Gender Specific Medicine in Endocrinology and Metabolism

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Educational aims

- To increase awareness of the role played by sex and gender in disease pathogenesis and progression
- To disseminate evidence for sex and gender specific influences on a select number of endocrine conditions
- To highlight those diseases where we have local data to support sex and gender specific medicine in endocrinology.

Key words
Gender, sex, medicine, endocrinology, metabolism

Abstract

There is increasing evidence for a distinct role(s) for sex and gender in disease onset, progression and response to treatment. This article will review the evidence for sex and gender specific differences in the field of endocrinology and metabolism, citing examples of such influences in a variety of endocrine disorders both internationally and locally.

Introduction

Gender can be defined as the spectrum of physical, biological, mental and behavioral characteristics particular to, and differentiating between, masculinity and femininity. Gender is generally influenced by cultural, psychosocial and educational factors. In contrast sex generally refers to the biological differences arising due to genetic and hormonal influences on males and females. In reality, the two terms are often used interchangeably.

Gene-environment interactions

It has become increasingly clear that disease and disease processes occur as a result of the interplay between genes and the environment, lending credence to the hypothesis that sex chromosomal linkage of specific genes together with environmental interactions forms the basis for the predominance of certain diseases in one sex as opposed to the other. It is interesting to note that the X chromosome carries almost 2000 genes responsible for encoding protein whilst the Y chromosome carries a distinct set of 78 genes. Researchers continue to report significant sex and gender differences in the incidence and prevalence of disease, in perception of disease as well as in disease progression and response to treatment. This paper will attempt to highlight a few of the gender specific differences which have been

documented in the field of Endocrinology and Diabetes with reference to studies of relevance to the Maltese population when available.

Pituitary gland

The pituitary gland has long been dubbed the master gland in the endocrine system. Benign pituitary adenomas can arise in the gland and have significant effects on the regulation of a number of other endocrine glands in the human body. An analysis of the incidence and prevalence of pituitary adenomas in Malta revealed that there is a lower prevalence of macroadenomas in females as compared males (29.5 vs 75%) with a significant increase in standardized incidence rates in females of child bearing age as compared to males. Females, on the other hand, have a higher prevalence of microadenomas (73.3/100,000 vs 11.6/100,000) with an SIR of 5.3/100,000 in women vs 0.63/100,000 in men.[1] The reason for this difference is unknown.

Thyroid gland

Gender specific differences have also been reported in a number of malignant endocrine tumours. In 2008, the highest incidence rate of thyroid cancer was estimated to be in France, where the female rate was five times higher than the rate of the lowest ranking country, Greece (18.6 versus 3.3 per 100,000 females). Age-standardised rates for Malta revealed a rate of 9.3 per 100,000 females vs 0.9 per 100,000 males as compared to Greece where the SIR was 3.3 per 100,000 in females vs 1.1 per 100,000 in males.[2] Males developing thyroid cancer, on the other hand, tend to present later than females and have a worse prognosis.[3]

Autoimmune disease

Similarly autoimmune diseases occur predominantly in women (Figure 1).[4] For example, 95% and 88% of Hashimoto's thyroiditis and Graves' disease respectively occur in females. To date we do not have any data regarding the incidence or prevalence of autoimmune disease in Malta and specifically none with respect to sex and gender differences.

A number of possible initiating factors and mechanisms have been postulated (Figure 2). There is a growing body of evidence that the observed sex and gender related differences are multifactorial in origin. Sex hormones, which determine biological differences, represent important

Figure 1: Gender distribution of the major autoimmune diseases. The numbers above the bars refer to the total number of disease cases (×1,000,000) in the USA.[4]

