Cardiovascular Disease in T1DM

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Cardiovascular disease (CVD) is a major cause of mortality in type 1 diabetes mellitus (T1DM) patients, and cardiovascular risk (CVR) remains high even in T1DM patients with good metabolic control.

Keywords: type 1 diabetes ; cardiovascular disease ; prevalence ; risk factor ; lipoproteins ; hyperglycemia ; risk stratification ; therapy ; management

1. Introduction

The prevalence of diagnosed type 1 diabetes (T1DM) among US adults in 2016 and 2017 was 0.5% [1] and is increasing worldwide, which may be partly related to reduced natural selection associated with health advances [2]. Over the past few decades, reduction in cardiovascular mortality and coronary cardiovascular disease in non-diabetic and diabetic patients has corresponded with an overall mortality reduction and significant improvement in life expectancy in patients with type 2 (T2DM) and type 1 diabetes mellitus (T1DM) [3][4]. These findings are reflected clearly in the two cohorts of the Pittsburgh Epidemiology of Diabetes Complication (EDC) Study, which found an increase of 14 years in life expectancy between T1DM patients diagnosed in 1950–1964 and those diagnosed in 1965–1980 [5][6]. This improvement seems to be related to the optimization of glycemic control, management of cardiovascular risk (CVR) factors, and interventional cardiology. However, the total risk of cardiovascular disease (CVD) remains higher in T1DM patients than in non-diabetic subjects, particularly in women, and it becomes the most important cause of morbidity and mortality in T1DM patients [7][8][9][10]. Compared to early-onset T2DM, T1DM is associated with a lower mortality and fewer complications [11][12]. The physiopathology underlying the relationship between cardiovascular events and T1DM is poorly understood, and assessment of CVR and management to reduce CVD has been extrapolated in part from studies conducted in T2DM patients and still represents a challenge for clinicians.

2. Clinical Atherosclerosis in T1DM Patients

The main epidemiological studies demonstrate that CVD events are more common and occur earlier in T1DM patients than in the general population, although CVD prevalence varies substantially depending on diabetes duration, age, and gender (Table 1). Krolewski et al. in 1987 [13], published the first observational study that included cumulative mortality rate (CMR) due to coronary artery disease (CAD) in T1DM patients. By 55 years of age, the total CMR due to CAD was 35 ± 5%, much higher than the corresponding rate for non-diabetic subjects in the Framingham Heart Study, which was 8% for men and 4% for women. Also, the combined CMR for clinical coronary heart disease (CHD), including angina and acute nonfatal myocardial infarction, and asymptomatic CAD detected by stress test was 33% among T1DM survivors ages 45–59.

Since then, many studies progressively have confirmed high CVD prevalence in T1DM patients compared with the overall population. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the standardized mortality ratio (SMR) for ischemic heart disease in a diabetic group (n = 1200) diagnosed before age 30 and taking insulin was 9.1 in men and 13 in women [14]. The Pittsburgh Epidemiology of Diabetes Complications (EDC) study demonstrated that CAD events were the leading cause of death in T1DM patients. The incidence of major CAD events in T1DM adults ages 28–38 was 0.98% per year and surpassed 3% per year after age 55 [15], with SMR ratios of CVD at 8.8 and 24.7 for men and women, respectively, in the Allegheny County Type 1 Diabetes Registry [9]. In the EURODIAB IDDM Complications Study, which included 3250 T1DM patients from 16 European countries, overall CVD prevalence was 9% in men and 10% in women. In addition, CVD prevalence increased with diabetes mellitus (DM) duration and age, at 6% in T1DM patients ages 15–29, and 25% in T1DM patients age 45–59 [16]. A study of the CVD prevalence rate was conducted on T1DM patients who were selected to be comparable in age (mean age of 28) and DM duration (18–20 years) to the EDC Study and the EURODIAB IDDM Complications Study [17]. This report confirms the high prevalence of CVD in TIDM subjects and was similar in both populations, (i.e., men 8.6% vs. 8.0%, women 7.4% vs. 8.5%, EURODIAB vs. EDC, respectively).

