Review article

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Type 1 diabetes mellitus and cardiovascular risk: A short review

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ABSTRACT

The incidence of cardiovascular disease is substantially increased in patients with type 1 diabetes compared to the general population. Robust evidence from the randomized Diabetes Control and Complications Trial (DCCT) and the long-term epidemiologic surveillance of its participants suggest that tight glycemic control by means of intensive insulin treatment is efficacious both in primary and secondary prevention of cardiovascular disease. New antidiabetic agents with proven cardiorenal benefit in patients with type 2 diabetes, such as Glucagen-Like Polypeptide-1 Receptor Agonists (GLP-1RA) and Sodium-Glucose co-Transporter-2 Inhibitors (SGLT-2inh), have been tested as adjunctive to insulin treatment in a few clinical trials in patients with type 1 diabetes. Despite their favorable effect on risk factors for atherosclerotic disease, such as body weight and blood pressure, the lack of evidence for a direct effect on cardiovascular outcomes and an increased risk for serious adverse events, such as diabetic ketoacidosis, limit their use in patients with type 1 diabetes. New metrics of glycemia, alterations in diabetes classification and precision medicine may contribute in an individualized approach of cardiovascular risk prevention in patients with diabetes.

KEY WORDS: *Type 1 diabetes, cardiovascular risk, GLP-1RA, SGLT-2inh, adjunctive treatment*

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in patients with Diabetes Mellitus (DM). Recent data from Cardiovascular Outcome Trials (CVOTs) in patients with type 2 diabetes (T2 patients) have changed treatment algorithm targeting primarily to the prevention of cardiorenal complications of the disease. Newer classes of antidiabetic medications, such as Glucagen-Like Polypeptide-1 Receptor Agonists (GLP-1RA) and Sodium-Glucose co-Transporter-2 Inhibitors (SGLT-2inh), seem to substantially reduce cardiovascular and renal outcomes in T2 patients, beyond their antidiabetic effect1. However, evidence concerning the safety and efficacy of these classes of antidiabetic drugs in patients with type 1 diabetes (T1 patients) is extremely limited. In this narrative review we try to explore the relationship between Type 1 diabetes and CVD focusing on clinical data that could augment optimal prevention strategies.

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Cardiovascular outcomes in T1 patients-Epidemiology

Observational studies in T1 males report a 3-3.6 fold increased risk for Acute Myocardial Infarction (AMI), stroke, need for coronary artery revascularization, or sudden cardiovascular death compared to the general male population. Similarly, women with Type 1 diabetes run a 5.9-7.6 fold higher risk for any of the above cardiovascular outcomes compared to those without diabetes[2,3]. In a large Swedish cohort the risk for non-traumatic lower limb amputation was reported up to 86 fold increased in T1 patients compared to the general population[4].

Well defined cardiovascular risk (CVR) factors such as hypertension, smoking, subclinical inflammation, microalbuminuria and sub-optimal glycemic control are strongly related to adverse cardiovascular events both in T1 and T2 patients. On the contrary, insulin resistance and dyslipidemia seem to contribute less to the total CVR in T1 than in T2 patients[5].

Coronary Arteries Disease (CAD) is the most prevalent macrovascular complication in patients with T1. Mortality from CAD is higher in men and increases substantially after the age of 40 with rates up to 6-8% within 14-18 years of surveillance[6,7]. Ischemic stroke, although less prevalent than CAD, is another "hard" cardiovascular outcome with a reported annual rate in EURODIAB study up to 0.74%, 2-3 fold higher than in general population[8]. Several pathophysiologic mechanisms have been proposed in numerous mechanistic and clinical trials in order to explain the relationship between T1 diabetes and CVD. A detailed analysis of these data has been done elsewhere and is beyond the purposes of this review[5].

How to reduce CVR in T1 patients - Evidence from Interventional Studies

In Diabetes Control and Complications Trial (DCCT) 1,441 T1 patients were randomized to receive intensive insulin treatment with multiple daily insulin injections or insulin pump targeting fasting plasma glucose 70-120mg/dl and postprandial glucose <180mg/dl, or conventional insulin treatment with 1-2 daily insulin injections aiming to avoid hypoglycemia and hyperglycemia[9]. After median follow-up of 6.5 years, patients in the intensive treatment group had significantly lower HbA1c compared to those on conventional treatment (7.4% vs 9.1%, p<0.001). Tight glycemic control resulted in significantly lower rates of microvascular complications (retinopathy, nephropathy and neuropathy) in patients on intensive insulin treatment. Nevertheless, there was no statistically significant difference between the two groups in the incidence of cardiovascular events.

