R E V I E W

Sex differences in type 2 diabetes: focus on disease course and outcomes

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Background: Women with type 2 diabetes (T2D) are less likely to reach the goals for hemoglobin A_{1c} compared with men, and have higher all-cause mortality. The risk of cardiovascular disease is elevated among both men and women with T2D, however, the risk has declined among men over recent years while it remains stationary in women. Reasons for these sex differences remain unclear, and guidelines for diabetes treatment do not differentiate between sexes. Possible causes for varying outcome include differences in physiology, treatment response, and psychological factors. This review briefly outlines sex differences in hormonal pathophysiology, and thereafter summarizes the literature to date on sex differences in disease course and outcome.

Methods: Systematic searches were performed on PubMed using "sex", "gender", and various glucose-lowering therapies as keywords. Earlier reviews are summarized and results from individual studies are reported. Reference lists from studies were used to augment the search.

Results: There is an increased risk of missing the diagnosis of T2D when screening women with only fasting plasma glucose instead of with an oral glucose tolerance test. The impact of various risk factors for complications may differ by sex. Efficacy and side effects of some glucose-lowering drugs differ between men and women. Men with T2D appear to suffer more microvascular complications, while women have higher morbidity and mortality in cardiovascular disease and also fare worse psychologically.

Conclusion: Few studies to date have focused on sex differences in T2D. Several questions demand further study, such as whether risk factors and treatment guidelines should be sex-specific. There is a need for clinical trials designed specifically to evaluate sex differences in efficacy and outcome of the available treatments.

Keywords: type 2 diabetes, gender, sex, complications, cardiovascular disease, treatment

Introduction

The prevalence of type 2 diabetes (T2D) is rising globally, due to, among other factors, obesity, physical inactivity, and aging superimposed on a genetic predisposition.[1,2] The World Health Organization estimates that the number of people with T2D will increase to 366 million by the year 2030. Hyperglycemia and diabetes are important causes of morbidity and mortality, due to cardiovascular disease (CVD), nephropathy, neuropathy, foot ulcers, and retinopathy.

Previous studies have shown that T2D affects women disproportionately.[3] Women with T2D generally have poorer glycemic control[4–6] and are less likely to reach the goals for hemoglobin A_{1c} (HbA$_{1c}$) compared with men.[7,8] Women with diabetes have higher all-cause mortality.[9] Among men with T2D, the mortality rate in CVD has declined at a rate comparable with non-diabetic men over the past decades but there

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is still an almost three-fold increase due to diabetes. The risk has decreased among non-diabetic women, but has not declined in women with T2D and remains nearly four-fold higher.[10] Reasons for these sex differences remain unclear, and guidelines for diabetes treatment do not differentiate between sexes. While many studies have included patients of both sexes, few have analyzed for sex differences.[11] Possible causes for varying outcome include differences in physiology, treatment response, and psychological factors. This review will briefly outline sex differences in hormonal pathophysiology, and thereafter summarize the literature to date on sex differences in disease course and outcome.

Methods

A survey of the English-language literature was conducted on PubMed, using the search terms "sex", "gender", "sex-specific", and "gender-specific" in combination with "diabetes", "metformin", "sulphonylurea", "glipizide", "glibenclamide", "glyburide", "glimepiride", "meglitinide", "repaglinide", "rosiglitazone", "pioglitazone", "thiazolidinedione", "exenatide", "liraglutide", "sitagliptin", "vildagliptin", "linagliptin", "saxagliptin", "alogliptin", "SGLT", and "dapagliflozin". No specific search was performed regarding insulin therapies, as review articles on this subject were found via the searches. Further searches were performed combining the term "diabetes" with "sex"/"gender" and "retinopathy", "nephropathy", "neuropathy", and "gastroparesis". The bibliographies of the articles were used to further augment the search. We have attempted to summarize results from previous reviews in the field as well as describing newer studies. Gestational diabetes, type 1 diabetes, and T2D in children and adolescents are not discussed in this review.

