REVIEW ARTICLE

Glycemia and cardiovascular risk: challenging evidence based medicine

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Abstract

Optimal glycemic control is well known to reduce effectively the risk of micro vascular complications both in type 1 and type 2 diabetes mellitus. However the role of glycemic control in decreasing the risk of myocardial infarction and ischemic stroke, the leading causes of death in patients with diabetes, has been so far controversial. In this review, based on data recently reported from large interventional studies, we discuss the possible causal relationship between glycemia and cardiovascular outcomes in type 1 and type 2 diabetes. Strict glycemic control right from the diagnosis of the disease may be effective in reducing long term incidence of cardiovascular (CV) disease in both T1 and T2 diabetics. Nevertheless such a strategy could be potentially harmful for T2 diabetics with long duration of sub optimal glycemic control and already established CV complications. Treatment targets in these patients should be individualized taking into account other aspects of glycemic control and diabetes complications such as hypoglycemia and autonomic neuropathy. Hippokratia 2011; 15 (3): 199-204

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Diabetes is at epidemic proportion worldwide. Patients with diabetes are at increased risk for micro- and macro vascular complications. The benefit of glycemic control in decreasing the risk for micro vascular disease is well established in both type 1 (T1) and type 2 (T2) diabetes[1,2]. However, the role of glycemic control in decreasing macro vascular complications has been so far controversial. Since myocardial infarction and stroke are the leading causes of death in patients with diabetes, strategies to reduce mortality through better glycemic control have to be tested in clinically relevant hard end points.

In this review article we discuss the relationship between glycemia and cardiovascular disease emphasizing data obtained by recent large clinical trials. We also discuss the possible impact of these studies on clinical practice.

Glycemia and cardiovascular risk in non diabetics

Epidemiologic evidence has shown that any elevation in glycemia, even within sub diabetic range, increases the risk of cardiovascular (CV) disease[3]. Glycosylated hemoglobin (HbA1c) is associated with carotid intima- media thickness, a well established index of atherosclerosis, in individuals with Normal Glucose Tolerance (NGT)[4]. In an epidemiological analysis of the HOPE study data[5] in individuals with and without diabetes, fasting plasma glucose was shown to be an independent risk factor for CV events even after adjusting for the presence of diabetes[6]. These findings support the hypothesis that it is the degree of hyperglycemia, rather than the presence or absence of diabetes that is related to future CV outcomes[7].

Individuals with Impaired Glucose Tolerance (IGT) are known to be at increased risk for T2 diabetes and CV disease[8]. Glucose levels after a glucose challenge are more closely associated with CV risk than fasting glucose levels[8, 9]. Therefore subjects with IGT have been a target group in numerous interventional studies for prevention of T2 diabetes. The risk of T2 diabetes is shown to be effectively reduced with lifestyle interventions that increase physical activity and reduce weight[10-12]. Medical treatment with metformin[12], rosiglitazone[13], and acarbose[14] could also be an effective albeit more expensive intervention. None of the above studies was empowered to consider cardiovascular outcomes following the reduction of the incidence of T2 diabetes. Nevertheless in a post hoc analysis of the STOP-NIDDM Trial data acarbose was reported to decrease the risk of myocardial infarction among subjects with IGT[15].

Recently, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), a double- blind, randomized, placebo controlled trial[16], investigated whether intervention with the short- acting insulin secretagogue nateglinide in individuals with IGT could substantially reduce the risk of diabetes and CV disease. A total of 9,306 subjects with IGT and either CV disease or CV risk factors were randomly assigned to receive nateglinide up to 60mg three times daily or placebo in addition to participation in a lifestyle modification program. After a median follow-up of 5.0 years nateglinide, compared with placebo, did not significantly reduce the cumulative incidence of diabetes, the core composite CV

outcome (a composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure), or the extended composite CV outcome (a composite of the core CV outcome and hospitalization for unstable angina or arterial revascularization). In addition nateglinide significantly increased the risk of hypoglycemia. The negative outcome of the NAVIGATOR Trial highlights the need for more interventional studies to determine whether there is a causal relationship between elevated postprandial glycemia and CV disease[8].

