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Commentary

Sex-Gender Awareness in Diabetes

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Abstract: Sex and gender can affect incidence, prevalence, symptoms, course and response to drug therapy in many illnesses, being sex (the biological side) and gender (the social-cultural one), variously interconnected. Indeed, women have greater longevity; however, this is accompanied by worse health than men, particularly when obesity is present. Sex-gender differences are fundamental also in both type 1 and type 2 diabetes. Just for example in the prediabetes situation impaired fasting glucose (expression of increased insulin resistance) is more common in men, while impaired glucose tolerance (expression of beta cell deficiency) is more common in female, indicating a possible different genesis of type 2 diabetes in the two sexes. In type 1 diabetes male and female are equivalent as incidence of the disease since puberty, while estrogens act as protective and reduce the incidence of type 1 diabetes in female after puberty. Considering macrovascular complications, diabetic women have a 3.5 fold higher increased cardiovascular risk than non diabetic women, against an observed increase of "only" 2.1 fold in male. Thus it is clear, although not fully explained, that sex-gender differences do exist in diabetes. Another less studied aspect is that also physician gender influences quality of care in patients with type 2 diabetes, female physicians providing an overall better quality of care, especially in risk management. The goal of this short commentary is to open the special issue of Diabetology: "Gender Difference in Diabetes" leaving to the individual articles to deepen differences in genesis, psychologists aspects and complications of the disease.

Keywords: type 1 diabetes; type 2 diabetes; cardiovascular disease; diabetic retinopathy; drug therapy in diabetes

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1. Introduction

Diabetes mellitus and cardiovascular diseases act as two sides of the same coin: diabetes is considered as an equivalent of ischemic cardiovascular disease while patients with ischemic cardiovascular disease often have diabetes or pre-diabetes. Diabetic women have a 3.5 fold higher increased cardiovascular risk than non diabetic women, against an observed increase of "only" 2.1 fold in male. Gender is considered as the social expression that transforms a female into a woman and a male into a man, while sex is the set of biological aspects of being female or male. The differences and inequalities in the state of health often derive from both biological (sex) and social-cultural (gender) differences that are variously interconnected, so I prefer to use the term sex-gender in this commentary, as it has been done before [1,2].

In view of the impact of sex hormones on glucose homeostasis and on the molecular pathways involved in insulin resistance, sex-gender specific mechanisms in the development of diabetic complications are more than suspected, but leave an unmet need of specific sex-gender therapeutic approaches.

There is scientific evidence that sex and gender can affect the incidence, prevalence, symptoms, course and response of many illnesses. Women have greater longevity, but this is accompanied by worse health than men, particularly when obesity is present: over the age of 65, women have three or more chronic diseases more often than men and suffer from greater disability [3]. Women have a higher prevalence of psychiatric, musculoskeletal and

some autoimmune pathologies compared to men of the same age. Sex-gender differences are fundamental also in both type 1 (insulin dependent, T1DM) and type 2 (non-insulin dependent, T2DM) diabetes.

2. Type 2 Diabetes

Regarding T2DM, sex-gender differences do have a role in the homeostasis of glucose, even in the prediabetic syndromes impaired fasting glucose (IFG), more related to insulin resistance and impaired glucose tolerance (IGT), more related to beta cell dysfunction. IFG is more prevalent in males, while IGT in women is a disease that occurs mainly due to insulin resistance and loss of beta cell function combined together differently [4,5], suggesting clear sex-gender different etiological mechanisms that lead to T2DM. T2DM has a higher prevalence in men, but since women are more numerous, there are more women than men affected [6–8].

Another area of sex-gender difference in glucose homeostasis is the bi-directional modulation of diabetes risk by testosterone in males and females. In males, testosterone protects against diabetes, as hypogonadism induced with anti-testosterone therapy for prostate cancer is reported to promote the development of T2DM. The same applies when physiological age related hypogonadism appears. On the contrary, testosterone administration in hypogonadal males improves insulin sensitivity, and has a multidimensional favorable effect on cardiovascular risk profile. The effects of testosterone are rather different in women. Women with testosterone excess exhibit initial β-cell hyper-function, which may predispose them to secondary β-cell failure and type 2 diabetes [1].

