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Risk factors for cardiovascular disease in women with diabetes

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Cardiovascular disease (CVD) is a well recognized complication of type 2 diabetes in both men and women [1–2]. A large number of studies have shown evidence of increased risk for CVD in patients with type 2 diabetes compared with the general population [3–6] and that this increased relative risk for CVD due to diabetes is greater in women than men. Interestingly, while mortality due to CVD appears to be declining in both the general population and in patients with type 2 diabetes [7], it remains controversial whether this decline in seen in both men and women. Indeed, analysis of the National Health and Nutrition Examination Survey (NHANES) suggested that the decline in all-cause mortality have occurred among men with diabetes, but not in women [8]. In patients with type 2 diabetes, some studies have reported greater mortality due to CVD in women compared with men [9–12] while others show higher mortality in men [13]. A recent analysis of the Framingham Heart study reported no sex differences in CVD mortality in patients with type 2 diabetes [2, 14]. Similarly divergent are the data in patients with type 1 diabetes in which mortality from CVD has either been shown to be either higher in women [3, 15], higher in men [16] or not different between the sexes [17–19]. Even though many of these conflicting findings are likely due to differences in study methodologies, it stresses the importance of examining the risk factors that contribute to the risk for CVD and its associated mortality in men and women separately.

Sex differences, or lack thereof, in the risk for CVD and its associated morbidity and mortality in patients with type 2 diabetes may be explained through sex differences in several common risk factors. These include, but are not limited to hyperglycemia, dyslipidemia and hypertension. While there has been a general trend in the improvements in some of these CVD risk factors as well as in advances in their prevention and treatment over the recent years, whether these improvements are seen both in women and men remains controversial.

In the current issue of *Gender Medicine*, Göbl et al present a study that examined sex differences in glycemic control, dyslipidemia and blood pressure in a Central European population of insulin treated patients with type 2 diabetes. The major findings of this study are: 1. women with type 2 diabetes have higher levels of LDL-cholesterol, HDL-cholesterol, systolic and diastolic blood pressure compared with age-matched men with type 2 diabetes; 2. No differences in HbA1c are observed between men and women with type 2 diabetes; 3. women have a higher chance to fail treatment goals in blood pressure but not in cholesterol

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and HbA1c levels. The authors conclude that women with type 2 diabetes have a more adverse cardiovascular risk factor profile than men, despite similar glycemic control.

Type 2 diabetes is a disease associated with chronically increased blood glucose levels as a result of both insulin deficiency and insulin resistance. Higher levels and wide fluctuations in fasting blood glucose, 2-hour postprandial blood glucose or HbA1c are characteristic of patients with type 2 diabetes, and these contribute to the development of microvascular and microvascular complications [20–23]. However, little is known whether these variations in glucose levels or HbA1c differ between women and men with type 2 diabetes and how this may impact their risk for CVD. The few studies that have in fact directly examined sex differences in blood glucose levels and glycemic control in patients with type 2 diabetes report better glycemic control in men than women. A cross-sectional analysis including 3,849 patients with type 2 diabetes found that women, whether or not they had CVD were less likely than men to have HbA(1c) <7% [24]. The prospective, Rancho Bernardo study showed that post-challenge hyperglycemia increases the risk for CVD more in women than men [25]. Similarly, in the San Antonio Heart Study, hyperglycemia was associated with increased CVD mortality more so in women than men [26]. The fact that hyperglycemia is more common in women than men may be somewhat surprising given the beneficial effects of estrogens on hyperglycemia by promoting insulin secretion [27–28] and reducing the incidence of type 2 diabetes itself [29–30]. However, studies have shown that estrogen levels decline in women with type 2 diabetes even before menopause [31–32], suggesting that the loss of the female sex as a protective factor against the development of CVD in type 2 diabetes may, in part, be explained through the decline in estrogen levels and therefore loss of the estrogen-induced insulin secretion.

The term “dyslipidemia” is commonly used to describe the disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Low HDL cholesterol, and high triglycerides have been shown to contribute to the risk for CVD in type 2 diabetes in general, but more so in women than in men [24, 33]. Interestingly, the present study by Göbl et al shows that women with type 2 diabetes exhibit higher levels of both LDL-cholesterol and HDL-cholesterol. The most likely explanation for this observation is that indeed, women more frequently have higher HDL levels than men and since elevated HDL levels are generally considered beneficial, women are less aggressively treated with lipid-lowering agents [34]. This lack in treatment in women could in turn lead to the observed elevated LDL levels as well. Interestingly though, since the consensus recommendations for treating elevated LDL levels are identical for men and women [24], it is surprising then to see that LDL levels are still higher in women than men, as reported in the present study by Göbl et al. This observation may suggest that even if women are treated as aggressively as men for dyslipidemia that the efficacy of lipid-lowering agents differs between the sexes. Weather or not this indeed is true is hard to establish, since most of the studies examining the efficacy of lipid-lowering agents in type 2 diabetes have either only included men or have not examined the data in a sex-specific manner [35–37]. Only one study reported equal efficacy of rosuvastatin and other statins in lowering LDL levels in post-menopausal women compared with age-matched men [38]. However, the study grouped non-diabetic and diabetic women, making it difficult to draw any conclusions on whether or not statins are equally effective in men and women with type 2 diabetes. Another aspect to consider when analyzing the contribution of dyslipidemia to the risk for CVD is the notion that perhaps elevated HDL levels are not as protective in patients with type 2 diabetes as they are in non-diabetics [39]. If this indeed is the case, then higher levels in both HDL and LDL in women compared with men with type 2 diabetes would suggest an even greater risk for CVD in women than presently acknowledged.