After the end of the interventional study all the participants of the DCCT were offered intensive insulin treatment and up to 93% of them were followed epidemiologically under their personal doctor's supervision for more than ten years in the Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The primary end point was a composite of non-fatal AMI, non-fatal stroke, death from cardiovascular causes, confirmed angina and need for coronary arteries revascularization[10]. After mean follow-up of 17 years, patients initially randomized in the DCCT to receive intensive insulin treatment had 42% lower risk for the composite primary outcome (95% CI: 9%-63%, p=0.02), and 57% lower risk for non-fatal AMI, non-fatal stroke and death from cardiovascular causes (95% CI:12%-79%, p=0.02) compared to those initially randomized to conventional treatment. At the end of the DCCT/EDIC glycemic control did not differ between the initial DCCT groups (HbA1c:7.8% vs 7.9%). Nevertheless, each 10% reduction of HbA1c during the DCCT was related to 20% reduction of CVR.

Furthermore, data from the extended 30 years-long surveillance of DCCT patients underscore the importance of tight glycemic control, even for a short period of time, and of "metabolic memory" in effectively reducing CVR[11]. Three decades after the DCCT, T1 patients initially randomized in intensive insulin treatment had a significantly 30% lower risk for any cardiovascular disease (95% CI: 7%-48%, p=0.016) and numerically 32% lower risk for the composite of non-fatal AMI, non- fatal stroke and death from cardiovascular causes (95% CI: -3%-56%, p=0.07) compared to the conventional treatment group.

Recently, Bebu et al analyzing data from DCCT/EDIC study identified risk factors related to the first and to subsequent cardiovascular events in T1 patients[12]. Glycemia is reported to be the most important modifiable risk factor for both the first cardiovascular event (defined as death from cardiovascular causes, congestive heart failure, non-fatal AMI, angina, need for coronary arteries revascularization) [CVD:HR 1.38(95% CI 1.21,1.56) for each 1% increase of HbA1c; MACE: HR 1.54 (95% CI 1.30,1,82)] and subsequent events [CVD: incidence ratio[IR]: 1.28(95% CI 1.09,1.51); MACE:IR 1.89 (95% CI 1.36,2.61)]. Therefore, tight glycemic control by means of intensive insulin treatment seems to be highly effective both for the primary and secondary prevention of CVD in T1 patients.

Adjunctive Treatments in Type 1 Diabetes

Several antidiabetic drugs used in the treatment of T2 diabetes have been tested in randomized trials as add on therapy to insulin in T1patients, including agents with

proven cardioprotective effect in T2 patients, such as GLP-1RA and SGLT-2inh[13]. However, most of these trials were of short duration and explored the efficacy and safety of these factors in T1 patients. None had cardiovascular events as outcomes and some of them reported the effect of these treatments on well established risk factors for CVD such as atherosclerosis, blood pressure and weight.

In the double-blind REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL) trial 428 patients with T1 diabets for more than 5 years, older than 40 years and with at least 3 risk factors for CVD were randomized to receive metformin 2000mg daily or placebo[14]. The primary endpoint was the progression of common carotid artery Intima-Media Thickness (cIMT). After three years, treatment with metformin had no effect on the progression of atherosclerosis as measured with the cIMT. In the phase III, randomized, double-blind, placebo-controlled trial Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) 833 T1 patients were randomized to receive dapagliflozin, an SGLT-2inh, 5mg or 10mg daily or placebo[15]. After 52 weeks of intervention patients randomized to dapagliflozin had a 2.95% and 4.54% decrease in weight with 5mg and 10mg respectively compared to those randomized to placebo. Among patients with history of hypertension Systolic Blood Pressure (SBP) was significantly reduced by 5.38mmHg with dapagliflozin 10mg. In another phase III, double-blind, placebo-controlled trial, European inTandem2 Study, 782 T1 patients were randomized to receive a dual SGLT-2, SGLT-1inh, sotagliflozin, at daily doses of 200mg and 400mg or placebo. After 52 weeks patients randomized to sotagliflozin had a significant weight loss of 2.18Kg and 2.92Kg with 200mg and 400mg respectively compared to those on placebo. SBP was significanlty reduced by 4.1mmHg with 400mg sotagliflozin in patients with history of hypertension. Although, dapagliflozin and sotagliflozin have been approved by some regulatory authorities as add-on treatment for overweight T1 patients with sub-optimal glycemic control on insulin alone, the increased risk of diabetic ketoacidosis limits their use in everyday clinical practice. In a recent systematic review and network meta-analysis of randomized trials comparing adjunctive treatments in T1 patients Avgerinos et al report 4.35Kg and 3.85Kg weight decrease with GLP-1RA exenatide and liraglutide, respectively compared to placebo and 3.6Kg, 3.48Kg and 3.14Kg weight loss with the SGLT-2inh canagliflozin, dapagliflozin and empagliflozin, respectively compared to placebo, results comparable to those observed with the same agents in T2 patients. Significant reduction of SBP by 3.61mmHg, 3.39mmHg and 3.27mmHg is also reported with empagliflozin, liraglutide and dapagliflozin, respectively compared to placebo[13]. On the contrary, the reduction in HbA1c observed with empagliflozin, dapagliflozin liraglutide and exenatide is of lesser extent than in T2 patients.