Glycemia and cardiovascular risk in T1 Diabetes

T1 diabetes is associated with at least a 10-fold increase in CV disease compared with age- matched non diabetic population[17]. An association between hyperglycemia and cardiovascular disease has been suggested by some[18] but not all[19] the observational studies of patients with T1 diabetes. The Diabetes Control and Complication Trial (DCCT)[1] randomized 1,441 patients with T1 diabetes without history of cardiovascular disease, hypertension or hypercholesterolemia to receive intensive or conventional therapy, treating them for a mean of 6.5 years between 1983 and 1993. At the end of the trial the absolute between groups difference in the mean HbA1c was 1.7% (7.4% in the intensive vs 9.1% in the conventional-treatment group). Patients in the intensive treatment arm significantly reduced the risk of micro vascular and neurologic complications of diabetes. During the DCCT fewer cardiovascular events occurred in the intensive than in the conventional treatment arm. Nevertheless the total number of events in this relatively young cohort was too small to determine whether the use of intensive treatment affected the risk of cardiovascular disease[20]. Therefore 93% of the patients assigned in DCCT were subsequently followed for approximately 11 years during the observational Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC)[21]. CV disease was defined as nonfatal myocardial infarction (MI), stroke, death from cardiovascular disease, confirmed angina or the need for coronary-artery revascularization. During the mean 17 years of follow-up intensive treatment reduced the risk of any cardiovascular event by 42% (p=0.02) and the risk of non fatal MI, stroke or death from cardiovascular disease by 57% (p=0.02). Microalbuminuria and albuminuria were associated with a significant increase in the risk of cardiovascular disease but the between treatment group differences remained significant ($p<0.05$) after adjusting for these factors. Notably, by the end of the EDIC the between treatment groups HbA1c did not significantly differ (7.9±1.3% in the intensive treatment vs 7.8 ±1.3 in the conventional treatment). The DCCT/EDIC demonstrated that 6.5 years of intensive diabetes therapy had a long- term favorable effect on reducing cardiovascular risk in T1 diabetics. These findings coordinate with previous observations that intensive compared to conventional therapy reduces the progression of atherosclerosis, measured by carotid intima-media thickness and the prevalence of coronary artery calcification[22].

Recently, in a systematic review and meta-analysis of randomized controlled trials comparing interventions to improve glycemic control with conventional treatment in T1 and T2 diabetes, Stettler et al reported that intensive glycemic control significantly reduced cardiac and peripheral vascular events in patients with T1 diabetes[23]. Interestingly, improved glycemic control was particularly beneficial in younger patients with shorter diabetes duration.

Glycemia and cardiovascular risk in T2 Diabetes

CV disease is the major cause of death in patients with type 2 diabetes since more than 60% of them die of myocardial infarction or stroke and an even grater percentage have serious, burdensome complications[24].

The question whether glucose control independently reduces CV complications seems to be still unanswered. The United Kingdom Prospective Diabetes Study (UKPDS)[2] randomized 4209 newly diagnosed T2 diabetes patients to receive either conventional therapy (diet alone) or intensive therapy (either sulfonylurea or insulin or metformin in overweight patients) for glucose control. After a median follow-up of 10.0 years, UKPDS showed a reduced risk of micro vascular complications in the intensive treatment arm but a non significant trend towards improvement (p=0.052) in the rate of myocardial infarction. Interestingly, in overweight patients who primarily received metformin, substantial reductions in the risk of myocardial infarction of 39% (p=0.01) and death from any cause of 36% (p=0.01) were observed. The results of the UKPDS, although not very compelling in reduction of CV risk, have been highly influential in subsequent diabetes management[25]. In a meta-analysis of three randomized controlled trials[2,26,27] comparing intensive interventions with conventional treatment in T2 diabetes, Stettler et al[23] reported beneficial effects of intensive treatment in peripheral vascular disease and stroke but not in cardiac events. Recently the UKPDS investigators reported the results of the 10 year post trial follow-up of the UKPDS patients[28]. One year after the end of the trial, no significant difference in HbA1c was present between the two treatment arms. Nevertheless in the original intensive therapy group there was a reduction in the risk of any diabetes related outcome (9%, p=0.04), of myocardial infarction (15%, p=0.01) and of death from any cause (13%, p=0.007), findings consistent with those of the EDIC Study in T1 diabetics [21]. The delayed beneficial outcome of early initiated intensive treatment both in T1 and T2 diabetes may reflect a legacy effect of optimal glycemic control even for a short period.