Body composition

The prevalence of obesity is similar between men and women overall, although sex differences exist in some populations.[12] Especially abdominal obesity is associated with T2D and CVD in both sexes, especially post-menopausal women.[13]

Women have a higher percentage of body fat[14] and more often develop peripheral adiposity, whereas men accumulate fat centrally (ie, android obesity).[15] About one third of overweight women develop the android phenotype.[16] After menopause, the tendency toward male-type obesity and lipid profile increases in women.[17,18] Among patients with T2D, 40% of men but as many as 70% of women display abdominal obesity, suggesting the association between T2D and abdominal obesity is stronger in women than in men.[13]

Visceral adipose tissue

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) differ in their sensitivity to insulin, sex hormones, and adrenergic stimulation.[18] At the same body mass index (BMI), men are often more insulin resistant than women due to a tendency toward VAT accumulation.[19]

Visceral adipocytes have a higher tendency toward lipolysis due to lower sensitivity to insulin's inhibiting effect and higher expression of glucocorticoid receptors, which contribute to lipolysis.[16,20] Compared to SAT, VAT thereby releases more free fatty acids (FFAs); it also produces inflammatory cytokines such as tumor necrosis factor α (TNFα). These substances are transported via the portal vein to the liver, where they induce hepatic insulin resistance and an atherogenic lipid profile.[16] Lower tendency to developing visceral adiposity, at least before menopause, may explain why women are relatively protected from T2D and CVD compared with men.[15,21]

Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of risk factors for CVD, in essence insulin resistance, hypertension, dyslipidemia, and abdominal obesity although the details of the definition vary.[18] Sex differences in the prevalence and components of MetS have been reviewed by Regitz-Zagrosek et al.[18,22] MetS has previously been more common in men than women, but the prevalence is increasing in women due to increasing obesity.[22]

Low and very low density lipoprotein (LDL and VLDL) and triacylglycerol (TG) are lower in pre-menopausal women compared with men, whereas high density lipoprotein (HDL) is higher.[15] After menopause, an increase in VAT occurs in parallel with increased prevalence of MetS, with a more atherogenic lipid profile and more hypertension.[18] In the Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) study, hypertension and apolipoproteins were the strongest contributors to MetS in men. In women, high weight and waist circumference as well as low HDL were more important contributors.[23]

Prevalence of abnormal glucose tolerance and T2D

Impaired fasting glucose (IFG) is more common in men, whereas impaired glucose tolerance (IGT) dominates among women, who instead have lower fasting plasma glucose (FPG).[18,22,24] Insulin resistance is closely linked to IFG, whereas disturbed β-cell function is related to elevated post-load glucose, ie, IGT.[25,26]

T2D has often been found to be more common in men[27] but the prevalence is equal or higher among women in some populations, possibly due to women living longer.[24,28]

Risk factors for T2D

Being overweight is the strongest risk factor for developing T2D in both sexes.[24] However, the BMI "threshold" at which insulin resistance develops differs depending on ethnicity, heredity, and sex.[29] Women are protected up to a higher BMI, as they accumulate lipids in SAT which induces less harm than that in VAT which occurs in men.[29,30] High waist circumference after correcting for height is a risk factor in both sexes, but may be a stronger predictor in women.[31,32] Age, a family history of T2D, and low HDL are risk factors for T2D in both men and women. High daily alcohol consumption, smoking, and systolic hypertension are stronger risk factors in men, whereas elevated TG and physical inactivity are stronger in women.[24]

Methods of diagnosing T2D

In a German study, undiagnosed T2D was more common in men than women (9.3% versus 6.9%). Half of the women found to have previously unknown T2D were only detected by 2 hour plasma glucose during an oral glucose tolerance test (OGTT), and would therefore have been missed if only screened by FPG.[33] The use of HbA_{1c} to diagnose T2D may also be a less reliable method in populations in which T2D is best diagnosed by 2 hour plasma glucose than by FPG.[33]

Sex differences in hormonal pathophysiology

Hormones regulating glycemic control are affected by sex and body type. These differences are outlined in brief below; details are available in the cited review articles.