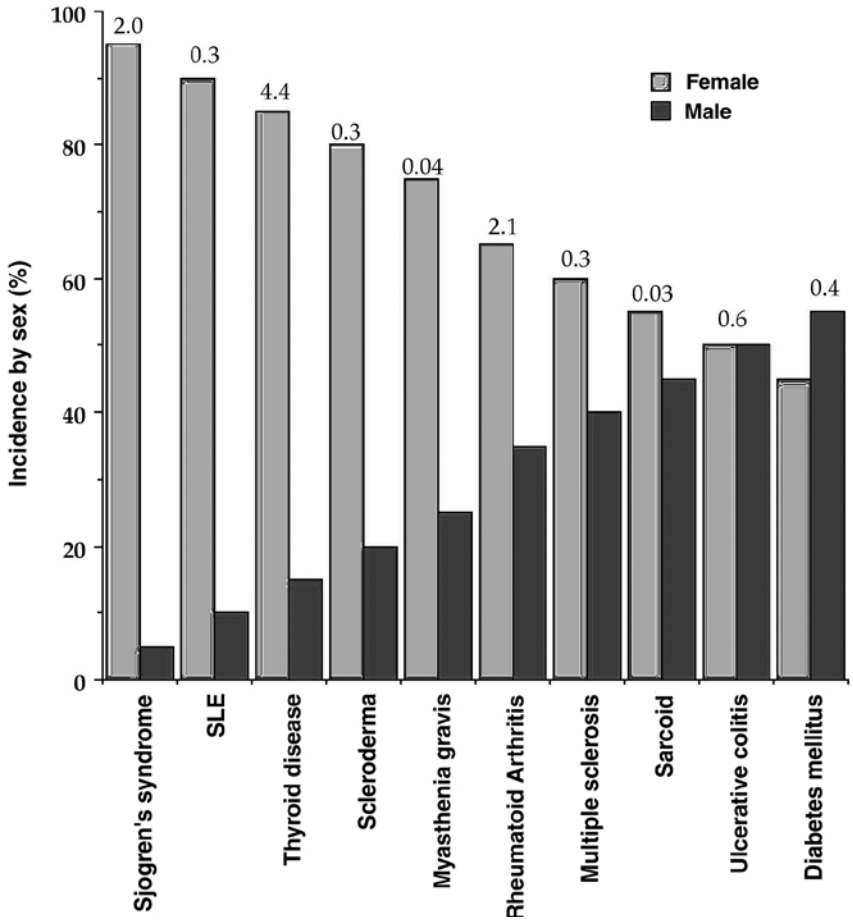
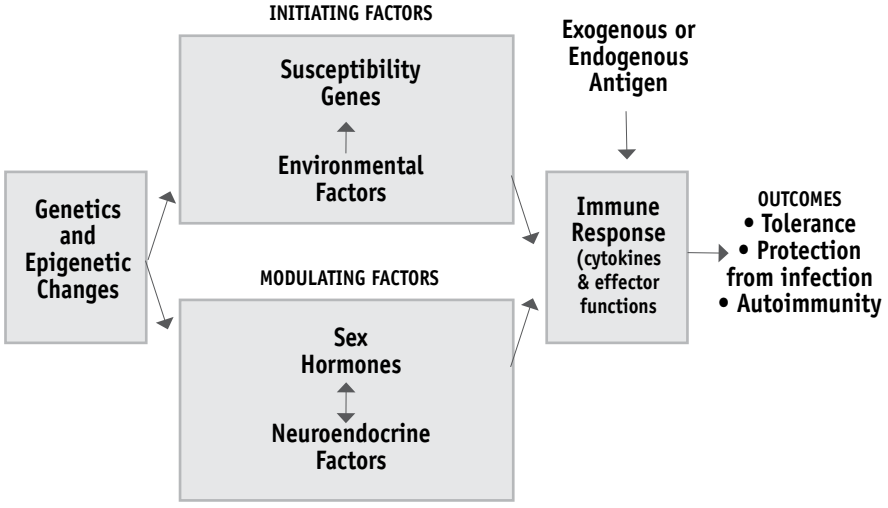


Figure 2: A model for the multifactorial nature of autoimmune disease.[5]



modulatory factors in the immune and autoimmune response.[5]

Parathyroid glands

Primary hyperparathyroidism represents another endocrinological condition that predominates in women The prevalence of primary hyperparathyroidism has been estimated to be 3 per 1000 in the general population and as high as 21 per 1000 in postmenopausal women. It is almost three times as common in women as men.[6,7]

