise that endocrinologists be largely involved in gender medicine and in what this relatively new approach can add to the clinical management of endocrine diseases[6-8]. Increasing epidemiological data shows that – among endocrinopathies – thyroid diseases rank second after diabetes and osteoporosis/osteopenia. All over the world, about 200 million people are possibly affected by some kind of thyroid dysfunction. The aim of this review is to sum up and briefly examine what we know about the impact of gender on the thyroid.

Epidemiology

Starting from the raw figures about prevalence, we know that thyroid diseases affect women 500% more than males[9-14]. It has been seriously discussed based on these high figures to perform thyroid function tests (TFT) as a screening tool for women aged >35 years to be added to other similar 'at-risk' categories (hypertension, hypercholesterolemia, etc.)[15,16]. There are several reasons on which a convincing explanation for these differences can be based. First of all, it is easy to suspect that the estrogen environment and the peculiar cyclical pattern of hormonal variations are strong promoters for thyroid dysfunctions among females. Second, there is a greater prevalence of autoimmune diseases in females than males. Of paramount importance, thyroid diseases are the most common endocrine factors affecting women in reproductive age[17-22]. Thyroid hormones have a powerful impact on the whole process, from puberty and menstruation (they can be early or late). Menstrual cycles can be short and light or longer and heavy, and irregular menstrual periods can follow on to amenorrhea. The ovulation phase, when the human egg is released for fertilization, is often affected by an overactive or underactive thyroid, up to complete anovulation. Hypersecretion of prolactin, as seen in severe hypothyroidism, contributes to blocking ovulation and inducing milk production by the breast. A hypothyroid gland is suspected to play a significant role in the pathogenesis of

ovary cysts. Suffering from a functional thyroidal disorder during pregnancy induces multiple forms of direct harm to fetal development in general and to the central nervous system in particular, and leave a post-partum thyroiditis in the mother. Moreover, a number of peri-partum complications may arise in hypothyroid mothers, such as pre-eclampsia, miscarriages, preterm delivery, stillbirth, and post-partum hemorrhage. Thyroid disorders may cause early menopause (before age 40 or in the early 40s). Later in women's life, hyperthyroidism can mimic early menopause[23,24], with a typical set of symptoms (amenorrhea, hot flashes, mood instability).

Hypo and hyperfunction

The prevalence ratio for functional alterations is female/males = 8:5, and tends to increase with ageing. Hypothyroidism in women is more frequent after 60 years of age. At the time of diagnosis, symptoms of overt autoimmune disease tend to be more apparent and specific in men than in women, but, in the latter, symptoms persist longer and are less effectively managed by therapy.

In women, symptoms are also experienced by healthy volunteer subjects studied as controls; this means that the presence and absence of symptoms is a more valuable hint for a diagnosis of hypothyroidism in men compared to women. After l-thyroxine therapy of new overt autoimmune hypothyroidism, women may experience more symptoms than men also treated for thyroid failure.

As to hyperfunction, it is very much the same: females show higher incidence of hyperthyroidism than males. Graves' disease is seven times more common in women than in men. Both sexes get worse as age increases.

Table 1. Hypothyroidism and hyperthyroidism in men and women

	%	P
Men		
Euthyroid	96.44	<0.01
Hypothyroid	3.02	<0.01
Hyperthyroid	0.54	<0.01
Women		
Euthyroid	82.9	<0.01
Hypothyroid	10.5	<0.01
Hyperthyroid	1.47	<0.01

Source: Modified from Meng et al[52].

It has been rightly said that one of the greatest achievements of modern laboratory medicine was the availability of reliable and cost-effective blood tests to monitor thyroid function[25]. Today, thyroid function tests are, by and large, the most frequently requested endocrine laboratory data. The advent of 3rd generation TSH tests changed the game: clinical presentation of functional thyroid abnormalities is often non-specific, even though these conditions are by no means infrequent and their treatment readily and effectively available. The sensible use of biochemical tests is the more cost-effective way to manage a clinical suspect. However, despite the huge success of these strategies in diagnosis and treatment, there are several limitations that healthcare providers have to consider[26-28].