3. Type 1 Diabetes

Regarding T1DM, less is known about sex-gender differences. In any case, T1DM is the only common autoimmune disease with a peak of onset of less than 15 years of age that is characterized by male: female ratio of about 1.5 worldwide, with an incidence of the disease similar between the two sexes until puberty and a decreases in women thereafter, although female T1DM patients have higher levels of GADAab (antibodies against glutamic acid decarboxylase) and a more severe loss of beta-cell function than male patients with the same age at diagnosis. The decrease in T1DM incidence in females after puberty might be due to increased estrogen activity; indeed, a decrease in estrogen activity is observed in female T1DM patients and at least some of the problems observed in T1DM women may in part be due to the relationship between decreased estrogen levels and insulin action [9]. T1DM onset can be observed at any age [10] but most epidemiological studies focus on the disease with clinical diagnosis during childhood and adolescence. Indeed, adult T1DM may be difficult to discriminate from certain forms of T2DM and from Latent Autoimmune Diabetes in Adults (LADA) [11,12], but in any case the geographical variations of T1DM incidence in adults parallel those reported in children. As we said before, after puberty the incidence of T1DM in women is decreased mainly due to estrogen activity, thus T1DM with adult onset is largely represented in males. In T1DM it is also important to recall that acute diabetes complications like non-ketonic hyperosmolar coma is diagnosed almost twice as often in women compared to men, while hypoglycaemia and diabetic ketoacidosis appears to be 1.5 times more common in females than in males. Rewers and colleagues indicated that the increased risk of diabetic ketoacidosis (DKA) among adolescent girls (relative to younger children) may be related to body image issues leading adolescent girls to skip insulin injections to promote weight loss [13]. Increased insulin resistance due to puberty or obesity may also play a role in the greater risk of DKA, as a higher insulin dose was a predictor of DKA at all ages. Eating disorders, frequent among children with diabetes, may also affect the risk of DKA but may be challenging to identify in this population. In one study using the Diabetes Audit and Research in Tayside Scotland database, it was suggested that poor adherence to insulin treatment in young adults with insulin-dependent diabetes mellitus is the major factor that contributes to long-term poor glycemic control and diabetic ketoacidosis [14]. A particular disease called

diabulimia, which consists of the arbitrary reduction or omission of insulin that results in rapid weight loss but puts the patient at risk of ketoacidosis, has been described as being more common among diabetic adolescents in whom prevalence of this disturbance reaches up to 38% in females compared to the estimated male prevalence of 16%.

4. Chronic Macrovascular Complications in Diabetes

Gender differences are particularly expressed also in diabetic chronic complications. Patients with diabetes have higher incidences of MI than those without diabetes [15]. Diabetic women have a higher risk of cardiovascular mortality, especially in the post-menopause stage, and it is clear that diabetic women lose their normal premenopausal protection against cardiovascular disease. Several studies show that the diagnosis of diabetes is made later in women, who, remaining exposed for a longer time to "uncontrolled" diabetes, have worse clinical conditions at diagnosis than men, with more severe obesity and less ease reaching the desired therapeutic targets. Women are also less likely to receive all diagnostic and therapeutic measures than their male counterparts, and mortality and disability after a first cardiovascular event are known to be higher than in men [16], particularly in the age range under 54 years. Interestingly, T2DM men had higher incidence rates of ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) than T2DM women as observed also in the general population [17]. Several studies have found an increased risk of death after myocardial infarction (MI) in patients with diabetes compared with those without diabetes, independently from T1DM or T2DM [18]. In two studies a sex-based difference has been found in a STEMI cohort with a 30-day higher mortality among women, whereas in a NSTEMI cohort and an unstable angina cohort mortality was lower among women [19,20]. Contrary to type 2 diabetes, which is usually characterized by increased cardiovascular risk due to overweight/obesity and increasing age, the literature on the potential sex and gender differences in type 1 diabetes concerning cardiovascular risk factors, metabolic control and drug therapy is scarce.

5. Chronic Microvascular Complications in Diabetes

As the role of sex hormones in chronic macrovascular complications is rather clear, the role in the field of microvascular complications is still an area of uncertainness. We do know that diabetic nephropathy progresses at a faster rate in diabetic females compared with diabetic males and women benefit less from treatment than men do. The connection between diabetic nephropathy and cardiovascular disease is in line with the increased cardiovascular disease seen in diabetic women.

In T2DM, sex-gender differences in diabetic retinopathy are still not very clear in the literature. In a recent paper by our group in more than 20,000 Sardinian type 2 diabetic patients, we highlighted how female T2DM, despite having a higher number of risk factors for diabetic retinopathy (elevated glycated haemoglobin, longer diabetes duration, hypertension), has less diabetic retinopathy than the male patients [21]. But this is true for T2DM, while in T1DM data are more scared and it appears that female might have a faster progression, more than difference in prevalence of retinopathy.