Cortisol

High cortisol levels increase insulin resistance, gluconeogenesis, the tendency toward accumulation of VAT, hypertension, and dyslipidemia.[13,34] Cortisol levels may be elevated in visceral obesity due to increased reduction of cortisone to cortisol by the enzyme 11β-hydroxysteroid dehydrogenase-1 (11βHSD-1) in VAT.[13] Some studies have suggested sex differences in cortisol production via the hypothalamus-pituitary-adrenal axis and/or 11βHSD-1, but results have varied between studies and the clinical implications remain unclear.[35]

Sex hormones

Sex hormones are fundamental to the biological differences between men and women, regulating not only sex characteristics and fertility but also metabolism and adipose tissue.[36] There are various articles regarding differences in sex hormone receptors.[37,38]

Testosterone

In men, testosterone stimulates lipolysis in adipose tissue. Low testosterone levels are associated with abdominal obesity and insulin resistance in men,[39] and are an independent risk factor for developing T2D.[40] Insulin sensitivity, visceral fat mass, blood pressure, and plasma lipids improve with testosterone substitution.[41,42] Men with higher testosterone levels (15.6–21.0 nmol/L) had a 42% lower risk of developing T2D in a meta-analysis.[43]

Unlike for men, increased androgen levels induce insulin resistance in women[44] and increase the risk of T2D and CVD.[43,45] This is exemplified in polycystic ovary syndrome (PCOS), which is associated with hyperandrogenism, insulin resistance, and an increased risk of developing T2D.[46] Mechanisms by which androgens induce insulin resistance in women include reduced glucose uptake[47] and increased lipolysis, especially from VAT.[36] Androgen levels may be elevated in women with central obesity and perhaps T2D.[43,48] Interestingly, women with T2D have higher bone density than non-diabetic controls, perhaps due to the anabolic effects of androgens.[49]

Sex-hormone binding globulin

Free (active) testosterone levels are regulated by sex-hormone binding globulin (SHBG). Insulin regulates SHBG by inhibiting its synthesis, and hyperinsulinemia thus results in low SHBG.[46] Low SHBG is seen in men and women with abdominal obesity; in women, this contributes to hyperandrogenemia.[13] Elevated androgen levels in PCOS result from a vicious cycle, in which high insulin levels stimulate ovarian androgen synthesis as well as lowering SHBG, which in turn further exacerbates hyperandrogenemia and thereby the insulin resistance.[46] High SHBG levels are protective against T2D regardless of sex, probably since low SHBG is a marker of hyperinsulinemia; however, it is more protective in women than in men.[43]

Estrogen

Estrogen is synthesized in the ovaries in premenopausal women, and via conversion from testosterone by aromatase in adipose tissue in men and women.[22] Obesity is associated with increased expression of aromatase messenger RNA in both sexes.[50] Elevated estradiol levels may be a risk factor for insulin resistance in men, whereas in women the decrease in estrogen levels after menopause coincides with increased risk

of elevated FPG.[24] Hormone replacement therapy may reduce insulin resistance, but also encompasses risks.[11,24]

Growth hormone and insulin-like growth factor-I

Growth hormone (GH) exerts anabolic effects, mainly via insulin and insulin-like growth factor-I(IGF-I), but is lipolytic and increases insulin resistance in fasting/starvation. IGF-I contributes to uptake of glucose and FFAs, and improves insulin sensitivity.[51] Sex differences in GH contribute to differences in body composition between men and women, and have been reviewed by Gatford et al.[52] Women have higher mean GH levels and GH pulse amplitudes compared with men.[52] There are no sex differences in serum IGF-I levels in healthy subjects, or in the decline in IGF-I that occurs with age.[53,54] However, serum levels of IGF binding protein-1 (IGFBP-1), which regulates IGF-I bioavailability,[55] are higher in women compared with men.[31,56] This is partially due to a stimulatory effect of estrogen on IGFBP-1 synthesis.[57]

