Current Diabetes Reports (2019) 19: 139
https://doi.org/10.1007/s11892-019-1240-4

LIFESTYLE MANAGEMENT TO REDUCE DIABETES/CARDIOVASCULAR RISK (B CONWAY AND H KEENAN, SECTION EDITORS)

Glucose Management and the Sex Difference in Excess Cardiovascular Disease Risk in Long-Duration Type 1 Diabetes

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Published online: 21 November 2019

Abstract

Purpose of Review The protection against CVD observed in women compared to men in the general population is essentially erased in type 1 diabetes. This review will discuss evidence regarding the role of glucose management on CVD risk by sex, with a particular focus on studies of long-duration type 1 diabetes of > 20 years.

Recent Findings Across studies, women with type 1 diabetes have similar or worse glycemic control compared to men, despite higher rates of intensive insulin therapy. The association between HbA1c and CVD risk does not seem to differ by sex, but few studies have reported on sex-specific analyses.

Summary Beyond HbA1c, there is a lack of published data regarding the relationship between other aspects of glucose management and CVD risk by sex in type 1 diabetes. Glucose management factors do not seem to directly account for the increased CVD risk in women with type 1 diabetes, but may influence other risk factors that play a more direct role.

Keywords Type 1 diabetes · Sex differences · Glucose management · Glycemic control · Diabetes management · Cardiovascular disease

Introduction

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality in individuals with type 1 diabetes, and despite improvements in diabetes management over the past few decades, the risk of CVD continues to be greatly increased compared to the general population [1, 2•]. The reasons underlying this increased risk are not fully understood, as the hyperglycemia that characterizes type 1 diabetes has itself been an inconsistent predictor of CVD incidence [3–11]. Notably, the protection against CVD observed in women compared to men in the general population is essentially erased in diabetes and women with type 1 diabetes have been consistently shown to have nearly equivalent absolute CVD risk as men with type 1 diabetes [3, 12, 13]. The excess relative risk in women may be attributable to a more adverse risk factor profile and/or treatment disparities, given the absence of an excess risk in women compared to men after risk factor adjustment [14, 15]. Sex differences in CVD risk factors appear early in the course of type 1 diabetes, beginning as early as adolescence [16, 17•]. Determining the underlying reasons for the relative lack of protection against CVD in women with diabetes is an important focus of ongoing research. This review will provide an overview of the current epidemiology of the CVD burden by sex in type 1 diabetes and discuss evidence regarding the role of glucose management on CVD risk by sex, with a focus on studies of long-duration type 1 diabetes, i.e., duration of > 20 years.

This article is part of the Topical Collection on *Lifestyle Management to Reduce Diabetes/Cardiovascular Risk*

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Overview of the CVD Burden in Type 1 Diabetes

The overall cumulative incidence for coronary artery disease by age 55 years has been estimated to be as high as 35% in type 1 diabetes, compared to < 10% in the nondiabetic population [18]. The risk of stroke is also elevated in type 1 diabetes and has been estimated to be approximately four times higher in type 1 diabetes compared to the nondiabetic

population [19, 20]. Likewise, the risk of peripheral vascular disease (PVD) is also higher in diabetes, with the incidence estimated to be approximately 5 times greater in individuals with diabetes compared to those without [21]. Using contemporary data, the Scottish Registry Linkage Study concluded that while the relative risk for CVD mortality associated with type 1 diabetes has indeed declined, a significantly elevated risk compared to the general population remains [1].