Significant sex specific associations between glucocorticoid receptor (GR) gene polymorphisms and the HPA axis responses to psychosocial stress as well as to glucocorticoid (GC) sensitivity have been reported.[8] In familial glucocorticoid resistance, which is inherited as an autosomal recessive or dominant disorder characterized by glucocorticoid receptor gene mutations, decreased cortisol effects and secondary ACTH release occur. Clinical presentation depends on age at presentation, biological sex of the subject and organ specific effects. Females can present with virilisation and menstrual irregularities, both sexes with precocious puberty, males with disorders of spermatogenesis and fertility whilst hypertension and hypokalaemic alkalosis occur in both sexes. This provides an excellent example of differential modulation of endocrine gland activity by glucocorticoids and sex steroids.[9]

Cardiometabolic disease

Diabetes and cardiometabolic disease, whilst not generally perceived as "endocrine" disorders, are similarly associated with significant pancreatic, hepatic, skeletal muscle and adipose tissue functional aberrations and are no exception to the influences of both gender and sex on the endocrine system in its broadest sense.

In Type1 Diabetes Mellitus (T1 DM), an autoimmune endocrine disorder, there is approximately a 1:1 gender distribution of the disease. However, there is a switch in the gender specific ratio with adulthood in that below 18 yrs of age, the incidence of TI DM in women is higher than in males but above 18 years of age, there is a reversal in this ratio.[10] Furthermore, the cumulative incidence of certain complications of diabetes such as End Stage renal Disease (ESRD) varies in an age and sex dependent fashion depending on the age of onset of the disease. For example, in the Finnish Diabetic Nephropathy study, the incidence of ESRD and diabetic retinopathy doubled in males compared to females if the age of onset of diabetes was above 15 years of age.[11]

Diabesity is a condition that has reaching epidemic status worldwide with biological and psychosocial factors, sex and gender widely accepted as playing a significant role in the aetiology of this condition. Gene expression, body fat distribution, adipocytokine activitiy and inflammation as well sex hormone levels have been shown to be modulated by a multitude of environmental factors including lifestyle, socioeconomic status, level of education, culture, migrations and epigenetics. In utero influences on fetal development including over- and undernutrition, alcohol, stress, smoking, and environmental toxins all can affect the eventual phenotype of the offspring. For instance, male infants born during times of starvation are more prone to develop DM.

The Scottish Care Information Diabetes Collaboration revealed that at all ages, males are diagnosed with DM at lower Body Mass Index (BMI) levels than women.[12] An analysis of insulin sensitivity and beta cell function in healthy subjects with normal glucose tolerance revealed that, women have better insulin sensitivity and secretion adjusted for age and BMI than men. On Oral Glucose Tolerance Testing (OGTT), these women had lower mean FBGs and higher 2 hourly blood glucose levels.[13] On further analysis, prolonged gut glucose absorption was observed in healthy women as compared to men which translated into a higher prevalence of Impaired Glucose Tolerance (IGT) in women[14]. This could explain why in the prediabetes stage, women are more likely to have impaired glucose tolerance (IGT) and men more often have impaired fasting glucose (IFG).

Age-dependent changes in sex hormone levels also lead to changes in metabolism. Postmenopausal females have lower insulin sensitivity, decreased beta cell function, worsening lipid profiles, and higher blood pressure readings as compared to premenopausal women. Such changes are less marked in men.[15] Whilst studies have revealed that lower levels of testosterone in men decrease metabolic risk, in women higher testosterone levels are associated with a higher prevalence of insulin resistance and the metabolic syndrome.[16]

Socioeconomic conditions

Modulation by socioeconomic factors has also been documented in the literature. Educational level attained has been shown to affect lifestyle, and the prevalence of overweight and obesity in both sexes. In females attaining a lower level of education the risk of diabetes and hypertension increases whereas in men it is the risk of stroke that increases.[17]

Conclusion

In conclusion, analysis of disease susceptibility and onset, disease course, progression and response to treatment reveals a multitude of intrinsic and extrinsic modulatory factors which can lead to differential effects and outcomes in males and females. Response to interventions and medications can also exhibit sex and gender specific differences and ultimately a holistic approach to the management of disease in individuals needs to take these differences into account. Future research needs to focus on further elucidation of the these factors and of the mechanisms involved in gender specific medicine.