Adiponectin

Adiponectin is a hormone synthesized exclusively in adipose tissue.[58] It increases insulin sensitivity of the liver and skeletal muscle.[59] Adiponectin synthesis is stimulated by insulin, IGF-I, and peroxisome-proliferator activated receptor γ (PPARγ) agonists, and inhibited by glucocorticoids, β-adrenergic stimulation, cytokines, and androgens.[60–62] Adiponectin levels decrease with insulin resistance and obesity,[63] which may explain why they are higher in women versus men,[29,64] and in controls versus patients with T2D. Low levels are a marker of insulin resistance,[63] whereas high levels have been associated with reduced risk of T2D[65] and CVD.[66]

Leptin

Leptin is an adipokine produced in the adipose tissue, involved in control of food intake.[18] Obesity is associated with "leptin resistance", ie, reduced signaling through leptin receptors.[67] Leptin levels are higher in women than in men, reflecting greater total percent fat mass.[68] Leptin is positively correlated with free estrogen in post-menopausal women, and with free testosterone in men.[69] Increased leptin levels are associated with CVD in men,[70,71] while they may be protective against CVD in women.[72]

Metabolic control

Women generally have poorer glycemic control[4–6] and are less likely to reach the goals for HbA$_{1c}$ compared with men,[7,8] despite better diet and more frequent self-monitoring of blood glucose.[6] Men are, however, more likely to be admitted to hospital with diabetes-related conditions or to present with excessively high blood sugar levels.[73]

Therapy to improve glycemic control

Studies on glucose-lowering therapies often include women but are rarely designed specifically to analyze for sex differences in efficacy, pharmacodynamics, pharmacokinetics or side effects.[16,24] Some of the pivotal studies on treatment of T2D have looked at the effect of sex on outcome, eg, the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[74] and Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[75] trials; most others, eg the United Kingdom Prospective Diabetes Study (UKPDS)[76] and A Diabetes Outcome Progression Trial (ADOPT)[77] trials, have not. Most studies found, when we performed searches on diabetes therapies in relation to sex, were listed only because they included women or stratified for sex; among those with results pertinent to women, studies were most often not primarily designed to look for sex differences, or were focused on PCOS. Many of the studies focused on sex were animal studies.

In a meta-analysis focused on the effect of sex on outcome with treatment to improve metabolic control in T2D, various forms of insulin, oral antidiabetic drugs (OADs), and dietary interventions all had less effect on HbA$_{1c}$ in women compared to men.[78]

Lifestyle interventions

Few studies have compared the efficacy of exercise interventions, or the benefits of various types of exercise, in men versus women. Intensive lifestyle intervention appeared to be equally effective in preventing T2D in men and women in the Diabetes Prevention Program (DPP),[79] although weight loss >3% prevented development of T2D more effectively in men.[80] However, among patients with T2D, women were found to be more successful at losing weight after initiation of glucose-lowering therapy.[81]

While some studies have shown that physical activity decreases the risk of CVD and cardiovascular events[82] and C-reactive protein (CRP; a marker of inflammation)[83] more in women, beneficial effects on risk factors for CVD have also been shown in studies with men. Thus, exercise is important to reduce morbidity and mortality in patients with T2D regardless of sex.[11]

Glucose-lowering therapy

In an Italian study, women were more often treated with metformin, thiazolidinediones (TZDs) or insulin

as well as combination therapy.[84] A German study reported men to have less intense pharmacological intervention and also less contact with their general practitioner.[85] However, other studies have reported the opposite, with more intense pharmacological treatment in men.[86,87]

Metformin

The pharmacodynamics of metformin do not differ by sex in healthy young adults.[88] Metformin has more beneficial effects on myocardial fatty acid and glucose metabolism in men compared with women.[89] Women treated with metformin to prevent T2D in the DPP reported more adverse events than men did (15% versus 10%), and were also less adherent to treatment.[90] In one study, men admitted to an intensive care unit with lactic acidosis secondary to metformin therapy had higher mortality than women,[91] while another found that treatment with metformin in spite of having a contraindication to such therapy was associated with a higher rate of hospitalization and mortality in women.[92]