As mentioned in the introduction above, the absolute risk of CVD has been shown to be similar by sex [3, 13]. A similar pattern has also been observed for coronary artery calcification, where women and men with type 1 diabetes have similar levels [22, 23]. This lack of CVD protection also means that women with diabetes have a greater excess risk of CVD compared to women in the background population than men, an effect that has been consistently shown across international studies [1, 12, 24–26]. In a 2015 meta-analysis, Huxley et al. reported a pooled SMR for CVD mortality of 11.3 in women versus 5.7 in men [26]. The difference in excess risk was slightly greater for coronary artery disease (CAD) events alone, with a pooled incidence ratio of 13.3 in women and 5.6 in men. More recent results from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study are consistent with these findings, also showing a greater excess relative risk in women of both CVD mortality and morbidity [2•]. The excess risk observed in EDC is even greater than that seen in women of comparable ages (30–39 and 40–44 years) in other recent reports using registry data from Scotland [1], Sweden [24], and Australia [27]. Differences in diabetes duration (i.e., length of exposure to diabetes) may explain some of the higher risk seen in the EDC cohort, which is an exclusively childhood-onset (< 17 years of age) type 1 diabetes cohort. The registries from Scotland, Sweden, and Australia include adult-onset cases of type 1 diabetes; thus, there is a shorter average diabetes duration (i.e., shorter cumulative exposure to hyperglycemia) at any given age, compared to the EDC cohort. Disentangling the independent effects of age at onset and diabetes duration on complication and mortality risk is an ongoing analytical challenge [28, 29]. Regardless, this higher risk in a US cohort reinforces the distressing prospect that individuals with type 1 diabetes in the USA are inadequately treated compared to their counterparts in other developed nations, a concern which has been raised in the past [30, 31]. Moreover, this differential excess risk seen in EDC compared to the aforementioned international registries is even greater in women than in men. This difference in excess risk by sex may be due to a greater detrimental effect of hyperglycemia in women, a difference in how diabetes affects other metabolic processes, such as lipid metabolism, in women compared to men, or a treatment bias that is unfavorable to women. These possibilities will be discussed later in this review.

HbA1c and CVD Risk in Type 1 Diabetes

The Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial (DCCT) and, its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study have shown a long-term reduction in CVD incidence associated with the use of intensive insulin therapy [32, 33]. After 17 years of follow-up, receiving intensive treatment during the 6.5 year DCCT was demonstrated to have reduced the risk of CVD by 42%, compared to conventional treatment [33]. In a subsequent report incorporating 30 years of follow-up, the former intensive treatment group continued to have a 30% reduction in CVD events compared to the former conventional treatment group [32]. The DCCT/EDIC investigators were also able to demonstrate that all of the treatment effect observed in the trial could be statistically explained by lower mean HbA1c levels experienced by the intensive treatment group during follow-up. Additionally, they more recently demonstrated that the effect of glycemia on CVD was increasingly mediated by traditional CVD risk factors over time [34]. These results stress the benefits of early, intensive glycemic control on reducing not only microvascular, but also macrovascular, complication risk in type 1 diabetes.

Observational Studies

In contrast with the strong association between HbA1c and CVD in DCCT/EDIC, HbA1c has not been a consistently strong predictor of CVD events in observational studies [5, 7, 8, 20, 35–37]. One potential explanation for the discrepancy between the DCCT/EDIC and observational studies is that, in the DCCT, intensive therapy was begun early in the course of diabetes, raising the suggestion that glycemia may play a role in the initiation of atherogenesis [38]. Another possibility is that the observational studies may have had too little variation in HbA1c within their respective cohorts to detect an association between HbA1c and CVD incidence. In contrast to the DCCT, where there was a large difference in HbA1c between the conventional and intensive treatment groups at the close-out of the trial (9.1% versus 7.4%, respectively), the observed range of HbA1c within the cohort studies has been comparatively narrow. For example, in the EDC, median HbA1c at baseline was 8.7% (interquartile range 7.7–9.7). There is also the possibility that HbA1c must approach 7%, as achieved by the intensive treatment arm in DCCT, to result in a significant reduction in CVD risk. This level of control was not achieved by many people in the observational studies, particularly

before intensive diabetes therapy was commonly utilized. In the EDC study, while HbA1c at study baseline did not predict CVD, decreasing HbA1c over time has been associated with a lower risk [9]. Additionally, more recent EDC analyses which incorporated repeated measures of HbA1c have shown an association between glycemic control over time and 25 year CVD incidence [39•, 40]. In the FinnDiane study, HbA1c variability over a median follow-up of 5.7 years, but not mean HbA1c over time, was predictive of CVD events [37]. Despite the inconsistent relationship between HbA1c and CAD, the association between poor glycemic control and an increased risk of PVD has been more consistent [5, 41, 42]. The stronger association between HbA1c and PVD may indicate that hyperglycemia is more strongly associated with the stable atherosclerosis which characterizes PVD, rather than plaque rupture which characterizes the acute coronary events [38, 43, 44].

