



REVIEW ARTICLE

Sex -Gender Difference in Diabetes: A Physiological and Psychological Point of View

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Abstract

Diabetes mellitus is considered as an equivalent of ischemic cardiovascular disease while patients with ischemic cardiovascular disease often have diabetes or pre-diabetes, acting as the two side of the same coin. Indeed women suffer more than men for the diabetic condition, in diabetic women cardiovascular risk rises some 3.5 fold higher in respect to non-diabetic women, while in men cardiovascular risk increases of “only” 2.1 fold with the condition diabetes, as firstly shown by Framingham study. Sex is the set of biological aspects of being female or male while with the term gender we should consider the social expression that transforms a female into a woman and a male into a man. The variously interconnected differences and inequalities in the state of health, often derived from both biological (sex) and social-cultural (gender) differences, suggest using the term sex-gender. In view of the impact of sex hormones on glucose homeostasis, the molecular pathways involved in insulin resistance suggests a sex-gender specificity mechanism in the development of diabetic complications leading to the unmet need of sex-gender therapeutic approaches. Of note, none of the 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. In order to provide a more precision based medicine 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. Future studies should consider sex-gender differences in the setting of randomized controlled trials with drugs.

General Aspects of Sex-Gender Differences

Gender is considered a social construct that generally transforms a female in woman and a male in man, whereas sex is generally considered the biological aspect of femininity and masculinity: Since the difficulty to dissect the two terms it would be more preferable to adopt THE TERM sex-gender, strongly suggesting that the two concepts are jointed [1,2]. Between 1971 and 2000, diabetic men have had a 43% relative reduction in the age-adjusted mortality rate (including cardiovascular mortality rate), which is similar to that of men without diabetes. In contrast, diabetic women did show reduction neither in total nor in cardiovascular mortality rate, indeed diabetic women doubled mortality [3]. Thus further insights into the sex-gender differences in the mechanisms that control development and progression of different illness, such as the cardiovascular function and diabetes mellitus (DM), are urgently required to eventually set different therapeutic approaches including sex-gender approach in all drug development processes.

Clinical studies are generally performed more in men and the results are simply applied to women [4]. Of note, none of the trials done so far are primarily designed to assess sex gender-differences of a determined drug on males and females

leading to the fact that most modern guidelines are based on studies predominantly conducted in Caucasian adult men or, at the best, mostly post-menopausal women. In 1993, the US National Institutes of Health (NIH) mandated the inclusion of women in NIH-funded clinical trials, but many investigators did not follow this mandate, and many of those who did include women did not analyze the results by sex, [5,6], minimizing the effectiveness of this policy. It is not surprising that in 2001 the US Government Accountability Office report found that eight of ten prescription drugs withdrawn from the market between 1997 and 2000 “posed greater health risks for women than for men” [7]. Actually, it is emerging that causes, risk factors, clinical manifestations, prognosis, therapeutics and outcomes are highly influenced by sex-gender [8]. To reach equity between men and women, in other word to get a precision medicine, sex-gender epidemiological reports, preclinical and clinical research and randomized controlled trials with drug, are mandatory to evaluate the impact of sex-

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Received: Jan 15, 2021; **Accepted:** Jan 29, 2021; **Published:** Feb 01, 2021

gender on the outcomes and to improve sex-gender awareness and competency in the health care system.

Some difficulties arise from the matter sex-gender itself and the difficulty to dissect between the two terms. It is well known from a long time that there are sex differences in the way symptoms are perceived, evaluated and acted upon. In an early study including 1648 adults (18 -59 years old) over a period of 7 years of outpatient services follow up, it has been shown that there is no apparent sex difference in the tendency to adopt the sick role when ill, while females are more likely to perceive symptoms than males. Additionally, level and type of role responsibility and concern with health are related to female symptom reports, but this does not apply to male. It is primarily the perception of symptoms and an interest and concern with health, which contributes to sex-gender differences in the utilization of medical services [9]. In a subsequent analysis of the same sample the authors indicate that the largest sex-gender differences in utilization rates occur in those categories which represent more mild morbidities and those where there is more discretion in defining illness and/or the need for care. Thus, the findings of this study provide further evidence for the hypothesis that sex differences in morbidity reports and utilization rates are due to differences in the way symptoms are perceived, evaluated and acted upon [10].

Chronic diseases persist over time and for the person affected impose the need to adapt to a new physical and psychological state. This it happens even if sometimes there are periods with total or “almost total” absence of symptoms. Indeed from the psychological point of view men and women highly diverge each other in many areas of social and individual life, not only with respect to a chronic disease and the literature outlines gender-related diversities.