Thiazolidinediones

TZDs are PPARγ agonists; insulin-sensitizing drugs used in the treatment of T2D.[93] Although some studies have suggested that TZDs may be more effective in women compared with men,[94–96] the majority of larger studies have not reported sex-specific differences.[93] There may be sex differences in pharmacokinetics, resulting in higher plasma levels in females.[68] TZDs lower CRP and leptin more in women than men.[24,97] However, women may also be more sensitive to side effects. Hypoglycemia[98] and fractures[68] are more common in women than men on TZDs. We have found pioglitazone to increase basal serum cortisol in women but not in men, although the clinical significance of this is unclear.[99] Women treated with rosiglitazone had higher mortality than men, while no differences were seen for other treatments eg, metformin.[100]

Medications affecting the incretin system

Sex does not appear to affect the pharmacokinetics, efficacy or safety of exenatide or liraglutide.[101–103] Predictors of weight loss and achievement of target HbA$_{1c}$ differed between men and women treated with exenatide (as well as metformin).[104] No impact of sex has been found on the pharmacokinetics of vildagliptin or saxagliptin,[105,106] while one study found that women treated with sitagliptin or alogliptin more frequently reported hypoglycemia.[107]

Other oral antidiabetic agents

No studies were found focused specifically on the impact of sex on treatment with sulphonylureas or dapagliflozin. Those that tested for the effect of sex did not find any such effect.[108–110]

Insulin therapy

Men on insulin glargine or neutral protamine Hagedorn (NPH) insulin were in a meta-analysis more likely to reach HbA$_{1c}$ targets, despite women having a greater reduction in FPG and higher weight-adjusted insulin doses.[78] Hypoglycemic events are both more common and more severe in women.[47] This may in part be explained by women having lower counter-regulatory responses to hypoglycemia.[111,112] Fear of such episodes are an important underlying reason for unwillingness to adhere to intensive insulin regimes.[113]

Complications

With the exceptions of CVD, few studies have focused exclusively on sex differences in complications of T2D. In general, the available data suggest that male sex is associated with a higher risk of both microvascular and macrovascular complications, although there are conflicting data.[24,114]

Diabetic retinopathy

Some studies have reported female sex to predispose to diabetic retinopathy (DRP);[115,116] one also reported an association with cytokine levels.[116] Others have found no differences in DRP frequency or severity between the sexes,[84] or an increased risk in men.[117,118] Proliferative DRP is a risk factor of CVD in both sexes, but several studies have found it to be a stronger risk factor in women.[24]

Neuropathy

Few studies have looked for sex differences in neuropathy in T2D. Two studies have found men to show signs of diabetic neuropathy more frequently,[24] and to develop neuropathy earlier.[119]

Nephropathy

Preclinical studies suggest protective effects of estrogen against nephropathy, as estrogen inhibits the renin-angiotensin-aldosterone system whereas testosterone upregulates it. Estrogen also increases the synthesis of nitric oxide (a marker of endothelial function) and reduces collagen synthesis by mesangial cells.[24] Nearly all degrees of nephropathy are more common in men than women, with the exception of stage 5 chronic kidney disease.[82] One study found albuminuria is a stronger risk factor for

CVD among men with T2D compared with women.[120] These differences may be due to sex differences in other factors such as hypertension.[24] Genetic factors may influence the risk of developing nephropathy differently in men and women.[11]

Gastroparesis

The prevalence and severity of symptoms of gastroparesis have been reported to be higher among women than men with T2D, particularly among obese women with long duration of T2D and high HbA_{1c}.[121]

Foot ulcers and lower limb amputations

Foot ulcers, gangrene, and lower limb amputation are more prevalent in men with T2D compared with women.[41,122] In one study, men diagnosed with T2D before 65 years of age were at especially high risk of foot ulcers and amputations, whereas for women the risk of amputation increased with age.[123] The mortality risk in conjunction with lower limb amputation may, however, be higher in women.[122]

Cardiovascular disease

Sex differences in CVD have been studied more intensely than those for other diabetic complications. Most results point to increased risk and poorer outcome in women. Explanations for this include differences in hormonal and vascular pathophysiology, differing impact of risk factors, and less aggressive treatment both preventively and following an event.