Sex Differences in Glucose Management and CVD Risk

There is substantial evidence for differences in glucose management between men and women with type 1 diabetes, though how these differences may be related to CVD risk is less clear. Table 1 provides a summary of recent studies that have reported on sex differences in glucose management factors and CVD risk and/or risk factors in those with type 1 diabetes for > 20 years' duration. In a cross-sectional analysis of the 12-year (2004–2005) follow-up data from the DCCT/EDIC, Larkin et al. showed that women were significantly less likely than men to achieve HbA1c targets of < 7% or < 8% [45]. This is despite the observation that women were more likely to be using insulin pumps (58% of women compared to only 38% of men) and similarly likely to engage in self-monitoring of blood glucose (SMBG) ≥ 4 times per day (61% of women versus 58% of men). A similar difference in intensity of therapy by sex was observed in the EDC study during the same time period (2004–2006), when 50% of women but only 43% of men reported engaging in intensive diabetes management, a composite definition of insulin therapy and SMBG defined as multiple-dose insulin injections or using an insulin pump and SMBG ≥ 28 times per week [47•]. In a more recent study of 28,802 patients with type 1 diabetes from 300 outpatient centers in Italy, women were more often using insulin pumps (20% versus 14% of men), but again had higher average HbA1c (8.2% versus 8.0% in men) [48•]. Similarly, a recent analysis of 50 general practice databases in Scotland also showed that women with type 1 diabetes had worse glycemic control than men (8.9% versus 8.7%), though no information on diabetes duration, insulin pump use/intensive insulin therapy, or monitoring of blood glucose was reported (ages ranged from 12 to 88 years) [50]. Finally, in a joint analysis of data from the Joslin Medalists and the Canadian Study of Longevity in Diabetes studies, two cohorts of very long (> 50 years) type 1 diabetes duration, women again had worse glycemic control but were more likely to be using an insulin pump than men [49•]. The consistent finding that, across studies, women achieve similar or worse levels of glycemic control despite higher rates of pump use and generally more intensive diabetes therapy than men suggests that women have greater difficulty reaching the same level of glycemic control compared to men. Importantly, in the aforementioned DCCT/EDIC analyses, the findings that women were more likely to be using insulin pumps, but less likely to meet HbA1c targets, persisted across age strata. The

Table 1 Recent reports on sex differences in glucose management factors and CVD risk and/or risk factors in type 1 diabetes with > 20 years duration

Study	Reference	Year	Results
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications	Larkin et al. [45]	2010	Women more likely to be using insulin pump and engage in SMBG, but less likely to achieve HbA1c targets of < 7or < 8% than men in cross-sectional analysis (2004–2005).
	DCCT/EDIC Research Group [46•]	2016	No difference in the association between HbA1c and CVD by sex.
Epidemiology of Diabetes Complications Study	Swasey et al. [47•]	2018	Women more likely to be using insulin pump and engage in SMBG over all time periods examined over 25 years (1986–1988 through 2011–2013). The proportion meeting the HbA1c target of < 7% increased over the same 25-year period and did not differ by sex.
	Miller et al. [39•]	2018	25-year trajectories of HbA1c did not differ by sex. The association between HbA1c trajectory and CVD incidence did not differ by sex, regardless of CVD manifestation.
Italian Outpatient Centers	Manicardi et al. [48•]	2016	Women were more likely to be using insulin pump, but had higher average HbA1c than men.
Joslin Medalists/Canadian Study of Longevity in Diabetes	Weisman [49•]	2018	Women were more likely to be using insulin pump, but had higher average HbA1c than men.

lack of a difference by age suggests that pregnancy or planning for pregnancy or hormonal changes related to menstruation did not seem to explain the observed sex differences.

