Sex differences in type 2 diabetes

Men tend to be diagnosed with type 2 diabetes at a younger age and lower body fat mass than women, and significantly more men than women have diabetes globally. Women with type 2 diabetes have a greater relative risk of cardiovascular disease and mortality than men, yet young women with type 2 diabetes are less likely to receive treatments for cardiovascular risk reduction than men. This review in *Diabetologia* summarises the key sex differences in type 2 diabetes diagnosis, complications (particularly cardiovascular disease), mortality risk, initiation and adherence to therapies, and the impacts of pregnancy and the menopause on diabetes risk and control in women. The authors highlight the increased risk of type 2 diabetes in women with polycystic ovary syndrome with higher testosterone levels, and in men with low testosterone levels. The authors call for improved screening for diabetes and cardiovascular risk factors in both men and women, and for early prevention and risk management strategies for both sexes.

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On a background of increasing type 2 diabetes prevalence in both sexes, and improved life expectancy in those with the condition, this review in *Diabetologia* aims to raise awareness of sex differences in type 2 diabetes risk, diagnosis, use of therapies and complications, in the hope that this will translate into improved management.

The review explores sex differences in key risk factors for developing type 2 diabetes, including insulin resistance, obesity and body fat distribution, prediabetes, endocrine factors such as sex steroid levels, impact of pregnancy and psychosocial factors. Young and middle-aged men show a higher prevalence of type 2 diabetes than women, and men are diagnosed with type 2 diabetes at a younger age and lower BMI than women. Postprandial hyperglycaemia increases with age in women, resulting in higher levels of undiagnosed diabetes in women over 60 years, and a higher prevalence of type 2 diabetes in women over 70 years compared to men.

Pre-menopausal women have higher muscle and liver insulin sensitivity and increased insulin levels on stimulation, which helps keep HbA_{1c} and fasting glucose lower than in men. However, after menopause, there are increases in blood pressure, LDL-cholesterol and HbA_{1c}, paralleling changes in body fat distribution, which contribute to impaired glucose tolerance and loss of these protective effects.

Even before developing type 2 diabetes, women are exposed to higher levels of major metabolic risk factors than men, and women (particularly white and younger women) usually have higher blood pressure and larger weight gain than men at diagnosis. Waist circumference correlates better than BMI with visceral adipose tissue in women, and levels of visceral fat are a much stronger risk factor for type 2 diabetes in women than in men. Waist circumference and BMI are both associated with mortality in people with type 2 diabetes.

Younger women can expand their peripheral gluteofemoral and subcutaneous fat stores, allowing more fat storage there and less as visceral fat, but after menopause this converts to a similar pattern of fat distribution to men, and cardiometabolic risk increases. Healthy women have more intramyocellular fat in the leg muscles, lower visceral fat, less fat in the liver and pancreas, and lower lipids in the myocardium and pericardium than healthy men. Intrapancreatic fat, with the potential to damage beta-cell function, increases with age, especially in women. However, liver and pancreas fat levels are similar in men and women once they develop type 2 diabetes.

Testosterone deficiency predisposes men to type 2 diabetes while, conversely, androgen excess increases risk in women. Women with polycystic ovary syndrome and excess testosterone are

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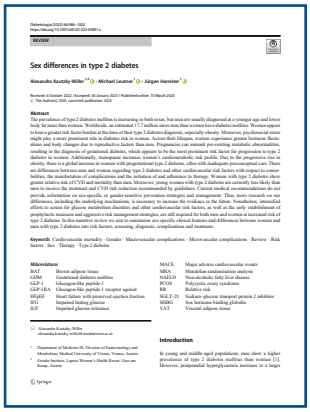

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four times more likely to have altered glucose levels than those with normal testosterone levels. Pregnancy may unmask pre-existing metabolic problems, and the incidence of gestational diabetes (GDM) is increasing; it is particularly common in older women and some ethnic groups. GDM is the greatest risk factor for development of type 2 diabetes in women, and the risk of developing type 2 diabetes over 3 years is as much as 70% higher in those with previous GDM compared to those without.

Men with type 2 diabetes appear to be more successful than women in achieving weight loss and body fat reduction, and in the DiRECT study type 2 diabetes remission was more durable at 2 years in men than women, possibly as a result of increased weight loss.

When examining the impact of psychosocial factors on development of type 2 diabetes, such as low educational level, low socioeconomic and occupational status, and low income, these appear to have more impact in women than in men. Prolonged night work increases diabetes risk only in women, as does shift work. Diabetes distress is very common in people with type 2 diabetes and is associated with comorbid depression and anxiety, and is more common in women.

The risk and prognosis of macrovascular complications in particular vary by sex as well. Cardiovascular disease is the leading cause of death in men and women, and type 2 diabetes contributes to premature mortality risk. Although women with type 2 diabetes are at a higher relative risk of cardiovascular complications and mortality than men with type 2 diabetes, the absolute cardiovascular event mortality remains greater in men than women with type 2 diabetes. A higher relative risk of cardiovascular mortality in women has been associated with newly diagnosed type 2 diabetes, especially in those who smoke, have high blood pressure or cholesterol, or are overweight, suggesting that more aggressive risk factor management may be appropriate from diagnosis in this group. Despite this, women are less likely than men to receive optimal guideline-recommended treatment to reduce cardiovascular risk, including statins, despite the fact that these drugs are equally effective in both sexes. This suggests that healthcare professionals may underestimate cardiovascular risk in women with type 2 diabetes.

Women are also less likely to be prescribed cardioprotective glucose-lowering therapies such as SGLT2 inhibitors and may be more likely to suffer treatment-related adverse events. Weight gain, oedema and fractures with thiazolidinedione treatment occurred mainly in women, suggesting that pioglitazone use should be limited in women, especially after the menopause. Similar HbA_{1c}-lowering effects are seen in both sexes with GLP-1 receptor agonists; however, women may lose more weight but also have more gastrointestinal side effects.

Women with type 2 diabetes have a greater relative risk of heart failure and hospitalisation for heart failure than men, and this is especially noted at younger ages. Hypertension is the main driver of heart failure, especially in women, with a threefold increase in heart failure amongst women with hypertension versus those without, compared to only a twofold increase with hypertension in men. The impact of type 2 diabetes on heart failure progression also appears to be greater in women than men, with women more frequently developing heart failure with preserved ejection fraction.

The authors of the review call for further exploration of these sex differences and for consistent implementation of guidelines in terms of both glucose lowering and cardiovascular risk reduction in all people with type 2 diabetes – irrespective of sex, age or ethnicity.

These sex differences, particularly the increased risk of cardiovascular events, heart failure and mortality, combined with apparent lower prescribing of protective medications and reduced medication adherence in some women with type 2 diabetes compared with men, should encourage us to review our practice. Are we optimising diabetes management and cardiovascular risk in both the men and women with type 2 diabetes we support? Where could we be more proactive? ■