Addressing cardiovascular risk factors in T1 patients-Guidelines

There is lack of evidence from high quality randomized clinical trials for the treatment of hypertension and dyslipidemia in T1 patients. Therapeutic targets and pharmaceutic treatments with proven cardiovascular benefit are based mainly on data extrapolation from large randomized interventional trials and meta-analyses in T2 patients[17]. Recently, ad hoc designed, web available calculators for the 10-years CVR in patients with T1 have been developed [18-20]. The use of such tools allows for an individual based approach for treatment targets.

For T1 patients without other CVR factors and 10-year CVR<15% a Blood Pressure(BP) target<140/90mmHg seems to be reasonable, while for those with 10-year CVR>15% or established CVD a BP target<130/80mmHg may offer additional benefit in preventing CVD. Angiotensin Converting Enzyme inhibitors (ACE-inh) or Angiotensin II receptor blockers are first-line treatments for hypertension in patients with T1, especially for those with albuminuria. Nevertheless, since these agents are contraindicated in pregnancy, their use in women with diabetes in reproductive age should be cautious.

In an observational study in T1 patients without CVD, lipid lowering with the use of statins was related to significant decrease in the incidence of CVD and death[21]. A moderate intensity statin is proposed for all patients with T1 above the age of 40 as well as for those in the age 20-39 with additional risk factors for Atherosclerotic Cardiovascular Disease (ASCVD) or 10-year CVR>10%. In patients with established CVD a high intensity statin is indicated for secondary prevention. Recently, in a joint committee, the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) classified patients with diabetes into three categories according to the CVR proposing different therapeutic targets for LDL cholesterol for each one of these classes[22]. Very high risk patients are those with established CVD or target-organ damage(defined as albuminuria, eGFR<30ml/min/1.73m^2, Left Ventricle Hypertrophy or retinopathy)or three or more risk factors(age, hypertension, dyslipidemia, smoking, obesity) or early initiated T1 diabetes with >20years disease duration. In these patients LDL<55mg/dl and at least 50% reduction of the baseline LDL should be the appropriate therapeutic targets. High risk patients are those with diabetes duration>10 years and at least one more additional CVR factor without target-organ dam-

age. LDL<70mg/dl and at least 50% reduction of initial LDL should be the lipid targets for this category. Finally, T1 patients below the age of 35 and T2 <50 years old with diabetes duration<10years and without other CVR factors are classified as moderate risk and should target LDL<100mg/dl. A moderate or high intensity statin is the first-line treatment for achieving LDL targets both in T1 and T2 patients based mainly on data from large clinical trials in T2 patients reporting substantial benefit in preventing CVD with the use of these agents. Data from additional treatment with ezetimibe or Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors to meet therapeutic targets are extremely limited in T1 patients. Statins should be used cautiously in women with diabetes in reproductive age since their use is contraindicated in pregnancy.

Antiplatelet agents such as aspirin and clopidogrel should be used for secondary prevention in patients with T1 diabetes and history of CVD. The use of these factors for primary prevention remains controversial and there is lack of evidence to support their use in T1 patients without CVD. Increased physical activity should be encouraged in T1 patients although there is lack of evidence to support beneficial effect on CVR. Smoking cessation should be also strongly recommended[23].

Conclusions-Future perspectives

T1 patients run increased risk for CVD. Based on the results of the DCCT/EDIC study optimal glycemic control with intensive insulin treatment is beneficial in reducing the risk for long term cardiovascular adverse events both in patients with and without history of CVD. Newer antidiabetic agents with proven cardiovascular benefit in T2 patients, such as dapagliflozin, sotagliflozin, empagliflozin, canagliflozin and liraglutide, have been tested in randomized clinical trials as add on treatment to insulin in T1 patients. However, there is lack of evidence for cardiovascular outcomes from the use of such medications in T1 patients, although some of them seem to have beneficial effects on CVR factors such as body weight and BP. More randomized clinical trials with prespecified cardiovascular outcomes are needed to explore potential benefits from the use of these agents in T1 patients.