While the aforementioned studies provide cross-sectional evidence of sex differences in glucose management, there are little data on long-term patterns of HbA1c and rates of intensive insulin therapy by sex in type 1 diabetes. In one recent paper, the proportion of EDC participants meeting the American Diabetes Association's HbA1c target of < 7% over 25 years was examined by sex [47•]. In these analyses, the proportion with HbA1c < 7% increased over time in both sexes and there was no difference in the proportion of men and women meeting the goal in each time period examined. This report also showed that women were consistently more likely to engage in intensive insulin therapy across all time periods [47•]. Here, in Fig. 1, we present previously unpublished sex-specific 25-year mean HbA1c trajectories of the EDC cohort. This cohort had a long diabetes duration, on average, during the entire follow-up: the mean diabetes duration was 19 years at the 1986–1988 study baseline ($n = 658$) and 43 years at the 25-year follow-up in 2011–2013 ($n = 228$). EDC participants were examined biennially between 1986 and 1998 and then again at 18 (2004–2006) and 25 years (2011–2013) of follow-up. Figure 1 shows the observed trajectories of mean HbA1c over the 25-year follow-up. It is clear from the graph that there was no significant difference in the level HbA1c over time by sex (Fig. 1). Notably, both men and women had a similar decrease in HbA1c beginning in 1994–1996, after the publication of the 1993 DCCT results establishing that intensive diabetes therapy delays microvascular complication incidence [51]. This decrease reflects the widespread adoption of intensive therapy into the general population with type 1 diabetes at that time and shows that the effect of intensive therapy on HbA1c did not meaningfully differ by sex. The patterns were similar when restricted to the subset of participants with data available at the 25-year follow-up ($n = 228$). With regard to how these HbA1c trajectories are related to CVD risk, in a recent EDC report using joint models to estimate the association between longitudinal trajectory of HbA1c and 25 year CVD incidence, no evidence of a difference by sex was found, regardless of the manifestation of CVD (coronary artery disease, stroke, or PVD) [39•]. The recent comprehensive analysis of CVD risk factors in DCCT/EDIC suggested that the association between mean HbA1c and CVD risk was slightly stronger in women (hazard ratio 1.42, 95% confidence interval 1.18, 1.70) compared to men (hazard ratio 1.23, 95% confidence interval 1.01, 1.49) but there was no significant interaction between sex and HbA1c with respect to CVD incidence when formally tested [46•].

Studies reporting on differences in rates of hypoglycemia by sex in type 1 diabetes are sparse, particularly in long-duration diabetes. There is some evidence that in short duration type 1 diabetes, female patients have a higher rate of hypoglycemia than male patients [52, 53]. During the DCCT, male and female participants had similarly high rates of hypoglycemia in the intensive therapy group (64 versus 59 events/100 patient years, respectively), but female participants had a significantly higher rate in the conventional therapy group (23 events/100 patient years versus < 15 in male participants) [53]. In a later joint publication from DCCT/EDIC and EDC, episodes of hypoglycemia were shown to have increased over time in both studies in concordance with increasing adoption of intensive insulin therapy, but these trends were