Men have a tendency to communicate their emotions not openly. In presence of a problem they tend to close, while women are more intuitive, have strong relational dispositions and express their emotions openly and ask for help more easily [11]. *Goleman* [12] in his studies investigated the influence of sex on emotional awareness, founding that both men and women do not differ in empathically recognizing the mood of the partner within the couple, but the difference is 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 them through body language and facial expressions. In the corporate context, the gender differences that emerged from the studies of *Tannen* [13] and *Gray* [14], reported that women, for biological and social reasons, are more focused on relationship, where content and relationship are intertwined with each other. On the other hand men focus more on the results and separate the contents from the relationship, thus it can be well understood that this creates problems in the communication between men and women often leading to conflicts as well. The meta-analysis published by

Hall [15] provides evidence for non-verbal gender difference that is well established for a range of behaviours and skills. *Hall* [15] suggests that women maintain a smaller personal distance, use their expressiveness more openly, use smiles and nods, their facial expressiveness is very marked, and they are more accurate in judging emotions and personality through non-verbal signals. However, not all non-verbal behaviours have been investigated sufficiently, in fact for some non-verbal behaviour and skills little or no gender difference is present, making difficult to draw a conclusion. In non-verbal communication differences are due both to physiological and purely socio-cultural factors [16].

An observational study on 70 couples [17], highlighted the diversity in relationships between women and men, the latter were more likely to look at their partners, exhibit positive facial expressions, briefly touch their partners, use gestures care and show closed body postures, while men, used more intimate contact. There are also clear gender differences in job satisfaction between women and men in both clerical and managerial positions.

It appears clear that psychological and social sex-gender differences are well defined and might be part of the gender behaviour for illness.

Sex-Gender Differences in Diabetes

Diabetes mellitus is considered as an equivalent of ischemic cardiovascular disease [18] while patients with ischemic cardiovascular disease often have diabetes or pre-diabetes [19] acting as the two side of the same coin. Indeed women suffer more for the diabetic condition, as firstly shown by Framingham study, in diabetic women cardiovascular risk rises some 3.5 fold higher in respect to non-diabetic women, while in men cardiovascular risk increases of “only” 2.1 fold with the diabetes condition [20].

Type 1 and type 2 diabetes (T1DM and T2DM) are the more common forms of diabetes [21]. The distinctions between the two forms are by virtue of certain broad characteristics, T1DM: early onset, insulin requirement, proneness to ketosis, and lean body mass index; T2DM: later onset, response to oral agents, metabolic syndrome, and high body mass index. Besides these two generally well known forms, other atypical diabetes forms exist. This concept enfolds not only rare monogenic diabetes syndromes but also clusters of phenotypically distinct forms of diabetes that span the spectrum between the two poorly defined poles of T1DM and T2DM. In this article for simplicity we will refer only to the two classic forms of diabetes: T1DM and T2DM.

Regarding prevalence the two forms of diabetes show clear sex-gender differences. T1DM is an autoimmune disease characterized by destruction of the beta cells [22]. Although T1DM can affect patients of all ages, most epidemiological studies of T1DM focus on disease forms with clinical diagnosis during childhood and adolescence, when the peak of incidence

occurs. Indeed clinically, adult T1DM is difficult to discriminate from certain forms of T2DM and from Latent Autoimmune Diabetes in Adults (LADA). From one large meta-analysis it appears that incidence of T1DM in adults parallel that one of childhood in the different countries, with a clear higher prevalence in the male sex [23]. In childhood the disease is characterized by a similar incidence, in the same geographical area, for male and female, since only after puberty a decrease in female incidence, mainly due to estrogen activity is seen [24]. Overall a male: female ratio of about 1.4 worldwide is seen, making T1DM the only common autoimmune disease showing a higher male prevalence, although female do show 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 [25]. Some data suggest sex differences in lipids and overweight in patients with T1DM. Although glycemic control and the frequency of diabetic complications appears comparable between the sexes, the overall adherence to guidelines, particularly with respect to the prescription of statins and aspirin, has been reported lower in women than in men [26].

