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Review Article

Relationship Between Glycemic Control and Cardiovascular Outcomes

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Abstract

Diabetes is a well-known cardiovascular risk factor in both T1DM and T2DM. They have a 4-10 higher risk of developing complications from CVD than the non-diabetic population. The importance of intensive glycaemic control to prevent CVD in T1DM was established in both "The Diabetes Control and Complication Trial" (DCCT) and "Epidemiology of Diabetes Intervention and Complications" (EDIC) trials. Despite the epidemiological evidence that poor glycaemic control can lead to higher incidence of cardiovascular events in T2DM, the intervention trials are still inconclusive.

In this report we will highlight the pathophysiology of the effect of hyperglycemia on the cardiovascular system, the effect of medications, and the major Randomized Control Trials (RCTs) looking specifically at the cardiovascular outcome of intensive glycaemic control in T2DM.

Key words: Diabetes; Cardiovascular outcomes; Glycaemic control.

INTRODUCTION

T2DM is known to have influence in cardiovascular disease. T2DM is considered to be an equivalent to Coronary Artery Disease (CAD) with greater development rate of ischemic incidences in diabetic compared non-diabetic individuals. It is frequently connected with accelerated atherosclerosis, in clinical settings presenting premature CAD[1]. While epidemiological evidence supports the negative role of bad glycemic control on CV outcomes, medical studies are in conclusive. Many trials demonstrated no advantageous results of intensive blood sugar control on primary CV endpoints, on the contrary, sub group analysis suggests that the advantageous effect depends on age, diabetes duration, prior glycemic control, existing cardiovascular disease, and hypoglycemia risk. Strict glycemic control on CV outcomes and fatality may be impeded by the hypoglycemia and could be promoted by using hypoglycemic medications exerting desirable cardiovascular system effects[2]. It is estimated that 60-80% of diabetic individuals will die from CVD, hence taking risk factors which triggers BP development is crucial[3]. Diabetes is almost always associated with hypertension and dyslipidemia and these increase the risk of CV further.

SEARCH STRATEGY

Available studies and abstracts were identified through PubMed and Medline data bases (From 1979-2019) and Cochrane data bases. Key search terms were glycaemic control and cardiovascular disease. All available studies and abstracts describing the relationship between glycaemic control and cardiovascular outcomes were included. The reference list of review articles was also searched.

DISCUSSION

Epidemiology

The main cause of morbidity and mortality in diabetes is CVD. CVD causes 70% of all deaths and death due to CVD are two to four times higher among them[4]. The risk of CVD is doubled in diabetic men and tripled in diabetic women[5].

About 70% of diabetic patients have hypertension and/or are on antihypertensive treatment and 65% have dyslipidaemia[4,6]. Diabetic patients have about 5-fold increased risk for a first Myocardial Infarction (MI) a 2-fold higher risk for another attack and with second MI have the worst prognosis[7].

CVD death rates and hospitalization rates for MI are 1.7 and 1.8 times higher respectively than the general population[6]. In several epidemiological studies diabetes counted for a big proportion of patients with heart failure and the prevalence was up to 30% in elderly patients with diabetes[8]. It was demonstrated that an increase of 1% in HbA1c is associated with 8% increment in heart failure[9,10].

Natural History

From the results of epidemiological and interventional trials the effect of post prandial hyperglycaemia on the risk of having CVD is greater than the effect of fasting hyperglycaemia. Postprandial hyperglycaemia, in Impaired Glucose Tolerance (IGT) and diabetic patients, is a more significant marker of cardiovascular disease than fasting hyperglycaemia[11].

ADA, IDF and AACE recommend elevated PPG values are associated with high risk of CVD independent of FPG[12].