Key points

- Clear evidence of sex related differences in disease incidence and prevalence.
- Disease manifestation and progression can be influenced by both sex and gender.
- Limited data are available with respect to gender and sex specific medicine in endocrinology.
- A holistic approach to disease diagnosis and management must take gender and sex specific aspects into consideration.
- Further research into this area are essential to facilitate appropriate, equitable and holistic health care provision.

References

1. Gruppetta M, Mercieca C, Vassallo J. Incidence and prevalence of pituitary adenomas in the Maltese islands. Pituitary 2013; 16:545–553.
2. European Age-Standardised rates calculated by the Cancer Research UK Statistical Information Team, 2011, using data from GLOBOCAN 2008 v1.2, IARC, version 1.2.
3. Yao R, Chiu CG, Strugnell SS, Gill S, Wiseman SM Gender Differences in Thyroid Cancer Expert Rev Endocrinol Metab. 2011; 6(2):215-243.
4. Fishman J, Wick JG & Koenig BA. Agenda for Research on Women's Health for the 21st Century: NIH Publication 99-4385.Vol.2, 15–19 (NIH, Bethesda, MD, 1999).
5. Whitacre CC Sex differences in autoimmune disease. Nature Immunology 2001; Vol 2(9), 777-780
6. Bilezikian J, Silverberg P, Shonni J. Primary hyperparathyroidism: Epidemiology and clinical consequences. Clinical Reviews in Bone and Mineral Metabolism 2002; 1 (1): 25–34. doi:10.1385/BMM:1:1:25.
7. Bolland MJ, Grey AB, Gamble GD, Reid IR. Association between Primary Hyperparathyroidism and Increased Body Weight: A Meta-Analysis. J Clin Endocrinol Metab 2004; 90 (3): 1525. doi:10.1210/jc.2004-1891.
8. Kumsta R, Entringer S, Koper JW, van Rossum EFC, Hellhammer DH, Wust S Sex Specific Associations between Common Glucocorticoid Receptor Gene Variants and Hypothalamus-Pituitary-Adrenal Axis Responses to Psychosocial Stress Biological Psychiatry 2008 Volume 62, Issue 8, Pages 863–869.
9. Charmandari E, Kino T, Chrousos GP Familial/sporadic glucocorticoid resistance: clinical phenotype and molecular mechanisms. Ann N Y Acad Sci 2004; 1024:168-173.
10. Rami B, Waldhor T, Schober E. Incidence of Type I diabetes mellitus in children and young adults in the province of Upper Austria, 1994-1996 Diabetologia 2001; 44 Suppl 3:B45-7
11. Hartjutsajo V, Maric C, Forsblom C, Thorn L, Wadén J, Groop PH; FinnDiane Study Group. Sex related differences in the long term risk of microvascular complications by age at onset of Type I diabetes. Diabetologia. 2011; 54(8):1992-9.
12. Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, McKnight JA, Morris AD, Pearson DW, Petrie JR, Philip S, Wild SH, Sattar N. Scottish Diabetes Research Network Epidemiology Group Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia. 2011; 54(12):3003-6.
13. Kautzky-Willer A, Brazzale AR, Moro E, Vrbíková J, Bendlova B, Sbrignadello S, Tura A, Pacini G. Influence of increasing BMI on insulin sensitivity and secretion in normotolerant men and women of a wide age span. Obesity (Silver Spring). 2012; 20(10):1966-73.
14. Anderwald C, Gastaldelli A, Tura A, Krebs M, Promintzer-Schifferl M, Kautzky-Willer A, Stadler M, DeFronzo RA, Pacini G, Bischof MG. Mechanism and effects of glucose absorption during an oral glucose tolerance test among females and males. J Clin Endocrinol Metab. 2011;96(2):515-24
15. Kautzky-Willer A, Handisurya A Metabolic diseases and associated complications: sex and gender matter. Europ J Clin Invest 2009; Europ J Clin Invest 2009; 39 (8): 631-648.39 (8): 631-648
16. Ding EL, Song Y, Malik VS, Liu S Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006 15; 295(11):1288-99.
17. Kautzky-Willer A, Dorner T, Jensby A, Rieder A. Women show a closer association between educational level and hypertension or diabetes mellitus than males: a secondary analysis from the Austrian HIS. BMC Public Health. 2012 May 30;12:392. doi: 10.1186/1471-2458-12-392