T2DM has a higher prevalence in men, but since women are more numerous, at the end there are more women with T2DM than men [27]. T2DM is mainly due to insulin resistance and loss of beta cell function differently combined together. A clear sex-gender difference in T2DM arise in the prediabetes phase since men have more insulin resistance shown by an higher prevalence of IFG (Impaired Fasting Glucose), while women have more loss of beta cell function represented by IGT [28,29]. Women are more frequently characterized by postprandial hyperglycaemia than men, a condition, typical of IGT, which is associated with increased oxidative stress and a higher cardiovascular risk, thus it is not surprising that diabetic women have a higher CVD risk.

Two facts must be considered in the sex-gender differences. One is that the standard oral glucose tolerance test is done with 75 grams of glucose irrespective of the different size between men and women. The second is that women have more fat than muscle in respect to men [30], this would suggest women should be more insulin resistance than men, but the opposite is correct. Indeed women have more insulin sensitivity than men [31]. The sex gender differences in DM are evident also for two particular forms of diabetes. Gestational diabetes is a typical female form of diabetes occurring during pregnancy and it is due to a progressive physiological rise in insulin resistance during the second and third trimester together with a coexisting decreased beta cell function, usually gestational diabetes recover after delivery [32]. Ketosis-prone T2DM (KPDM, Flatbush Diabetes) is a rather rare syndrome occurring in the non-Caucasian population and the typical patient is male, middle-aged, overweight, or modestly obese with a family history of type 2 diabetes. KPDM presents with new-onset severe hyperglycemia and ketosis or frank diabetic ketoacidosis, but GADab and islet cell antibody are negative.

These patients require initial insulin, fluid and electrolyte replacement treatment, following several weeks to months of insulin treatment, their metabolic abnormalities improve, and they may be managed by diet alone or diet plus oral antidiabetic agents [33].

Several sex-gender differences, beside prevalence, are present in the genesis of T2DM, starting at the glucose homeostasis level. T2DM is characterized by a different combination of insulin resistance and beta cell function/volume decrease. Hormonal difference in glucose homeostasis, might account for some of the observed differences between male and female in T2DM. Sexual hormones act at many physiological pathways, for example estrogen and testosterone have opposite effect on renin-angiotensin-aldosterone system (RAAS). In general, estrogen reduces the activity of RAAS whereas testosterone increases it [34]. An important class of antihypertensive and heart protective drugs such as those targeting the RAAS [(Angiotensin Converting Enzyme Inhibitors (ACEs) and Angiotensin Receptor Blockers (ARBs)] may prevent CV events more efficaciously in men than in women [35]. An area of hormonal difference in glucose homeostasis is the bi-directional modulation of diabetes risk by testosterone in males and females. Male hypogonadism is reported to predict the development of T2DM being the prevalence of hypogonadism in men with T2DM between 20% to 60%. Subjects treated with Androgen-Depletion Therapy (ADT) for prostate cancer exhibit primary testosterone deficiency, making possible to determine the causative role of testosterone deficiency on incident diabetes. In a large population-based study of 70,000 men aged 66 years or older, diagnosed with prostate cancer and without prior diagnosis of diabetes, ADT with GnRH analogues was associated with a 44% increased risk of incident diabetes while orchiectomy gave a 34% increased risk compared to controls [36]. Similarly, an observational study of over 37,000 men with prostate cancer in the Veterans Healthcare Administration reported that ADT with GnRH analogues was associated with a 28% increased risk of incident type 2 diabetes while orchiectomy caused a 16% increased risk compared to controls [37]. Thus, severe testosterone deficiency is instrumental in predisposing to hyperglycemia and diabetes in these patients. These effects of androgen depletion in men involve the combination of insulin resistance and visceral adiposity associated with decreased β -cell function [38,39]. Testosterone replacement therapy in hypogonadal men improves insulin sensitivity, decreases abdominal fat mass and disturbances in lipid and glucose metabolism, and has a multidimensional favourable effect on cardiovascular risk profile [40-42], although this aspect is not generally agreed [43]. The effect of testosterone is rather different in women. It is well known that low concentrations of Sex-Hormone Binding Globulin (SHBG), which increases free circulating testosterone, is a strong independent risk factor for the development of type 2 diabetes in women and postmenopausal women with impaired glucose tolerance

exhibited higher androgen activity than those with normal glucose tolerance, notable androgen activity correlates with the degree of glucose intolerance [44,45]. On the other hand the pathophysiological role of testosterone in women appears quite different since women with testosterone excess exhibit an early exaggerated acute insulin response to glucose, with subsequent secondary pancreatic β -cell dysfunction with a robust relationship between β -cell function and free testosterone [46-48]. Thus, women with testosterone excess exhibit, at first, β -cell hyper function, which may predispose to secondary β -cell failure and type 2 diabetes, while men with testosterone deficit show insulin resistance and decrease in β -cell function.