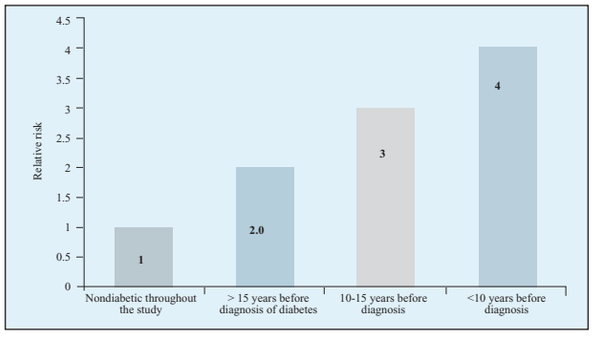

Figure 1 : Risk of heart attack or stroke prior to diabetes diagnosis adjusted for BMI, smoking and parental history of premature CAD.

Cardiovascular Risk Profile in Type I & Type 2 Diabetes

In general, the Framingham study showed diabetes to be a cardiovascular risk factor.

In T1DM[13]

- EDIC Trial showed long-term risk benefit with glucose control
- Pittsburgh EDC prospective study showed albuminuria as a main risk factor
- Age and duration of diabetes
- BMI and mortality show a U-shaped relationship
- Low BMI, smoking, nephropathy and autonomic neuropathy are associated with increased mortality
- Hypertension and hypercholesterolemia should also be treated
- Aggressive primary prevention is vital after the age of 40 yrs
- Markers of insulin resistance predicts cardiac event better than HbA1C.

In T2DM[14,15]

- Unlike T1DM, in T2DM the ACCORD, ADVANCE and VADT trials do not show cardiovascular risk reduction with intensive glucose control. But UKPDS did show good cardiovascular outcome
- Pittsburgh EDC and EURODIAB studies proved HbA1C is not a predictor of CHD but better for peripheral vascular disease
- Management of hypertension and dyslipidaemia should be more focused in Type 2 than in Type 1 Diabetes.

Legacy Effect and Glycaemic Memory

Metabolic Memory means that the target organs (Heart, eyes, extremities and kidney) remember the early glycemic milieu which predicts the long-term effects.

Good metabolic control achieved during first five years of DM being diagnosed & not at a later stage, has proven beneficial with regards to micro- & macrovascular events.

Also implying that poorly controlled diabetes would lead to irreversible mitochondrial or vascular alteration predisposing or progressing to overt complications in the long-run.

This concept emerged with results of DCCT trial which showed that intensively managed diabetics had reduced progression of microvascular complications. At the end of six and half years, all patients were put on intensive therapy, however, the arm on intensive regime from the beginning still fared better as found in EDIC Trial in terms of microvascular & macrovascular complications like CVD and carotid intima thickness.

UKPDS also demonstrated that Type 2 Diabetics, in intensive arm had lesser events of microvascular and cardiovascular events compared to standard arm throughout the study and even in follow up period, re-emphasizing benefits of early metabolic control[2,3].

Pathophysiology

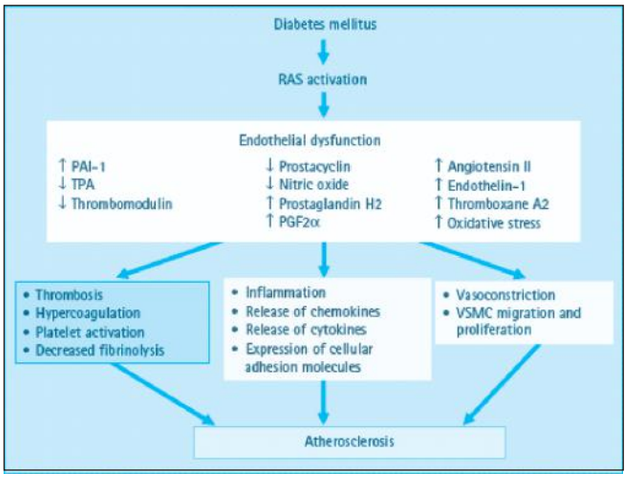

Figure 2 : Pathophysiology of T2DM and CVD.

Hyperglycaemia[16]

- High blood glucose is associated with increased oxidative

stress, enhanced leukocyte-endothelial interaction and glycosylation of protein, including lipoproteins, apo-lipoproteins, and clotting factors

- Following a complex series of dehydration and oxidation reactions, Advanced Glycosylation End Products (AGEs) are formed
- AGEs are associated with severity of cardiovascular disease and complications of diabetes by activation of pathways of cytokine production and transcription factors.