The assessment of glycemic control in DCCT and other interventional studies in T1 patients was based almost exclusively on HbA1c. The relationship of HbA1c with both microvascular and macrovascular complications of diabetes is well established and its use as therapeutic target remains the cornerstone in diabetes treatment. Recently, the wide use of continuous glucose monitoring systems and the increasing demand for systematic evaluation of the obtained data both for clinical and investigational purposes has led to the development of new metrics, such as the time in which glucose value ranges within 70-180mg/dl [Time In Range (TIR)], and new therapeutic targets based on these metrics. Analyzing data from 7-point self-monitoring of blood glucose from participants in DCCT, investigators reported a strong negative relationship between TIR and incidence of both retinopathy and microalbuminuria. They estimated a mean 10-12% difference in TIR between patients with and without microvascular complications, reflecting a mean 1.0-1.4% difference in HbA1c and 2.5 more hours spent daily in the euglycemic range[24]. Since cardiovascular events were very limited in DCCT there is no evidence about the relationship of TIR with macrovascular complications. More interventional trials with TIR as primary outcome for glycemic control assessment are expected to elucidate in the future the impact of 24h glycemia and glucose variation on CVR and to explore different treatment interventions targeting to effectively reduce this risk.

Finally, the wide heterogeneity within patients initially classified as type 1 or type 2 diabetics in terms of phenotype, genetic characteristics, insulin resistance and individualized risk for micro and macrovascular complication underscores the need for a new classification of diabetes[25]. As a step towards precision medicine such a novel classification will focus primarily on individualized assessment of cardiovascular risk and tailored interventions to effectively reduce it.

Conflict of interest

None to declare.

ΠΕΡΙΛΗΨΗ

Σακχαρώδης Διαβήτης τύπου 1 και καρδιακός κίνδυνος: Βραχεία ανασκόπηση

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Η επίπτωση της καρδιαγγειακής νόσου είναι σημαντικά αυξημένη σε ασθενείς με Σακχαρώδη Διαβήτη τύπου 1 (ΣΔ1) σε σχέση με τον γενικό πληθυσμό. Δεδομένα από την τυχαιοποιημένη κλινική δοκιμή DCCT, και τη μακροχρόνια επιδημιολογική παρακολούθηση των συμμετεχόντων σε αυτή προσφέρουν ισχυρές ενδείξεις ότι ο αυστηρός γλυκαιμικός έλεγχος με την εντατικοποιημένη ινσουλινοθεραπεία είναι αποτελεσματικός τόσο στην πρωτογενή όσο και στη δευτερογενή πρόληψη του καρδιαγγειακού κινδύνου. Νεότεροι αντιδιαβητικοί παράγοντες με αποδεδειγμένα καρδιονεφρικά οφέλη σε ασθενείς με Σακχαρώδη Διαβήτη τύπου 2 , όπως οι GLP-1RA και οι SGLT-2inh, έχουν δοκιμαστεί ως θεραπεία προσθήκης στην ινσουλίνη σε λίγες κλινικές δοκιμές σε ασθενείς με ΣΔ1. Παρά την ευνοϊκή επίδραση τους σε παράγοντες καρδιαγγειακού κινδύνου, όπως το σωματικό βάρος και η αρτηριακή πίεση, η έλλειψη δεδομένων για άμεσες καρδιαγγειακές εκβάσεις και ο αυξημένος κίνδυνος για σοβαρές ανεπιθύμητες ενέργειες, όπως η διαβητική κετοξέωση, περιορίζουν τη χρήση τους σε ασθενείς με ΣΔ1.Νεότεροι γλυκαιμικοί δείκτες, τροποποιήσεις στην ταξινόμηση του διαβήτη και η ιατρική της ακρίβειας αναμένεται να συνεισφέρουν μελλοντικά στην εξατομικευμένη εκτίμηση και πρόληψη του καρδιαγγειακού κινδύνου στους ασθενείς με Σακχαρώδη Διαβήτη. .

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Διαβήτης τύπου 1, καρδιαγγειακός κίνδυνος, GLP-1RA, SGLT-2 αναστολείς, θεραπεία προσθήκης στην ινσουλίνη*

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