Mental illness is often associated with diabetes and recently, besides T1DM and T2DM a new form of diabetes has been postulated: type 3 diabetes (T3DM) that it is considered as dementia-Alzheimer. It is notable that many sex-gender differences are present in Alzheimer diseases [49,50].

Mental disorders are more frequent in women, who suffer from depression and anxiety disorders twice as compared to men, as reported in 2017 by the World Health Organization. Indeed both anxiety and depression are in close relationship with diabetes, and can negatively affect the compliance to therapy. It must be considered that working women are the category most at risk for stress-related diseases [51-53].

Diabetes in its chronic nature, due to the several acts that the disease imposes, like insulin therapy, constant glycemic control, physical activity, food restrictions and so on, causes an upheaval in patient and his family psychosocial balance, this it happens regardless of whether the onset occurs in childhood, adolescence, or adulthood.

The strong emotional impact resulting from the diagnosis of diabetes is evident from literature data that widely highlight this aspect in subjects with both T1DM and T2DM. There are also gender differences affecting the responses to the disease due to biological, cultural, social, environmental and economic influences, able to modulate the response to the disease in both sexes. Diabetic patients have a higher percentage of psychological disorders and also specific conditions related to diabetes compared to the general population [54]. Among the most frequent disorders we can find anxiety disorders and a recently published study of long-standing type 1 diabetics patients, found different prevalence for depression and anxiety between female and male patients (31.7% vs. 14.9% and 23.2% vs. 13.0% respectively) [55]. There are forms of anxiety strictly related to the pathology, for example the fear of hypoglycemia is very present, as those who have experienced it live in a constant state of anxiety, for this purpose it is important, when evaluating this aspect, to distinguish the symptoms specific of anxiety from those caused secondarily by hypoglycemia. Depression is two to three times higher in people with diabetes mellitus, the majority of the cases remaining under-diagnosed [56]. Considering severe depression, prevalence rates in T1DM and T2DM are

usually in the order of about 21% and 27% [57]. More recently a meta- analysis [58] confirmed an increased 24-38%. Risk of developing depressive symptoms in T2DM patients. Perceived family support is a protective factor against depression [59], while in respect to lifestyle, women are generally more inactive than men, showing a deeper knowledge of the disease but they are more neglected. This aspect probably derives from the social role that the woman plays, the daily tasks as well as work weigh. Men treat their diabetes more in a family setting and are less constant in self-monitoring, while women tend to experience their diabetes as an individual responsibility [60-64]. A Swedish study that analyzed diabetic patients in two age groups (20-30 and 50-60 years), showed worse quality of life and mental well-being in female. This could also explain the difficulty in carrying out constant physical activity, female have a 40% higher risk of suffering from insomnia resulting from the experienced stress, they have more comorbidity such as cognitive impairment, functional limitations and depressive disorders. The presence of depression doubles the risk of mortality. Indeed men experience depression and anxiety less frequently, generally looking more positively to the disease.

An important aspect which should deserve attention is the sex-gender psychological attitude of the care-giver in respect of the patient. Indeed since women are considered with less risk and tend to reach less ambitious targets than men [65], it would be possible to speculate that, generally speaking, a male doctor might be more prone to consider a woman with less attention than a man, giving to the latter a more aggressive pharmacological attention. These peculiar, even psychological, aspects of sex-gender differences should deserve more attention and investigation.

The influence of the doctor sex-gender in exercising the profession deserves a lot of attention and is still a definitely unexplored topic with, very few data in the literature. The increasing strong female presence in medicine has already highlighted both the different communication style and technical skills or professional aspects in which women differ from men [66], the latter showing an increased prescription of drugs and instrumental investigations besides guidelines. In a large study [67] on T2DM out-patients (51,053, 48.6% male) followed by 3,096 physicians (66.3% male), female physicians provide an overall better quality of care, independently from the patient gender [68]. Female doctors use empathic communication and inform their patients more about lifestyle and risk factors. Another important aspect to be considered is also the relationship that is established between a female doctor and a female patient, and a male doctor and a male patient, from this point of view it appears that same-sex dyads benefit most from communication time.