6. Pharmacological Treatment in Diabetes

Of note, none of the randomized clinical trials done so far, are primarily designed to assess sex gender-differences in the benefit from a specific intervention strategy, de facto excluding fertile women from experimentation. This is a very import issue since usually drugs are tested mainly in men and women after menopause and the results are applied to fertile women, where they haven't really been tested. Further characterization of these differences in glucose homeostasis, might enable us to understand new factors that could be fundamental, both to prevent diabetes, and to find adequate and precise therapy for diabetes and for the prevention of its complications. Some sex-gender difference in drug use come from the observation of real-world life. Metformin is able to increase

plasma lactate levels significantly higher in female than in male patients, thus, women with diabetes should deserve a greater caution than men when treated with metformin, with the aim of preventing lactic acidosis [22]. On the other hand a recently published paper has shown that female patients seem to be more responsive than males to the cardiovascular protection offered by metformin [23], and again metformin seems to have a protective effect from breast cancer in women [24]. Thiazolidinediones therapy raises the risk of bone fractures more frequently in women, while regarding a new class of drugs, namely dipeptidyl-dipeptidase-4 (DPP4) inhibitors a reduction in bone fracture independent from sex-gender has been found [25,26]. Regarding drugs targeting the RAAS [(angiotensin converting enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs)], they may prevent cardiovascular events more efficaciously in men than in women, and again women are less responsive to aspirin treatment than men in trials aimed at primary prevention of cardiovascular events [27,28].

Large-scale trials focused on the pharmacological treatment of micro-macrovascular complications are needed to evaluate the differences in treatments according to sex-gender, in order to develop new gender-oriented molecules. To date, we only know that some drugs are less effective or less tolerated in women. The lack of knowledge of the exact initiation mechanism of diabetes is the main cause of the partial failure on microvascular complications control in diabetes and this is also true for gender-oriented medicine.

Epigenetics has amply demonstrated how present and past experience sometimes indelibly marks our body. For a gender-oriented medicine, it is necessary to put together multidisciplinary teams where the most varied skills can be expressed.

Other aspects, such as gender differences according to ethnicity, migration and psychological aspects, are generally little studied. These topics will be addressed in detail by specific papers that will be included in this special issue.

Men and women are different in behaviour, in the expressiveness of emotions and in certain specific cognitive abilities: men are more rational, women are more intuitive. Even with respect to emotional intelligence, men and women do not differ in empathically recognizing the mood of the partner in the couple, but the difference lies in the fact that men are more reluctant to show their emotions, minimizing them. Environmental and cultural conditioning probably favour differences in the expression of emotions, while women feel free to express themselves through body language and facial expressions. These psychological sex gender differences are important in terms of reaction to the disease and compliance to drug treatment.

Adherence to drug treatment implies of course patient and physician collaboration, thus emphasizing the role of patient and care provider dyads. Nevertheless, guidelines do not deeply consider the sex-gender of care providers, forgetting that he/she is a person and every individual is sexed and gendered. However, the importance of the sex-gender of a care provider is emerging [29]. The influence of physician sex gender in health quality is known since a long time. In particular, several years ago in a large survey it has been concluded that women are more likely to undergo screening with Pap smears and mammography if they are under a female rather than a male physician, particularly if the physician is an internist or family practioner [30]. Physician gender influences quality of care in patients with type 2 diabetes. Female physicians providing an overall better quality of care, especially in prognostically important risk management [31].

7. Conclusions

Greater knowledge and awareness underlying these premises, will allows to orient ourselves towards realization of an optimal path of personalized/precision medicine, which goes beyond just biological data, including the socio-biographical context where the person lives. To move towards gender-oriented medicine, it is necessary to put together multidisciplinary teams where the most varied skills can be expressed. In order to reach equity between men and women, sex-gender epidemiological reports, preclinical and clinical research are mandatory to evaluate the impact of sex-gender on the outcomes

and to improve sex-gender awareness and competency in the health care system. It is mandatory that future studies should consider sex-gender differences in the setting of randomized controlled trials with drug.

This is why, during the two days, of the virtual web-meeting GENDER DIFFERENCES IN DIABETES held in Olbia, Italy the 4th and 5th of December 2020 (https://www.simdoeducation.com/on-demanddifferenzedigenere, accessed on 5 December 2020), different specialists, psychologists, psychotherapists, anthropologists, cardiologists, diabetologists, nephrologists, nutritional biologists and pharmacologists with experience in the field, coming from different regions of Italy, have discussed the topic of gender differences, to emphasize that the sex-gender medicine is not the medicine for women, but the medicine for men and women, for boy and girl. Starting from this meeting, a multicentre observational trial on gender differences to some drugs in Real-Life, will start shortly within the scientific society SIMDO (Italian Society Metabolism Diabetes Obesity).

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