The UK General Practice Research Database (GPRD), one of the most robust analyses of CVD risk that includes data from more than 7400 T1DM patients with a mean age of 33 ± 14.5 years and mean DM duration of 15 ± 12 years, reported that CVD events occurred about 10 to 15 years earlier in T1DM patients than in the matched non-diabetic control group. During a mean follow-up of 4.7 years, the hazard ratio (HR) for major CVD events was 3.6 and 7.7 in T1DM men and women, respectively, after stratification by year of birth and gender [18][19].

Another comparative study, published by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group and Collaborators, comprises an analysis of the long-term cumulative incidence of CVD events in T1DM patients [20]. Either intensive or conventional therapy patients in the DCCT/EDIC study cohort (*n* = 1441) were compared with a similar subset of the EDC population (*n* = 161) after 18.5 years of follow-up. The cumulative incidence of CVD in the DCCT/EDIC conventional treatment group was similar to the EDC cohort, with 14% cumulative incidence, but was significantly higher than the 9% of the DCCT/EDIC intensive treatment group. These findings reflect that the frequency of acute complications in T1DM patients, especially for those under intensive therapy over time, was lower than that previously published.

Recently, some observational studies reported that although the situation has improved for T1DM patients over the past few years, cardiovascular event rates and cardiovascular mortality rates for CVD remain higher in T1DM patients than in the overall population [7][21][22]. A registry-based observational study conducted in a Swedish population of 34,000 T1DM patients reported a higher risk of total death and CVD death rates—two- to nine-fold times and three- to 10-fold times, respectively—in T1DM patients than in matched controls, depending on glycated hemoglobin (HbA1c) levels [22]. In the Scottish Care Information-Diabetes Collaboration (SCI-DC) database, the age-adjusted incidence rate ratio (IRR) for a first CVD event associated with T1DM (*n* = 21,789) vs. the non-diabetic population (3.96 million) was higher in women (3.0: 95% CI 2.4–3.8) than in men (2.3: 2.0–2.7), while the IRR for all-cause mortality associated with T1DM was comparable at 2.6 (2.2–3.0) in men and 2.7 (2.2–3.4) in women [21]. The estimated loss of life expectancy for patients with type 1 diabetes in Scotland at age 20 was approximately 11 years for men and 13 years for women compared with the general population without T1DM [7]. Finally, in the Swedish National Diabetes Registry, T1DM patients with disease onset before age 10 experienced a 30-fold increased risk of CHD and acute myocardial infarction (AMI) in their early adult years, and women displayed a 60- and 90-fold increased risk of CHD and AMI, respectively. Early onset type 1 diabetes resulted in a loss of 17.7 and 14.2 years of life expectancy for women and men, respectively [8].

In conclusion, CVD incidence is much higher and happens earlier in T1DM patients, women are more affected than men, and the incidence is much more pronounced in patients with early diabetes. In T1DM, relative CVD risk, age-adjusted, was 4- to 10-fold times higher, and CVD events occurred about 10 to 15 years earlier than matched non-diabetic subjects. CVD prevalence depends on DM duration, glycemic control, and age of patients included in the cohorts.

3. CVD Risk Factors in T1DM Patients

The pathophysiology underlying cardiovascular events in T1DM patients remains unclear, and conventional CVD risk factors' relative role in T1DM is not well-defined. Conventional risk factors—such as hyperlipemia, HBP, and smoking—are related to CVD in T1DM patients [23][24]. However, in contrast to what usually happens with T2DM patients, these risk factors are rarely present when T1DM diagnosis occurs and appear some years after a diabetes diagnosis. In fact, the Framingham model in the Pittsburgh EDC study underestimates the prediction of cardiovascular events in T1DM because conventional CVR factors cannot explain increased CVR in T1DM patients, suggesting the presence of specific risk factors for these subjects [25]. For instance, T1DM patients have long-term hyperglycemia that is unrelated to other associated metabolic disorders compared with T2DM patients. Below, we review the specific risk factors in the CVD pathophysiology, as well as those factors that are relevant to the evaluation and management of T1DM patients.