Type 2 diabetes and hypertension are in many ways interrelated diseases and both significantly increase the risk for CVD and lowering blood pressure has been shown to improve cardiovascular prognosis in patients with type 2 diabetes [40–43]. However, whether there are sex differences in blood pressure levels in patients with type 2 and to what degree these differences may alter the risk for CVD is controversial. The present study by Göbl et al shows that women with type 2 diabetes have higher systolic as ell as diastolic blood pressure. Furthermore, the study concludes that women have a greater chance of failing therapeutic goals for treatment of their blood pressure. Similar observations were made by others [24, 44–45]. These observations are somewhat surprising given that in non-diabetic women, blood pressure levels are lower compared with age-matched non-diabetic men, at least until menopause [46–48]. This observation suggests that diabetes eliminates the protective effect of the female sex with respect to hypertension. The observation by Göbl et al also that women with type 2 diabetes have a greater chance of failing therapeutic goals for treatment of their blood pressure is also somewhat surprising given that in general, women are more compliant than men regarding taking medication. There are several possible explanations for the observed failure to achieve therapeutic goals in women: 1. that women with type 2 diabetes are not being diagnosed with high blood pressure or treated as aggressively as men with type 2 diabetes; 2. That the medication used to treat high blood pressure is not as effective in women as in men; 3. That the pathophysiology of hypertension is different in men and women and thus the targets being treated are missed with existing/conventional therapy. It is likely that the actual truth lies in all of these explanations, underscoring the importance of examining the pathophysiology of hypertension associated with type 2 diabetes in a sex-specific manner.

Even though the present study by Göbl et al did not directly examine the contribution of obesity on the risk for CVD, a few words should be added about the potential contribution of obesity, either as a direct risk for CVD or an indirect risk, via contributing to the onset of type 2 diabetes. It is well established that visceral obesity poses a much greater risk for CVD than subcutaneous adiposity, which is why pre-menopausal women use to be considered to have a lower risk of obesity-related disorders, including CVD [49–50]. However, with the epidemic of obesity and its associated cardiometabolic complications, obese women no longer hold the advantage over men when it comes to development of CVD. In fact, evidence suggests that visceral adiposity in obese women increases the risk for CVD to a much greater extent than in men [51–52]. This observation may be surprising given that adipose tissue is a known source of estrogens which, in turn, have known cardioprotective effects [53–56]. This suggests that estrogens, depending on their source and whether their action is paracrine or endocrine, may exert beneficial as well as detrimental effects on target organs.

Increasing evidence suggests that diabetes is a state of an imbalance in sex hormone levels. In particular, women with type 2 diabetes commonly exhibit increases in circulating testosterone alongside decreases in estradiol levels [31–32, 57]. In essence, this perturbation in hormone levels in women results in a hormonal profile that resembles that of a man, with a higher testosterone/estrogen ratio. This perturbation may be one of the likely explanations as to why in the setting of diabetes, the female sex as a protective factor against CVD appears to be diminished. Based on this assumption, it would be reasonable to think that hormone supplementation to restore the normal testosterone/estrogen ratio would be beneficial in women with type 2 diabetes with CVD complications. Indeed, a few studies have shown that hormone therapy in women with type 2 diabetes is associated with a reduction in visceral adiposity and improvement in lipid and glucose metabolism, all of which are risk factor of CVD [58–60]. While the precise mechanisms by which sex hormones exert their effects and contribute to development of CVD are still being investigated, both clinical and experimental studies suggest that sex hormones are important regulators of fat, glucose and

lipid metabolism, blood pressure, cardiovascular and renal function [55–56, 61–64]. In essence, sex hormones may be important regulators of multiple biological processes, dysfunction of which may contribute to the risk for CVD.

In conclusion, the study by Göbl *et al* confirm previous reports that women with type 2 diabetes are at a greater relative risk for developing CVD than age-matched men. The fact that this sexual disparity exists despite comparable glycemic control suggests that other pathophysiological mechanisms may contribute to this increased risk of CVD in women with type 2 diabetes. Based on current evidence, it is apparent that presentation and diagnosis of CVD differs in women and men with type 2 diabetes and thus the method and timing of treatment should be sex-specific. Finally, additional clinical studies examining the factors contributing to the risk of CVD in women with type 2 diabetes are warranted.

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