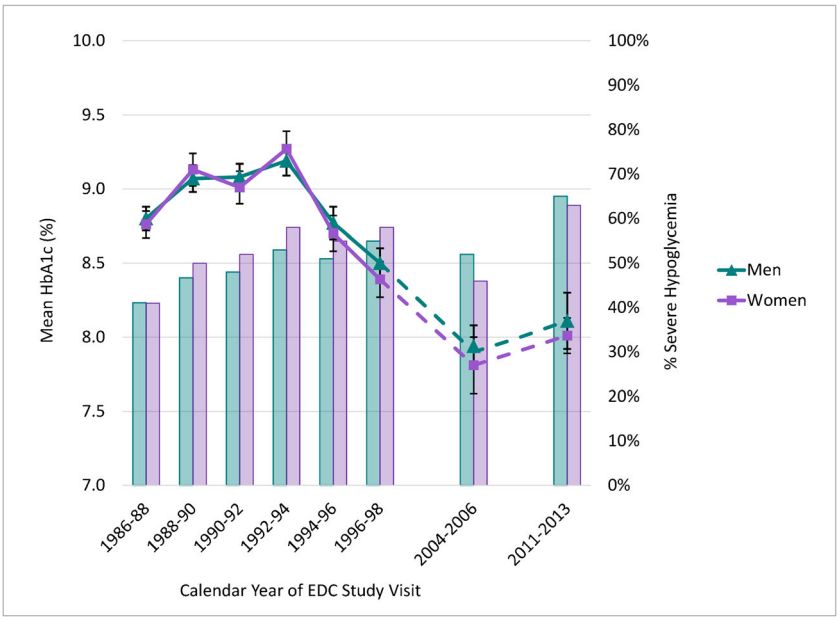

Fig. 1 Observed longitudinal trajectories of mean HbA1c and percent reporting severe hypoglycemia (defined as hypoglycemia resulting in seizure or unconsciousness or requiring assistance from another person) in men (*teal*) and women (*purple*) in the Epidemiology of Diabetes Complications (EDC) study (*error bars* are standard errors). Sex differences were not statistically significant for either measure at any time point

not reported separately by sex [54]. Here, the bars in Fig. 1 show the rates of severe hypoglycemia (defined as resulting in unconsciousness or requiring the assistance of another person) in the EDC study over time (previously unpublished). Rates of hypoglycemia rose in both sexes over the first 10 years of follow up and fell in year 18 when glycemic control was at its best level. At year 25, hypoglycemia increased, likely reflecting the aging of the cohort (mean age 51.3 years) [55]. Women tended to be slightly more likely to report hypoglycemia than men during the first 10 years of follow-up, but less likely than men after glycemic control improved, but these sex differences were small and not statistically significant at any time point.

In type 2 diabetes, hypoglycemia has been linked to an increased risk of CVD but there are very few studies examining the association between hypoglycemia and CVD risk in type 1 diabetes [56]. Additionally, we are not aware of any studies that have reported on whether this association differs in men and women. An analysis of the association between the number of episodes of hypoglycemia and CVD risk in the EURODIAB study found no association, regardless of the severity of hypoglycemia, but it did not report results from sex-specific analyses [57]. In contrast to these results, two more recent studies have found an association between hypoglycemia and increased risk of CVD incidence [58, 59], but again, neither study reported on sex-specific analyses. The major difficulty in examining the relationship between hypoglycemia and CVD risk is the association between intensive insulin therapy and increased hypoglycemia [53]. Disentangling the protective effect of intensive therapy from the potentially deleterious effect of hypoglycemia on vascular disease is a major analytical challenge.

The Association Between Glucose Management and Other CVD Risk Factors

As there is no strong evidence that differences in glucose management or HbA1c level directly account for the greater relative risk for CVD in women with type 1 diabetes, other cardiovascular risk factors must play a more direct role. While a comprehensive discussion of CVD risk factors and how they may differ between the sexes is outside the scope of this review, we will briefly discuss important findings, emphasizing how these factors may relate to glucose management.

Differences in CVD risk factors by sex, particularly lipid derangements, appear early in the course of type 1 diabetes, beginning as early as adolescence [17•]. It has been observed that changes in glucose control are associated with concomitant changes in lipid profile in youth with type 1 diabetes [60]. The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study has provided evidence that lipids and measures of fat distribution explain a substantial proportion of the excess coronary artery calcification seen in women with type 1 diabetes [23]. In these analyses, women with type 1 diabetes exhibited a more adverse adiposity profile than control women, a difference not observed in men. Additionally, adjustment for adiposity variables, including waist-hip ratio and visceral fat, or adjustment for LDL and HDL cholesterol eliminated the diabetes-by-sex interaction with respect to coronary artery calcification. The EDC study has also provided evidence that differences in distributions of lipid levels by sex can lead to differential relationships with CVD outcomes and may at least partially explain the excess risk seen in women. For example, while higher HDL-c is generally protective, HDL-c > 60 mg/dl offered no additional protection against CAD over an HDL-c 50–60 mg/dl in women [61]. On the other hand, in men, CAD incidence decreased linearly as HDL-c increased across the range of values. Furthermore, very high HDL-c (> 80 mg/dl) was associated with an *increased* risk of CAD in women. In men, this association between very high HDL-c and CAD was not observed, but few had HDL-c levels > 80 mg/dl. Specific subfractions of HDL-c may also play a differential role in CVD risk by sex. In the Joslin Medalists, the HDL-c subfractions containing apolipoprotein AI and AII were lower in women with prevalent CVD compared to those without CVD, but did not differ by CVD prevalence in men [61].