References

1. Xu, G.; Liu, B.; Sun, Y.; Du, Y.; Snetselaar, L.G.; Hu, F.B.; Bao, W. Prevalence of Diagnosed Type 1 and Type 2 Diabetes among US Adults in 2016 and 2017: Population Based Study. BMJ 2018, 362, k1497.
2. You, W.-P.; Henneberg, M. Type 1 Diabetes Prevalence Increasing Globally and Regionally: The Role of Natural Selection and Life Expectancy at Birth. BMJ Open Diabetes Res. Care 2016, 4, e000161.
3. Preis, S.R.; Hwang, S.-J.; Coady, S.; Pencina, M.J.; D'Agostino, R.B.; Savage, P.J.; Levy, D.; Fox, C.S. Trends in All-Cause and Cardiovascular Disease Mortality among Women and Men with and without Diabetes in the Framingham Heart Study, 1950–2005. Circulation 2009, 119, 1728–1735.

4. Chen, L.; Islam, R.M.; Wang, J.; Hird, T.R.; Pavkov, M.E.; Gregg, E.W.; Salim, A.; Tabesh, M.; Koye, D.N.; Harding, J.L.; et al. A Systematic Review of Trends in All-Cause Mortality among People with Diabetes. Diabetologia 2020, 63, 1718–1735.
5. Nishimura, R.; LaPorte, R.E.; Dorman, J.S.; Tajima, N.; Becker, D.; Orchard, T.J. Mortality Trends in Type 1 Diabetes: The Allegheny County (Pennsylvania) Registry 1965–1999. Diabetes Care 2001, 24, 823–827.
6. Miller, R.G.; Secrest, A.M.; Sharma, R.K.; Songer, T.J.; Orchard, T.J. Improvements in the Life Expectancy of Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study Cohort. Diabetes 2012, 61, 2987–2992.
7. Livingstone, S.J.; Levin, D.; Looker, H.C.; Lindsay, R.S.; Wild, S.H.; Joss, N.; Leese, G.; Leslie, P.; McCrimmon, R.J.; Metcalfe, W.; et al. Estimated Life Expectancy in a Scottish Cohort with Type 1 Diabetes, 2008–2010. JAMA 2015, 313, 37–44.
8. Rawshani, A.; Sattar, N.; Franzén, S.; Rawshani, A.; Hattersley, A.T.; Svensson, A.-M.; Eliasson, B.; Gudbjörnsdottir, S. Excess Mortality and Cardiovascular Disease in Young Adults with Type 1 Diabetes in Relation to Age at Onset: A Nationwide, Register-Based Cohort Study. Lancet Lond. Engl. 2018, 392, 477–486.
9. Secrest, A.M.; Becker, D.J.; Kelsey, S.F.; Laporte, R.E.; Orchard, T.J. Cause-Specific Mortality Trends in a Large Population-Based Cohort with Long-Standing Childhood-Onset Type 1 Diabetes. Diabetes 2010, 59, 3216–3222.
10. Huxley, R.R.; Peters, S.A.E.; Mishra, G.D.; Woodward, M. 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. 2015, 3, 198–206.
11. Constantino, M.I.; Molyneaux, L.; Limacher-Gisler, F.; Al-Saeed, A.; Luo, C.; Wu, T.; Twigg, S.M.; Yue, D.K.; Wong, J. Long-Term Complications and Mortality in Young-Onset Diabetes: Type 2 Diabetes Is More Hazardous and Lethal than Type 1 Diabetes. Diabetes Care 2013, 36, 3863–3869.
12. Amutha, A.; Anjana, R.M.; Venkatesan, U.; Ranjani, H.; Unnikrishnan, R.; Narayan, K.M.V.; Mohan, V.; Ali, M.K. Incidence of Complications in Young-Onset Diabetes: Comparing Type 2 with Type 1 (the Young Diab Study). Diabetes Res. Clin. Pract. 2017, 123, 1–8.
13. Krolewski, A.S.; Kosinski, E.J.; Warram, J.H.; Leland, O.S.; Busick, E.J.; Asmal, A.C.; Rand, L.I.; Christlieb, A.R.; Bradley, R.F.; Kahn, C.R. Magnitude and Determinants of Coronary Artery Disease in Juvenile-Onset, Insulin-Dependent Diabetes Mellitus. Am. J. Cardiol. 1987, 59, 750–755.