Epidemiology

Women are relatively protected from CVD before menopause,[124] while after menopause the risk of CVD increases to levels equal to those in men.[68,125] Despite this, it has not been confirmed that hormone replacement therapy after menopause decreases the risk of CVD.[126]

Insulin resistance and T2D are associated with an increased risk of CVD, up to 50% more so in women than men.[11,22,24] It appears that T2D obliterates the protective effect of estrogen.[24] In a meta-analysis of subjects <60 years of age, with high risk of developing CVD, the incidence of CVD during follow-up was lower in women compared to men in the absence of T2D, while in the presence of T2D the risks were similar.[127] The risk of CVD increases at least three- to six-fold in women with T2D, compared with two- to four-fold in diabetic men.[128,129] The true frequency of CVD may still be underestimated in women with T2D, as they are more likely than men to have asymptomatic defects in myocardial perfusion.[130]

Carotid stenosis and ischemic stroke are more common in women than in men with MetS and T2D. Results from studies have varied as to whether there are sex differences in the incidence of stroke in T2D patients, but the mortality rate may be higher in women.[24]

Diabetes is also a risk factor for coronary artery spasm in women with T2D,[131] while men with T2D suffer more peripheral arterial disease.[121] Insulin resistance has a negative impact on metabolism in the myocardium, which may explain why T2D is associated with an increased risk of heart failure.[132] While survival in heart failure is generally higher in women than in men, this sex difference is attenuated in T2D.[132]

Risk factors for CVD

T2D is associated with increased frequency of risk factors for CVD regardless of sex, but the increase is relatively greater in women.[29]

Abdominal obesity, which increases in women after menopause, is a stronger risk factor for CVD in women compared with men.[22,133] Obese women with T2D also have higher frequency of left ventricular dysfunction and arterial stiffness than men.[24] Hyperinsulinemia has not been directly linked to an increased incidence of CVD in either sex.[68]

Women with T2D are more likely than men to have hypertension,[134,135] with more deleterious effects on cardiovascular health.[24] Total cholesterol and LDL may be more important risk factors for CVD in men, while TG has a greater impact in women[22,24] and is often elevated in women with T2D.[136] Low HDL is a stronger predictor in both non-diabetic and diabetic women compared with men.[137] Women with T2D have higher LDL and blood pressure at diagnosis despite lower HbA_{1c}, and are less likely than men to subsequently meet target levels for these risk factors.[84,138]

Prognosis and treatment outcome

CVD and myocardial infarction are associated with increased mortality in women with T2D compared with men.[139–141] The relative risk for mortality due to CVD is higher in diabetic compared with non-diabetic women, whereas no such difference is seen for men.[142] T2D may even be a stronger risk factor for mortality, than a history of previous CVD, in women with T2D.[143]

The effect of certain medications may also differ between the sexes in some clinical conditions. Angiotensin-converting enzyme (ACE)-inhibitors and β-blockers reduce mortality in men but not in women with asymptomatic left ventricular dysfunction, while both sexes benefit in symptomatic

dysfunction.[144] Most studies on statins have been conducted in men, and a meta-analysis showed that they might have less effect on mortality in women.[145] Similarly, ezetemibe[146] and fibrates[93] may be less effective in women compared with men with T2D. Among patients with T2D, aspirin as primary prevention reduces the risk of stroke more in women, but that of myocardial infarction more in men.[147] However, there is a lack of trials specifically designed to evaluate sex differences in pharmacological treatment of CVD, and the exclusion of women of fertile age may affect the results.[148]

Poorer outcome after percutaneous transluminal coronary angioplasty was found in older studies but not in more recent ones, including studies regarding drug-eluting stents.[24] After coronary angioplasty stenting, the odds ratio for restenosis after adjustment for age was 1.30 (95% confidence interval [CI] 0.99–1.70) in patients with T2D compared with non-diabetics in a meta-analysis of six studies.[149] The rate of restenosis has either been found not to differ between men and women,[149] or even to be lower in women with T2D.[150,151]

