Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 1 diabetes

Dario Pitocco[1,2*], Mauro Di Leo[1], Linda Tartaglione[1], Francesca De Leva[1], Alessandro Rizzi[1] & Alfredo Pontecorvi[1,2]

ABSTRACT

This review examines if the relative risk for Cardiovascular Disease (CVD) events and mortality in diabetic women (in comparison with non-diabetic women) is to be greater than that in diabetic men. It has been proposed that this finding is due to gender disparities in treatment intensity. Considering that cardiovascular complications are an important cause of death in patients with Type 1 diabetes, comprehensive treatment, including therapy for lowering blood glucose levels, blood pressure, blood lipid levels, and physical activity would be beneficial to reduce diabetes complications, the occurrence of cardiovascular and cerebrovascular events, and the related mortality.

Introduction

Over the past decade, researchers, health-care workers, the public and policy makers have expended considerable effort to enhance our understanding of gender differences in Cardiovascular Disease (CVD) and to analyze the impact of heart disease in women. Similarly, in diagnoses of Type 1 Diabetes (T1DM), researchers have hypothesized that females experience more aggressive disease progression [1]. Female patients appear to present with more disease symptoms and signs of a more disruptive disease process when clinical T1DM appears [2]. Do age and gender affect insulin sensitivity and insulin secretion in women with T1DM differently than the general population and, more specifically, men with T1DM? Do biological and psychosocial differences between men and women play a role in the progression of T1DM and its complications? Do gender-based differences exist in diabetes?

Literature Review

A series of recent studies has demonstrated that diabetes affects males and females differently due to the effects of hormones, menopause and other factors. Heart disease is the leading cause of mortality in women with diabetes, and women are also at a higher risk of stroke [3]. In contrast, the prevalence of advanced kidney disease generally does not differ by gender [4]. Some research has hypothesized that female diabetic patients unconditionally lose their general gender-based survival advantage [5], although glycated hemoglobin (HbA1c) is only slightly and insignificantly higher in female patients. All risk factors associated with cardiovascular disease appear to have a greater impact among diabetic females than among their male counterparts [6,7]. Risk factors include increased uric acid levels [8], low physical activity, obesity, insulin resistance linked to polycystic ovarian syndrome [9], and increased coronary artery calcification [10]. However, a recent Swedish study found no gender difference in terms of the extent of coronary heart disease in men and women of similar age [11]. The prevalence of diabetic retinopathy does not seem to differ by gender in T1DM [12]. However, some research confirms an observation made in clinical practice: women

[1]*Fondazione Policlinico Universitario Agosnito Gemelli IRCCS, Roma, Italy*

[2]*Department of Endocrinology, Università Cattolica del Sacro Cuore, Roma, Italy*

[*]*Author for correspondence: dario.pitocco@policlinicogemelli.it*

KEYWORDS

- gender
- Type 1 diabetes
- complication
- cardiovascular risk
- metabolic control