14. Moss, S.E.; Klein, R.; Klein, B.E. Cause-Specific Mortality in a Population-Based Study of Diabetes. Am. J. Public Health 1991, 81, 1158–1162.
15. De Ferranti, S.D.; de Boer, I.H.; Fonseca, V.; Fox, C.S.; Golden, S.H.; Lavie, C.J.; Magge, S.N.; Marx, N.; McGuire, D.K.; Orchard, T.J.; et al. Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement from the American Heart Association and American Diabetes Association. Diabetes Care 2014, 37, 2843–2863.
16. Koivisto, V.A.; Stevens, L.K.; Mattock, M.; Ebeling, P.; Muggeo, M.; Stephenson, J.; Idzior-Walus, B. Cardiovascular Disease and Its Risk Factors in IDDM in Europe. EURODIAB IDDM Complications Study Group. Diabetes Care 1996, 19, 689–697.
17. Orchard, T.J.; Stevens, L.K.; Forrest, K.Y.; Fuller, J.H. Cardiovascular Disease in Insulin Dependent Diabetes Mellitus: Similar Rates but Different Risk Factors in the US Compared with Europe. Int. J. Epidemiol. 1998, 27, 976–983.
18. Soedamah-Muthu, S.S.; Fuller, J.H.; Mulnier, H.E.; Raleigh, V.S.; Lawrenson, R.A.; Colhoun, H.M. High Risk of Cardiovascular Disease in Patients with Type 1 Diabetes in the UK: A Cohort Study Using the General Practice Research Database. Diabetes Care 2006, 29, 798–804.
19. Soedamah-Muthu, S.S.; Fuller, J.H.; Mulnier, H.E.; Raleigh, V.S.; Lawrenson, R.A.; Colhoun, H.M. All-Cause Mortality Rates in Patients with Type 1 Diabetes Mellitus Compared with a Non-Diabetic Population from the UK General Practice Research Database, 1992–1999. Diabetologia 2006, 49, 660–666.
20. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group; Nathan, D.M.; Zinman, B.; Cleary, P.A.; Backlund, J.-Y.C.; Genuth, S.; Miller, R.; Orchard, T.J. Modern-Day Clinical Course of Type 1 Diabetes Mellitus after 30 Years' Duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983–2005). Arch. Intern. Med. 2009, 169, 1307–1316.
21. Livingstone, S.J.; Looker, H.C.; Hothersall, E.J.; Wild, S.H.; Lindsay, R.S.; Chalmers, J.; Cleland, S.; Leese, G.P.; McKnight, J.; Morris, A.D.; et al. Risk of Cardiovascular Disease and Total Mortality in Adults with Type 1 Diabetes: Scottish Registry Linkage Study. PLoS Med. 2012, 9, e1001321.
22. Lind, M.; Svensson, A.-M.; Kosiborod, M.; Gudbjörnsdottir, S.; Pivodic, A.; Wedel, H.; Dahlqvist, S.; Clements, M.; Rosengren, A. Glycemic Control and Excess Mortality in Type 1 Diabetes. N. Engl. J. Med. 2014, 371, 1972–1982.

23. Lepore, G.; Bruttomesso, D.; Nosari, I.; Tiengo, A.; Trevisan, R. Glycaemic Control and Microvascular Complications in a Large Cohort of Italian Type 1 Diabetic Out-Patients. Diabetes Nutr. Metab. 2002, 15, 232–239.
24. Rodrigues, T.C.; Canani, L.H.; Gross, J.L. Metabolic syndrome, insulin resistance and cardiovascular disease in type-1 diabetes mellitus. Arq. Bras. Cardiol. 2010, 94, 134–139.
25. Zgibor, J.C.; Piatt, G.A.; Ruppert, K.; Orchard, T.J.; Roberts, M.S. Deficiencies of Cardiovascular Risk Prediction Models for Type 1 Diabetes. Diabetes Care 2006, 29, 1860–1865.