The most frequent etiology of thyroid functional abnormalities is autoimmunity. It accounts for over 90% of non-iatrogenic hypothyroidism in iodine sufficient countries[29-33]. The origin of autoimmune disease is a disruption in the immune tolerance of self-antigens. This is thought to occur in genetically susceptible individuals after exposure to environmental triggers. However, what is often overlooked is that a very significant component of the genetic contribution to autoimmunity is gender, with the presence or absence of a Y chromosome influencing the risk for autoimmune disease[34-36].

Replacement therapy. A number of studies have shown possible differences in terms of requirements of l-thyroxine in primary hypothyroidism between men and women[37]. The differences are probably linked to overweight and indicate a need for greater doses in women, both pre- and post-menopausal compared to men, in order to get the expected TSH target values (0.4-3.5 µg/l). Further studies are probably required to better define the TSH/l-T4 dose relationship and to seek to obtain significant improvements in attaining a timely and cost-effective euthyroid balance in these patients.

Anti-thyroid drugs. A very interesting recent study from Israel[38] investigated possible differences in therapeutic response to anti-thyroid drugs (ATD) related to gender. The authors concluded that no major role in the clinical response to ATD can be directly assigned to gender either in remission and in recurrence rates. No serious evidence was found against the use of ATD as a first-line therapy in hyperthyroidism.

Thyroid cancer

Female prevalence in cancer incidence and its peak registered in pre-menopausal subjects suggests that the female sex hormones play a significant role in developing thyroid cancer. The clear association with breast cancer, a neoplasm that almost exclusively affects the female gender, makes this hypothesis stronger. There is

convincing evidence of a significant increase in the odds of developing either thyroid or breast cancer as a secondary malignancy after diagnosis of the other. This link is expected to show increasing importance as long as the trend of thyroid cancer keeps on rising and steps forward in management and treatment for both cancers continue[39-42].

The American Thyroid Association (ATA) claims that women are much more exposed than men to proliferative thyroid diseases. Risk increases when therapeutic estrogens are used and decreases after menopause. The following items are currently matter of active investigation:

- the reported imbalance between the isoforms of estrogen receptor (ER), α and β, could be responsible for cell proliferation;
- there are few studies comparing the ERα/ERβ profile in thyroid tumor tissue and normal thyroid tissue;
- it has been hypothesized that endogenous sex steroids may help modulate normal/pathological thyroid growth;
- recent works on rat thyrocytes suggest possible gender-specific responses when exposed to sex steroids.

A better understanding of sex hormones and the autonomous regulation of ER expression and actions on thyroid tumors is needed to study targeted therapies that can modulate ER interactions in tumorigenesis[43-45].

The link between estrogens and cancer has not been found yet, but estrogen receptors could play a pivotal role in preventing cancer proliferation and its consequences, namely neo-angiogenesis and metastatic spread.

Gender is a critical factor; it can significantly modify tumor incidence linked to aging. We still need studies powerful enough to fully elucidate all the main risk agents that cooperate in determining the increase in tumor incidence where gender difference is more relevant. At presentation, male subjects usually show more advanced lesions, with a more aggressive tissue subtype, and are generally older than females. We know that gender is not an independent prognostic factor for disease-free survival. Thus, an extended screening program could give early diagnoses, and it is sensible to expect significant healthcare benefits from it.

Male gender is among the worst independent prognostic factors for papillary thyroid carcinoma. A recent metanalysis found a 50% increase in recurrence in males compared to females, even worse than age. Other data does not confirm these conclusions. A TSH concentration below the reference range was associated with a significant increase in tumor risk in women but not in men[46-48].

Another possible explanation for gender differences in thyroid cancer incidence is the greater confidence of women in physician's advice and their more frequent use of diagnostic services.

Calcitonin is the preferred biochemical marker for medullary carcinoma, but its use is hampered by the lack of evidence of universal cut-off values. A recent paper from Germany[49] looks for possible differences in calcitonin reference ranges related to age and gender in a pediatric population. The authors conclude that a difference does exist between males and females (with higher values for the boys), independent of thyroid inflammatory states, and this must be taken into account in interpreting the data.