with T1DM [13] show more severe signs of insulin resistance and a greater tendency to have other autoimmune diseases, such as celiac disease [14]. The higher rate of insulin resistance in women with T1DM associated with disturbed monthly hormonal variations and the early loss of the potentially beneficial impact of estrogen have been proposed as key factors. Endothelial dysfunction seems to be influenced by hormonal status [15]. Insulin resistance is also correlated with a worse cardiovascular outcome in women than in men with T1DM [5]. Some authors ascribe the greater risk of CVD to the reduced exposure to the protective action of estrogen [16]. Moreover, when compared to healthy women, women with T1DM present a higher dehydroepiandrosterone sulphate ratio and higher testosterone levels [1]. In addition, menarche is delayed in women with T1DM and menopause occurs later. The reduced exposure to the protection of estrogen could imply higher levels of androgens in women, which may promote atherosclerosis and CVD. However, data about different androgen levels in women with T1DM are disputed and inconclusive. Some authors find increased levels of testosterone while other authors find no difference in testosterone levels between healthy women and women with T1DM [17]. Another possible pathway to the higher risk of CVD in women with T1DM may be a higher pro-thrombotic status due to hyperglycemia and related oxidative stress. Oxidative stress is an accepted risk factor for the onset of cardiovascular events. The increased oxidation of proteins and the decreased activity of antioxidant mechanisms are crucial in the pathogenesis of diabetic complications, especially CVD. Compared to men, women with T1DM have lower levels of total antioxidant capacity (TRAP) and increased levels of lipid hydroperoxides [5]. Interestingly, this difference has been established even in subjects with a history of disease of less than 10 years. Increased oxidative stress causes endothelial activation and could determine the activation of another actor of thrombosis, platelets. In this regard, patients with T1DM have higher urinary thromboxane (TXM) excretion than healthy subjects, and women have significantly higher levels than their male counterparts. TXM is a marker of platelet activation, which may be induced by endothelial and oxidative stress. This higher response in women can lead to enhanced platelet activation, such that it may play a role in CVD onset [18]. Although the exact pathological mechanism is unclear, it is crucial to highlight the higher risk of mortality in women and the need for a focus on CVD prevention. A recent large-scale study on Chinese patients with T2DM showed that the 10-year risks of CHD and stroke were lower in women than in men with T2DM [19]. The reasons could be that HbA1c levels were significantly lower in women with T2DM than in men with T2DM and the rate of current smoking was significantly lower in women than that among the men. In another study, males had less likely to achieve ideal blood pressure control as compared to females, and being female was associated with lower odds of having a blood pressure ≥ 120/80 mmHg and it is known that high blood pressure is consistently found to be a major risk factor for diabetes complications [20]. In the same study, however, males with T1D had significantly lower BMI and HbA1c. These data could explaine why the increased mortality in females was related to greater cumulative exposure to hyperglycemia in females as compared to males. Some research shows that the prescription of statins or aspirin as a form of secondary prevention tends to be lower for women than for men [21,22]. An Italian study including around 29,000 adults with T1DM showed that women have a 33% greater likelihood of an HbA1c >8% (64 mmol/mol) [23]. Worse metabolic control has been also observed in girls and female adolescents [24]. At the same time, women with T1DM have more centrally distributed fat, which may contribute to their relatively higher cardiovascular disease risk [25]. In addition, innate distinctions in the genders' physiology and disparities between genders in the medical care provided for major cardiovascular risk factors may exist [26]. This has been attributed to an underestimation of patient risk, a less aggressive approach and poorer compliance among females [27]. In contrast, another study found no relevant differences between females and males in terms of the quality of diabetes care [28], suggesting that factors other than gender disparities in treatment are responsible. Depletion of the central distribution of fat through exercise and dietary adjustments may help ameliorate the subsequent involvement of cardiovascular disease. Moreover, psychosocial stress has a greater impact on women than men [29]. In addition, diabetic men with coronary heart disease are significantly more likely to receive oral combination drugs, ACE inhibitors and calcium channel blockers. This suggests that diabetic men might be more

carefully treated than women [30]. In T1DM, the greater difficulty in achieving good metabolic control in women and the better blood pressure control in men may be related to factors other than gender-related differences in medication use or diagnostic methods [23].

Discussion

Lower adherence to statin prescriptions was found in females than in males in the T1DM subjects, achievement of treatment goals for lipids. Women are also significantly less likely than men to use aspirin, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers [21], which suggest that risk-reducing therapies are underused in women with diabetes. Women with lower education levels and lower incomes exhibit poorer profiles for almost all biomarkers (i.e., glucose, triglycerides, insulin, waist circumference, diastolic blood pressure; exceptions include fasting plasma glucose and systolic blood pressure). However, evidence of these associations in men has been mixed. The strong association between socio-economic status and biomarkers, especially among women, reinforces the need to focus on health promotion, enhanced health policies and reductions in disparities [31]. Efforts to increase the amount of attention paid to cardiovascular risks in diabetic females seem to have some benefits. As such, improving the guideline-based clinical practice of drug therapy and compliance with such therapies must be a major target for all diabetic patients regardless of gender [32]. Moreover, in women with Type 2 Diabetes Mellitus (T2DM), research has found smaller reductions in HbA1c and reduced achievement of glycemic goals than in males with T2DM [33]. In this regard, differences in gender responses to therapy should be examined when differentiating treatment for patients with DM.