Sex-Gender Differences in Diabetes Acute Complications

It is important to recall that acute diabetes complications like diabetic hyperosmolar coma is diagnosed almost twice in women

than men, while hypoglycaemia and diabetic ketoacidosis are almost 1.5 times that of men. Dietary prescriptions are an integral part of diabetes treatment, this could favor the onset of eating disorders [69,70], which are found more frequently in women to the extent of 60-80% [71,72]. A particular form of eating disorder in T1DM has been called diabulimia, which consists in the arbitrary reduction or omission of insulin that results in rapid weight loss but puts the patient at risk of ketoacidosis. It is more common among diabetic adolescents in whom prevalence of this disturb reaches up to 38% in female as compared to the estimated male prevalence of 16% [73].

Sex-Gender Differences in Diabetes Chronic Complications

The previous observations e.g. the role of sexual hormones in glucose homeostasis suggest that women and men may have a different attitude to develop chronic diabetic complications. Actually, it is clear that diabetic women lose their normal premenopausal protection against cardiovascular disease [74,75] and have more frequent and more severe macrovascular (cardiovascular) complications than men, while the role of sex-gender in the field of microvascular complications is still area of uncertainty. Sex-gender differentiation in diabetic microvascular complications have been considered by several studies that have shown a link between micro-and macrovascular disturbances in T2DM patients suggesting a common pathway of developing micro-and macrovascular disturbances. In any case should be kept in mind that if generally macrovascular complications raise in the prediabetes and metabolic syndrome state, microvascular complications develop when blood glucose is elevated over the estimated cut-off of 126 mg/dl [76,77]. Microvascular complications can cause an excess risk for cardiovascular morbidity/mortality being diabetic nephropathy, already at the stage of microalbuminuria, and diabetic autonomic neuropathy risk factors for cardiovascular diseases. Less is known about the role of retinopathy but recent findings indicate association between diabetic retinopathy and heart muscle perfusion disturbances. Sex gender differences in diabetic retinopathy are rather controversy, in a recent study in Sardinia we were able to find that male have more prevalence of diabetic retinopathy at any stage, in spite of the fact that women show longer diabetes duration, worse metabolic control and more hypertension and renal chronic failure, indicating the possibility that women are in some ways protected against diabetic retinopathy [78].

Depression associated with diabetes is also linked with poorer adherence to medications and self-care activities such as self-monitoring of blood glucose levels and adhering to a proper diet and exercise program [79-82]. In addition, irrespective of their sociodemographic variables, lifestyle or health status, depressed patients with DM dies earlier than other people [83]. Some patients with type 2 diabetes are reluctant to start insulin and may delay it. This process, called “psychological insulin resistance”, affects at a greater extent females (32.0%)

than males (21.1%) [84]. Since delayed insulin therapy lead to worse metabolic control, it is clear that this might be considered as another cause of worse metabolic control as commonly seen in diabetic women as compare to diabetic men.

Conclusion

There is scientific evidence that sex and gender can affect the incidence, prevalence, symptoms, the course and response to many illnesses. The role of sex-gender is fundamental in diabetes. There are differences between the sexes as regards the homeostasis of glucose, prediabetes syndromes, type 1 and 2 diabetes, their complications and their treatment. Further characterization of these differences in glucose homeostasis, might help to understand new factors that could be fundamental, both to prevent diabetes complications than to plan randomized clinical trials in order to develop new sex-gender oriented drugs for the therapy of diabetes and its complications. Better understanding gender differences in response to drug therapy, will allows us also to use drugs already available today in a more effective, oriented way in the light of a precision medicine, including even the socio-biographical context where the person lives. By now, epigenetics has largely demonstrated to be able to mark in a indelible way our body. Therefore, to move towards gender oriented medicine it is necessary to put together multidisciplinary teams where the most varied skills can be expressed. It is of fundamental importance to remember that in a chronic disease patients experience with respect to the disease cannot be ignored, many studies document a multitude of psychological conditions closely related to diabetes. The mistake to be avoided is to have a dichotomous vision in which mind and body are two separate entities, this leads to misunderstanding the problems deriving from a chronic highly invasive condition that wears down motivation and creates the substrate for developing disorders that, not only invalidate the treatment process, but lead to blaming the patient for his failures. The possibility of having the psychologist in the team would lead to a more accurate screening and would help doctors to provide adequate support where necessary. This would significantly increase patients’ adherence to treatment and decrease diabetic complications and eventually mortality due to diabetes.

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Citation: Tonolo G, Taras MA (2021) Sex -Gender Difference in Diabetes: A Physiological and Psychological Point of View. *Women's Health and Complications* 4(1): 001-006.

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