The beneficial effect of intensive treatment on CV risk reduction observed in UKPDS post-trial is not confirmed by the results of three other large randomized trials that were recently reported. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Trial[29] 11,140 T2 diabetics were randomly assigned to receive either standard or intensive glucose control defined as the use of gliclazide plus any other drug required to achieve

an HbA1c of 6.5% or less. After a median follow-up of 5.0 years the mean HbA1c was lower in the intensive control group (6.5% vs 7.3%) reducing the incidence of combined major macro vascular and micro vascular events (p=0.01) primarily because of a reduction in the incidence of nephropathy (p=0.006). There were no significant effects of the intensive glucose control on major macro vascular events (p=0.32), death from cardiovascular causes (p=0.12), or death from any cause (p=0.28). Similarly in the Veteran Affairs Diabetes Trial[30] 1,791 type 2 diabetics sub- optimally controlled, 40% with established cardiovascular disease, were randomized to receive either intensive, targeting in an absolute reduction of 1.5 percentage points in the HbA1c, or standard glucose control. After a median follow-up of 5.6 years HbA1c was lower in the intensive-therapy group (6.9% vs 8.4%). Nevertheless there was no significant difference between the two groups in the incidence of major cardiovascular events (p=0.14), or in the rate of death from any cause (p=0.62). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was another Trial designed to determine whether intensive glucose control would reduce the rate of CV events[31]. In this Trial 10,251 type 2 diabetics with median baseline HbA1c 8.1% were randomly assigned to receive either intensive therapy targeting an HbA1c level within normal range, below 6%, or standard therapy targeting HbA1c 7.0-7.9%. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher all- cause and cardiovascular cause mortality in the intensive-therapy group (p=0.04 and 0.02 respectively) led to discontinuation of the intensive therapy after a mean follow-up of 3.5 years. Notably hypoglycemia requiring assistance and weight gain of more than 10Kg were more frequent in the intensive-therapy group (p<0.001), while the rate of non-fatal myocardial infarction was significantly lower in the intensive therapy arm (p=0.004). The results of the ACCORD Trial raised concern about not only the effectiveness but also the safety of intensive glycemic control in T2 diabetics. Prespecified subgroup analysis of the participants of the Trial suggested that patients in the intensive group without history of CV event before randomization (p for interaction=0.04) or whose baseline HbA1c level was 8% or less (p for interaction=0.03) may have had fewer fatal or non fatal CV events than did patients in the standard therapy group. Preliminary non-prespecified exploratory analysis of episodes of severe hypoglycemia and differences in the use of drugs, including rosiglitazone, weight change and other factors did not identify an explanation for the excess mortality in the intensive treatment group.

The results of the ACCORD, ADVANCE and VAD Trials should be interpreted in the context of comprehensive care of patients with diabetes. Interventions for simultaneous optimal control of co morbidities often present in T2 diabetics, such as hypertension and hyperlipidemia, have been shown to be a more effective strategy in reducing CV risk than targeting only glycemia per se[32]. Moreover the ACCORD trial reported a potentially harmful effect of lowering glucose within the normal range, especially in patients with history of CV disease. These findings raise the need for an exploratory insight in certain aspects of complications of glycemia and its treatment which may affect CV risk, such as hypoglycemia and cardiac autonomic neuropathy.