Conclusion

The major cardiovascular risks affecting women with T1DM may be overcome through an appropriate diet and greater psychological support. The emerging gender-specific studies indicate that although men and women share similar risk factors for CVD, certain risk factors are more potent in women. These include tobacco abuse, depression and other psychosocial risk factors. Notably, the INTERHEART study identified DM as a potentially modifiable risk factor for MI [34]. While studies have examined the pathophysiological mechanisms involved in the higher risk that women face, it is time to reinforce the need to concentrate on health promotion and to enhance efforts to prevent CVD given this particular gender-based risk.

Financial Competing Interests Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Turtinen M, Harkonen T, Parkkola A *et al.* Sex as a determinant of type 1 diabetes at diagnosis. *Pediatr. Diabetes.* 19(7), 1221-1228 (2018).
2. Akesson K, Hanberger L, Samuelsson U. The influence of age, gender, insulin dose, BMI, and blood pressure on metabolic control in young patients with type 1 diabetes. *Pediatr. Diabetes.* 16(8), 581-586 (2015).
3. Huxley R, Peters S, Mishra G *et al.* Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet. Diabetes. Endocrinol.* 3(3), 198-206 (2015).
4. Costacou T, Orchard T. Cumulative kidney complication risk by 50 years of type 1 diabetes: The effects of sex, age, and calendar year at onset. *Diabetes. Care.* 41(3), 426-433 (2018).
5. Secrest A, Becker D, Kelsey S *et al.* All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: The Allegheny county type 1 diabetes registry. *Diabetes. Care.* 33(12), 2573-2579 (2010).
6. Seghieri C, Policardo L, Francesconi P *et al.* Gender differences in the relationship between diabetes process of care indicators and cardiovascular outcomes. *Eur. J. Public. Health.* 26(2), 219-224 (2016).
7. Marra G, Cotroneo P, Pitocco D *et al.* Early increase of oxidative stress and reduced antioxidant defenses in patients with uncomplicated type 1diabetes: A case for gender difference. *Diabetes. Care.* 25 (2), 370-375 (2002).
8. Meisinger C, Thorand B, Schneider A *et al.* Sex differences in risk factors for incident type 2 diabetes mellitus: The Monica Augsburg cohort study.

Arch. Intern. Med. 162(1), 82-89 (2002).