There is also substantial evidence that insulin resistance in type 1 diabetes may diminish the female protection against CVD. The CACTI study has shown that adults with type 1 diabetes have increased insulin resistance compared to nondiabetic controls [62] and, more recently, that this effect of type 1 diabetes on insulin resistance appears to be greater in women [63]. A greater burden of insulin resistance in women with type 1 diabetes may explain why they remain at equivalent risk of CVD as men, despite more intensive insulin therapy, on average. The reasons for greater insulin resistance in women with type 1 diabetes compared to women without diabetes are unclear, but it is thought that differences in estrogen levels may play a role [64, 65]. Women with type 1 diabetes have been shown to have lower levels of estradiol and estrogen activity [66] and a differential hormonal milieu [67] compared to nondiabetic control women. Lower estrogen levels have been associated with greater insulin resistance in both animal models and in humans [68]; thus, this is a mechanism that warrants further investigation.

Differences in diabetes-related distress and depression may also play a differential role in CVD risk in women with type 1 diabetes. Higher levels of diabetes distress and depression have both been associated with worse diabetes management [69–73], and women with type 1 diabetes have been shown to have higher levels of diabetes distress than men [74, 75]. In the EDC study, depression was a strong risk factor for CAD in women only [3], so these factors may play an important role in the pathway between glucose management and the greater excess of CVD in women with type 1 diabetes.

Finally, treatment biases that disfavor women may also play a role in the greater excess CVD risk in women with type 1 diabetes. In an illuminating paper, Larkin et al. reported that, in DCCT/EDIC, women were less likely to be treated with statins even if they had elevated LDL cholesterol levels [45]. This finding was also observed in the EDC study, where in a contemporary (1996–2012) follow-up of young adults < 45 years old, women were about half as likely as men to report taking lipid-lowering medications, despite similar levels of LDL cholesterol [2]. Similar differences in treatment by sex have also been shown in type 2 diabetes, where women are less likely to have lipids assessed [76, 77], be prescribed lipid-lowering medications [76–79], or advised to use aspirin therapy [76, 80, 81] and are also less likely to achieve target blood pressure and lipid levels than men [79, 81].

Conclusions

While the DCCT clearly established the importance of intensive diabetes therapy to prevent both micro- and macrovascular complications in type 1 diabetes, there is an obvious need for population-based studies that focus on the differences in CVD risk between men and women. Within the setting of a clinical trial, sex differences in the management of glucose levels do not exist, but differences in risk factor treatment by sex are readily apparent in observational studies, including in the observational EDIC follow-up study to the DCCT [45]. The association between HbA1c itself and CVD risk does not seem to differ by sex, based on the results of the few studies that have reported on this issue [39•, 46•]. However, there is a lack of published data regarding the relationship between other aspects of glucose management and CVD risk by sex in type 1 diabetes, which is particularly important, as HbA1c does not provide an assessment of glucose variability. The consistent and concerning finding that women have worse glycemic control despite more intensive diabetes therapy supports the hypothesis that diabetes leads to a relatively greater metabolic derangement in women than men and calls for research focusing on this issue. In general, trials are needed to establish guidelines for blood pressure and lipid goals, the primary CVD risk factors identified in normoglycemic populations, specific to those with type 1 diabetes [82], and potential sex differences should be a primary focus of these studies. In addition to trials that focus on these traditional CVD risk factors, studies with a primary focus on sex differences in nontraditional risk factors are needed as well. The association between estrogen and insulin resistance, as well as the link between psychosocial factors, including diabetes distress and depression, and poor glucose management are important avenues of future research. From a clinical perspective, awareness regarding potential for treatment biases by sex should be addressed to ensure that all individuals with type 1 diabetes are receiving care according to the appropriate guidelines.

Compliance with Ethical Standards

Conflict of Interest Rachel G. Miller and Tina Costacou declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent Research protocols for the EDC study were approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent. This article does not contain any studies with animal subjects performed by the authors.

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