Hypoglycemia and cardiovascular events

Hypoglycemia may affect cardiovascular events by several mechanisms[33]. Primarily, hypoglycemia stimulates the release of catecholamines, which increase myocardial contractility, workload and cardiac output inducing myocardial ischemia in patients with coronary heart disease (CHD). Hypoglycemia is also associated with a significant lengthening of the corrected QT interval (QTc) in subjects with and without diabetes predisposing to a high risk of ventricular tachycardia and sudden death. Increased catecholamines secretion and hyperinsulinemia may lead to hypokalemia during hypoglycemic events potentiating cardiac repolarization abnormalities. Several inflammatory markers including C-reactive protein, interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-a, and endothelin-1 have been shown to be increased during hypoglycemia potentiating endothelial injury and abnormalities in coagulation and platelet function, resulting in increased risk for CV events. Recent studies suggest that vessel wall stiffness is increased during hypoglycemia in patients with T1 diabetes of longer duration than those with shorter duration of diabetes[34]. Thus hypoglycemia may increase the risk of CV events, especially in patients with longer duration of diabetes.

Although the association between hypoglycemia and CV events seems to be well established on the basis of pathophysiology, epidemiological evidence and even more evidence from interventional studies are largely controversial. In a retrospective review of 14,670 patients with CHD, recruited for the Bezafibrate Infarction Prevention Study (a secondary prevention prospective multicenter randomized placebo controlled double blind trial) hypoglycemia defined as blood glucose <70mg/dl was a predictor of increased all-cause mortality (HR: 1.84) but not of increased CHD mortality[35]. In the Veterans Affairs Cooperative Study on Glycemic Control and Complications in T2 Diabetes more cardiac events were documented after institution of intensive glycemic control versus standard control (32 vs 20%) but this was not significantly different[26]. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, although severe hypoglycemia was more frequent in the insulin-provision group (9.2%) than in the insulin-sensitization group (5.9%) major CV events were not significantly different[36]. In the ACCORD trial in both the intensive and standard treatment arms patients with severe hypoglycemia had a higher mortality rate than those without severe hypoglycemia[31]. Notably the relative risk of death associated with severe hypoglycemia was higher for the standard arm than for the intensive arm (2.87 vs 1.28) de-

spite the larger number of severe hypoglycemic episodes in the intensive arm. This suggests that severe hypoglycemia per se in a certain subgroup of patients may be associated with mortality rather than the strategy of treatment used (standard vs intensive). Based on a post hoc analysis, patients most prone to the detrimental effects of hypoglycemia had several of the following characteristics: they were likely to be women, Afro-American, older patients with a longer duration of diabetes, higher HbA1c and high albumin-to-creatinine ratio. In the VAD Trial there was an increased incidence of severe hypoglycemia in the intensive treatment group but there was no significant difference in cardiovascular events between the two treatment arms[30]. In the ADVANCE study although there was an increased risk of hypoglycemia in the intensive treatment arm, there was no association between hypoglycemia and CV mortality[29]. In this study the number of patients who had severe hypoglycemia in the intensive treatment arm was extremely low (<3% vs 16% in the ACCORD and 21% in the VADT) partly reflecting the smaller proportion of patients on insulin in the intensive treatment arm (41%) than in the ACCORD (77%) or in the VADT (90%). The DCCT study enrolled T1 patients on insulin. Despite the three fold increased risk for severe hypoglycemia in the intensive treatment arm of the DCCT, CV mortality significantly decreased after long term follow up[1,21] . These findings highlight the different CV risk of hypoglycemia in T2 versus T1 Diabetes.

The question whether hypoglycemia increases the risk for stroke or dementia remains controversial although severe hypoglycemia has been well known to induce focal deficits and transient ischemic attacks reversible with the correction of blood glucose. In a longitudinal cohort study by Whitmer et al patients with multiple episodes of hypoglycemia had an increased risk for dementia[37]. Conversely in the ADVANCE trial severe cognitive dysfunction increased the risk of severe hypoglycemia[38]. The Fremantle diabetes study found that dementia was a risk factor for hypoglycemia while hypoglycemia itself was not found to increase the risk for dementia[39]. In the DCCT despite frequent hypoglycemia, intensively treated T1 diabetics did not experience cognitive decline[1,21].

Cardiac autonomic neuropathy and cardiovascular risk

Cardiac Autonomic Neuropathy (CAN) represents a significant cause of morbidity and mortality in diabetic patients. It is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia. Therefore, it has important clinical and prognostic relevance[40].