Hypothesized causes of increased CVD morbidity and mortality in women with T2D

Differences in blood pressure, lipids, etc may partly explain the increased mortality in female compared with male diabetes patients according to some,[141,152] but not all, studies.[153] It has been speculated that elevated androgen levels contribute to the increased risk of CVD in women with T2D, but studies on women with PCOS have not confirmed this hypothesis.[13]

The coagulation system and endothelial function may be more disturbed in women with T2D. While women normally have higher fibrinolytic potential and endothelial function (nitric oxide availability) compared with men, these protective effects are reduced in T2D[154] and the coagulation system is reset to a more pro-thrombotic state.[155] Inflammation leads to endothelial dysfunction and insulin resistance, and is associated with worse cardiovascular outcomes in women.[24] Compared with more "classic" risk markers, those for inflammation and angiogenesis (TNFα, CRP, vascular endothelial growth factor) better account for the increased risk of CVD in women with T2D.[156] Inflammation (elevated CRP) may explain the increased risk of coronary artery spasm in diabetic women.[131] Cellular defense mechanisms against oxidative stress may also be relatively more impaired in women.[157]

Women may be less aggressively treated during an acute cardiovascular event, and/or receive less primary or secondary prevention of CVD. During the acute event, cardiac catheterization, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery are less frequently used in women.[24] Diagnosis may be delayed as women less frequently report "classic" symptoms, such as central chest pain.[158] Data on medication for risk factors vary between populations. In some cohorts, more men than women were treated with lipid-lowering drugs,[8] ACE-inhibitors and/or calcium channel blockers,[86] and/or aspirin.[8,84] Others have reported a higher degree of use of lipid-lowering and anti-hypertensive agents in women.[84]

Cancer

T2D is associated with an increased risk of several forms of cancer, eg, pancreatic, renal, colorectal, liver, endometrial, breast, and bladder cancer. Proposed mechanisms include endogenous and exogenous hyperinsulinemia, IGF-I, and inflammation.[159,160]

T2D may be a stronger risk factor for colorectal cancer in women than in men,[161] while bladder cancer is more common in men with T2D.[162] Mortality rates in cancer are higher in female cancer patients with T2D compared to men.[163] The mortality rates in the same study were also higher for sex-specific cancers (ovary, uterus, prostate) compared with in non-diabetic cancer patients.

Oral insulin sensitizers, ie, metformin and particularly TZDs, are associated with 21%–32% reduced risk of incident cancer compared with treatment with insulin secretagogues (sulphonylurea or meglitinide), even after correction for multiple other risk factors, and especially in women.[164]

Depression and quality of life

Sex differences in the ability to cope with life with diabetes have recently been reviewed by Siddiqui et al.[165] In summary, women with T2D appear to fare worse psychologically, and suffer more depression, anxiety, and low energy levels compared with diabetic men. Women with T2D also have more depression than non-diabetic women.[166] Social class and employment status (ie, psychosocial stress) are stronger predictors of T2D in women than in men in some,[167] but not all studies.[168,169] These factors could potentially contribute to the lower degree of achievement of HbA$_{1c}$ targets in women compared with men. Of note, even though the prevalence is higher in women, depression and anxiety are more common among both men and women with T2D compared with the general population.[170] Depression may even be a more important reason for non-compliance with diabetes treatment among men compared to women.[171]

Summary and conclusion

In summary, a number of studies have suggested sex differences in risk factors and treatment outcome both for T2D and its complications. Data indicate that men with T2D suffer more microvascular complications, while women have higher morbidity and mortality in CVD and also fare worse psychologically. There is a reasonable degree of evidence for some differences, eg, the increased risk of missing the diagnosis of T2D when screening women with only FPG instead of OGTT. However, in most areas discussed in this review, there is still a lack of knowledge on the true impact of sex. Several questions demand further study, such as whether elevated TG and/or low HDL should be considered a stronger risk factor in women or whether different risk factors altogether need to be implemented; whether treatment with longer-acting insulins will benefit women more due to their increased risk of hypoglycemia; and, in the long run, whether treatment guidelines should be different for men and women. There is especially a need for clinical trials designed specifically to evaluate sex differences in efficacy and outcome of the available treatments.

Disclosure

The authors have no conflicts of interest to declare.

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