Dyslipidaemia[17]

- High triglycerides, high LDL and low HDL are the hallmarks of dyslipidaemia in diabetes
- Small LDL cholesterol are more susceptible to oxidation, easily penetrate and get more firmly attached to the vascular wall than large LDL, making it more atherogenic
- Oxidized LDL helps in attracting leukocytes into the vessel wall, contributing to the development of atherosclerotic plaques
- Hyperglycaemia causes glycation of LDL, increasing the half-life, and in turn accelerating atherogenesis.

Hypercoagulability[18-20]

- Independent of platelet dysfunction, diabetes induces a hypercoagulable state
- Increased levels of PAI-1 decrease fibrinolytic activity and tissue factor and factors VII and XIII are increased
- There is also a relative decrease in antithrombin III and protein C
- Many of these abnormalities also correlate with the presence of hyperglycaemia and proinsulin split products
- Von Willebrand's factor and factor VIII are also both increased, possibly due to endothelial dysfunction.

Reactive Oxygen Species[18-20]

- ROS promotes atherosclerosis by blocking eNOS synthase, further increasing the production of other ROS, especially superoxide anion in endothelial cells and vascular smooth muscle cells
- PGI-2 inactivation causes the build-up of its precursor, prostaglandin endoperoxide (PGH 2) which induces vasoconstriction and endothelial dysfunction. In addition, PGH-2 promotes the conversion of PGI-2 to thromboxane A2 by TxA 2 synthase
- Peroxynitrite is also responsible for uncoupling eNOS by targeting its zinc tetrathiolate cluster.

Inflammation and Endothelial Dysfunction

- Endothelial lining of the blood vessels plays a crucial role in maintaining free blood flow, tone and acting as thrombo-resistant between the subendothelial layer and the blood
- Associated with the following atherosclerotic risk factors, hypertension, hypercholesterolemia and oxidized LDL
- The role of inflammation in the pathophysiological process of endothelial dysfunction has been documented through histological studies and is crucial to the pathophysiology of atherosclerosis
- The first step in the inflammatory processes is modification of macrophage by oxidized LDL resulting in releasing a range of inflammatory substances, growth factors and cytokines[21].
- Molecules implicated in the process of inflammation included:
  - Intercellular Adhesion Molecule (ICAM)-1
  - Macrophage and granulocyte-macrophage colony stimulating factors
  - Monocyte Chemo tactic Protein (MCP)-1
  - Soluble CD40 ligand
  - Macrophage and granulocyte-macrophage colony stimulating factors
  - Tumor Necrosis Factor alpha (TNF)
  - Interleukin (IL)-1, IL-3, IL-6, IL-8, and IL-18[22].

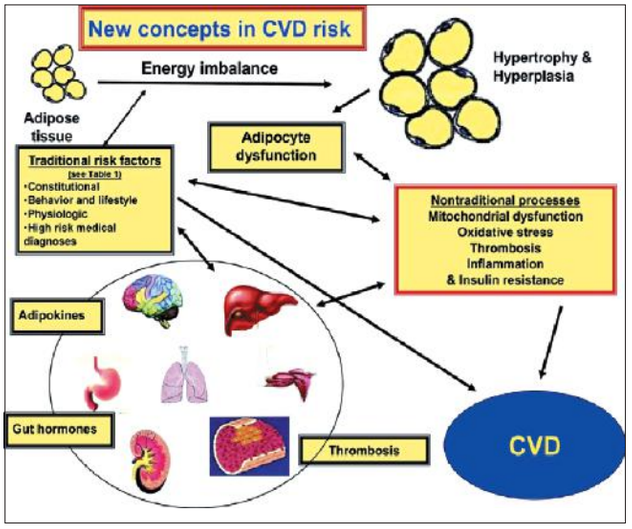

Figure 3 : New Concepts in CVD risk.