9. Toulis K, Goulis D, Farmakiotis D *et al*. Adiponectin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. *Hum. Reprod. Update*. 15(3), 297-307 (2009).
10. Colhoun H, Rubens M, Underwood S *et al.* The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *J. Am. Coll. Cardiol*. 36(7), 2160-2167 (2000).
11. Ritsinger V, Hero C, Svensson A *et al.* Characteristics and prognosis in women and men with type 1 diabetes undergoing coronary angiography: A nationwide registry report. *Diabetes. Care.* 41(4), 876-883 (2018).
12. Bhaskaran K, Edwards E, Lee H *et al.* Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: A cohort study in the clinical practice research Datalink 2004-2014. *BMJ. Open.* 7(2), e014444 (2017).
13. Millstein R, Pyle L, Bergman B *et al*. Sex-specific differences in insulin resistance in type 1 diabetes: The CACTI cohort. *J. Diabetes. Complications.* 32(4), 418-423 (2018).
14. Craig M, Prinz N, Boyle C *et al*. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: International comparison across three continents. *Diabetes. Care*. 40(8), 1034-1040 (2017).
15. Gobl C, Bozkurt L, Yarragudi R *et al*. Biomarkers of endothelial dysfunction in relation to impaired carbohydrate metabolism following pregnancy with gestational diabetes mellitus. *Cardiovasc. Diabetol*. 13, 138 (2014).
16. Gunness A, Pazderska A, Ahmed M *et al.* Measurement of selected androgens using liquid chromatography-tandem mass spectrometry in reproductive-age women with type 1 diabetes. *Hum. Reprod*. 33(9), 1727-1734 (2018).
17. Salonia A, Lanzi R, Scavini M *et al.* Sexual function and endocrine profile in fertile women with type 1 diabetes. *Diabetes. Care*. 29(2), 312-316 (2006).
18. Zaccardi F, Rizzi A, Petrucci G *et al. In vivo* Platelet activation and aspirin responsiveness in type 1 diabetes. *Diabetes*. 65(2), 503-509 (2016).
19. Yao M, He J, Sun X *et al.* Gender differences in risks of coronary heart disease and stroke in patients with type 2 diabetes mellitus and their association with metabolic syndrome in China. *Int. J. Endocrinol*. (2016).
20. Huxley R, Peters S, Mishra G *et al.* Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet. Diabetes. Endocrinol*. 3(3), 198-206 (2015).
21. Larkin M, Backlund J, Cleary P *et al.* Disparity in management of diabetes and coronary heart disease risk factors by sex in DCCT/EDIC. *Diabet. Med*. 27(4), 451-458 (2010).
22. Kautzky-willer A, Stich K, Hintersteiner J *et al*. Sex-specific-differences in cardiometabolic risk in type 1 diabetes: A cross-sectional study. *Cardiovasc. Diabetol*. 12(1), 1 (2013).
23. Manicardi V, Russo G, Napoli A *et al.* Gender-disparities in adults with type 1 diabetes: More than a quality of care issue. A cross-sectional observational study from the AMD annals initiative. *PLoS. One*. 11(10), e0162960 (2016).
24. Samuelsson U, Anderzen J, Gudbjornsdottir S *et al*. Teenage girls with type 1 diabetes have poorer metabolic control than boys and face more complications in early adulthood. *J. Diabetes. Complications*. 30(5), 917-922 (2016).
25. Krishnan S, Fields D, Copeland K *et al.* Sex differences in cardiovascular disease risk in adolescents with type 1 diabetes. gender. *Medicine.* 9(4), 251-258 (2012).
26. Rossi M, Cristofaro M, Gentile S *et al.* Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: A cross-sectional observational study from the AMD annals initiative. *Diabetes. Care.* 36(10), 3162-3168 (2013).
27. Huxley R, Barzi F, Woodward M. Adverse effects of diabetes on multiple cardiovascular disease risk factors in women: The strong heart study. *Br. Med. J*. 332, 73-76 (2006).
28. Bugiardini R, Yan A, Yan R *et al.* Canadian acute coronary syndrome registry I and II investigators. factors influencing underutilization of evidence-based therapies in women. *Eur. Heart. J.* 32(11), 1337-1344 (2011).
29. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr. Rev.* 37(3), 278-316 (2016).
30. Kramer H, Raum E, Ruter G *et al.* Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes: Results from the DIANA study. *Cardiovascular. Diabetol*. 11, 88 (2012).
31. Kavanagh A, Bentley R, Turrell G *et al*. Socioeconomic position, gender, health behaviours and biomarkers of cardiovascular disease and diabetes. *Soc. Sci. Med*. 71(6), 1150-1160 (2010).
32. Kautzky-Willer A, Stich K, Hintersteiner J *et al*. Sex-specific-differences in cardiometabolic risk in type 1 diabetes:

a cross-sectional study. *Cardiovascular. Diabetol.* 12, 78 (2013).

33. McGill J, Vlajnic A, Knutsen P *et al.* Effect of gender on treatment outcomes in type 2 diabetes mellitus. *Diabetes. Res. Clin. Prac.* 102(3), 167-174 (2013).

34. Anand S, Islam S, Rosengren A et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur. Heart. J. 29(7), 932-940 (2008).