Gender-related thyroid and cardiovascular risk

In recent years, much interest has been focused on the different effects of thyroid hormones on lipid metabolism in males compared to females. Thyroid hormones favor the elimination of neutral sterols and bile acids, and reduce the intestinal absorption of cholesterol. A direct impact on LDL-C receptors and a scavenger role for circulating LDL-C has been shown in experimental models. The increasing expression of hepatic cholesterol 7-α hydroxylase gene induced by thyroid hormones is probably responsible for their well-known ability to decrease cholesterolemia; furthermore, they could stimulate the lipase activity of the liver, contributing to the global effect. On the other hand, TSH has an opposite effect on lipid metabolism: its receptors are expressed on many different tissues and, when switched on by thyrotropin, can stimulate a complex signaling system driven by AMP that induces the expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A-reductase, a rate-limiting enzyme in cholesterol synthesis, which can modulate lipoprotein metabolism and facilitate cholesterol uptake by the liver. TSH can generate serum lipid profiles independent of thyroid hormones. Furthermore, a significant direct TSH effect has been observed on total cholesterolemia levels. It has been convincingly demonstrated that a 1 μIU/ml increase in the TSH level adds 0.016 mmol/l to total cholesterolemia[50-52].

As widely known, males show a tendency to hypercholesterolemia (both total and LDL) from the earliest age up to the mid-seventies, but then a decrease is seen for the late decades. Females show a steadfast increase up to oldest age; as a result, after menopause, hypercholesterolemia prevalence is higher than in males. The very same can be seen in hypertriglyceridemia. The direct correlation between increasing levels of serum TSH and lipidemia is strongly gender-specific for triglycerides and HDL cholesterol. Low levels of TSH seem to protect males against hyperlipemia; high TSH concentrations in females herald damaging hyperlipidemia[53-56].

Final remarks

Sex and gender play a key role in determining occurrence and clinical course of thyroid diseases. The modern concept of 'gender medicine' throws new light on many aspects of this topic. Besides the multiple pathophysiological factors, the most recent discoveries in endocrinology, the relevant prevalence of these abnormalities, and many aspects defining psychological and cultural behaviors are deemed to impact on health care today more often than in the past and are to be taken into consideration by caregivers. As practicing physicians, we are now aware that real differences do exist, both in diagnosis and in therapeutic options, between men and women. Prevention strategies, symptoms, diagnostic pathways, and drug prescriptions: all of them are gender-dependent, in a way. We cannot meet the standards of personalized medicine, let alone appropriateness, if we fail to take into account gender diversity, either in strategic planning and in good clinical practice. Medical faculties, research institutions, hospitals and governments must cooperate in favoring basic and clinical research, deepening our knowledge and, most importantly, stimulating the birth of a new mindset in junior doctors and other healthcare professions.

This review aimed to summarize the multiple factors and the wide range of gender-related variables impacting on diagnosis and treatment of thyroidal diseases. We need to expand our own knowledge and help educate the new generations in a deeper and wiser approach for this fascinating area of clinical endocrinology.

In conclusion, gender medicine represents a hard, yet very exciting challenge for endocrinologists. We are just reading the very first chapter of this novel, and much work is still to be done.

"…We have promises to keep, and miles to go before we sleep" (Robert Frost).

Key messages

- Convincing data show that thyroid is far more often affected by metabolic and endocrine alterations in women than in men, with relevant differences in clinical course and outcomes.
- Possible explanations: first, the estrogen environment and the peculiar cyclical pattern of hormonal variations can target the female thyroid; second, the greater prevalence of autoimmune diseases in women than men.
- The higher prevalence in cancer incidence with its peak registered in pre-menopausal subjects suggest that female sex hormones play a significant role in developing thyroid cancer.
- Male gender is one of the worst independent prognostic factors for papillary thyroid carcinoma, even worse than age. A recent meta-analysis found a 50% recurrence increase in males compared to females.
- Much interest has been focused on the different effects of thyroid hormones on lipid metabolism of men compared to women. A direct correlation between increasing levels of serum TSH and lipidemia is strongly gender-specific for triglycerides and HDL cholesterol. Low levels of TSH likely protect males against hyperlipemia; high TSH values in females, instead, seem to anticipate relevant damage by hyperlipidemia.

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