In a large cohort of T1 and T2 diabetics, Ziegler et al using predefined heart rate variability (HRV) tests and spectral analysis of the R-R intervals, found that 25.3% of T1 and 34.3% of T2 diabetics had abnormal findings[41].

Experimental data implicate a number of pathogenetic pathways that may impact autonomic neuronal function in diabetes such as formation of advanced glycation end products, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation and activation of genes involved in neuronal damage[42].

In the EURODIAB Prospective Cohort Study of 2,787 T1 diabetics, CAN was the strongest predictor for mortality during a 7-year follow-up, exceeding the effect of traditional cardiovascular risk factors[43]. A meta-analysis of 15 studies including 2,900 diabetics reported a pooled relative risk of mortality of 3.45 (95% CI 2.66-4.47) in patients with CAN[44]. The increased mortality risk associated with CAN has important clinical implications. Hypoglycemia, a major barrier in achieving optimal glycemic control, impairs hormonal and autonomic responses to subsequent hypoglycemic events. Hypoglycemia unawareness may promote a reduced threshold for malignant arrhythmias and sudden cardiac death[45].

In a meta-analysis of 12 studies Vinik et al[42] reported a consistent association between CAN and the presence of silent myocardial ischemia. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study of 1,123 T2 diabetics, CAN was a strong predictor of silent ischemia and subsequent CV events[46]. The presence of CAN was also linked to the development of diabetic cardiomyopathy in T1 diabetes since LV dysfunction often precedes or occurs in the absence of significant CHD or hypertension in these patients[47].

Recently the investigators of the ACCORD trial carried out exploratory post hoc analysis to identify subgroups at higher or lower risk from the intensive intervention according to various baseline characteristics[48]. Among the baseline medical history subgroups, participants with self-reported history of neuropathy/nerve problems had a greater risk of mortality in the intensive glycemia arm compared with the standard glycemia arm (p value for interaction=0.0008). Moreover the above interaction remained highly significant (p=0.006) after adjusting for age, sex, waist circumference, smoking, diabetes duration, hypoglycemic agents used, history of retinopathy, history of amputation and systolic blood pressure. However the presence of peripheral neuropathy at baseline as documented by pedal amputation or a score>2 on the clinical examination portion of the Michigan Neuropathy Screening Instrument (MNSI) was not associated with increased mortality in the intensive arm.

In terms of stroke and CAN, a recent study in 1,458 patients with type 2 diabetes reported that the presence of CAN, assessed by standard HRV testing, was one of the strongest predictors of ischemic stroke together with age and hypertension[49].

Conclusions

Despite an abundance of data recently reported from large randomized trials the relationship between glycemia and CV risk remains largely controversial. Although glycemia even in the sub diabetic or the pre diabetic range correlates with certain cardiovascular risk markers,

the question whether preventing type 2 diabetes by lifestyle or pharmaceutical interventions would also reduce effectively CV risk is still unanswered.

It seems that in T1 diabetes targeting optimal glycemic control as early as possible in the course of the disease and before other co morbidities are present is an effective strategy to reduce long term macro vascular complications.

Strict glycemic control right from the diagnosis of the disease may also be effective for patients with T2 diabetes in reducing long term incidence of CV disease. In T2 diabetics with long duration of sub optimal glycemic control and already established CV complications aggressive reduction of glycemia in the range close to normal is not shown to be protective from future CV events. Moreover such a strategy could be potentially harmful. Therefore treatment targets should be individualized. Furthermore clinical evaluation of certain aspects of glycemia and its treatment that could have a potential impact on CV outcomes, such as hypoglycemia and CAN is warranted. In patients with long standing T2 diabetes simultaneous optimal control of all co morbidities seems to be a more prudent approach to reduce CV risk than targeting glycemia per se.

As it may take long time before the beneficial effect of optimal glycemic control on reducing CV risk become obvious, future prospective interventional trials should have a longer duration in order to be more informative and definitive in their final conclusions. They should also be focused on diabetics with short duration of disease, since these patients may have less co morbidities and their diabetes may be the main predictor of future CV complications. As CV disease is the hardest end point in diabetes, future antidiabetic therapies for type 2 diabetes should be evaluated not only for their efficacy in reducing glycemia but also for their impact on CV risk.

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