Clinical Trials with Cardiovascular Outcome as the Primary Endpoint

The United Kingdom Prospective Diabetes Study

The United Kingdom Prospective Diabetes Study (UKPDS) was a large study and set of sub studies that enrolled almost 5000 newly diagnosed T2DM aged 25-65 between 1977 and 1991, with a median study duration of 10 years. It aimed to demonstrate the effects of glycaemic control on both microvascular and macrovascular diabetic complications and also to study different therapy strategies in sub study sets[23].

The UKPDS demonstrated that an 11% reduction in HBA1C resulted in a 25% risk reduction in microvascular complications but there was no significant improvement in macrovascular complications although there was a statistically insignificant decrease in myocardial infarction (Relative risk reduction

16% p = 0.052) but no improvement in all-cause mortality[24]. However half of the study population had evidence of diabetic related complications at diagnosis[25]. Within 9 years of study entry, a fifth of the study population had suffered a macrovascular event, of which one third proved fatal[26].

However despite the difference in HBA1C being lost between intervention groups after discontinuation of the treatment, at 10 year follow up a "legacy effect" remained where by the intensive arm continued to have reductions in macrovascular events compared to the conventional arm, with relative risk of MI of 15% (p=0.01) and all-cause mortality 13% (p=0.007) and significant reductions also occurring in the Metformin treatment group[27].

DCCT/EDIC Follow Up Trial

The Diabetes Control and Complications Trial (DCCT) and its follow on, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, were two landmark trials that showed significant effects of intensive glucose control (Table I) over conventional control in T1DM, in the prevention of micro and macrovascular complications of diabetes[28,29].

Table I : Elements of intensive management in the DCCT/EDIC.

i) Maintaining a near normal target HbA1C of ≤6.0
ii) Insulin injections - at least three times a day or use of Insulin pump
iii) Self-monitoring of blood glucose ≥4 times daily and adjusting insulin dose accordingly
iv) Adhering to a diet and exercise plan and altering insulin according to food intake and exercise
v) Regular communication with the health care team and at least a monthly visit.

Although the DCCT showed improvement in the CVD outcomes, they were not as significant as the EDIC findings (Table II) likely because, the study population were younger at the time of DCCT.

Table II : Findings of EDIC Study in the Intensive treatment group.

Event	Risk reduction
Any CVD event	42%
Stroke, MI or death from CVD	57%

VADT and ACCORD Trials

The intensification therapy of diabetes in VADT and ACCORD trials didn't show significant improvement in cardiovascular risk due to insufficient sample size (High mortality)[27,28].

Table III : Comparison of the ACCORD and VADT trials[30-31].

	ACCORD trial[30]	VADT[31]
Years of trial	Started in 2001 Determined the effect of intensive glucose lowering on CV outcomes by HBA1c level assessment in Type 2 DM.	Duration 5.6 year
Number of patients	10251	1791
Duration of diabetes	Mean Duration of diabetes 10 years	Average diabetes duration 11.5 years
Age	Average age 62 years	Average age 60 years
HbA_{1C}	Average baseline of HbA1c 8.1%	HbA1c 9.4% (Mean baseline)
Groups	Divided into 2 groups: i) Intensive Glucose Control (IGC) with a target levels of HbA1c <6% ii) Standard Glucose Control (SGC) witha target of 7% - 7.9% HbA1c	Divided into Intensive -control groups. Standard -control groups.
Result	• On February2008, the trial was halted due to increased mortality rate in the IGC. • The episodes of serious hypoglycemia in participants following the IGC > participants in the SGC. • CVD that caused death was related to severe hypoglycemia.	• IGC had higher mortality due to CVD causes than SGC and more sudden deaths. • Hypoglycemia episodes higher in IGC than in SGC.

KUMAMATO and ADVANCE Trials

ADVANCE Trial[32]

This was a randomized prospective study that studied the effect of intensive glucose control on vascular outcome including both macrovascular complications and microvascular complications. The results after a median of 5 year follow up yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.

KUMAMATO Trial[33]

This was a randomized prospective 6-year study that was done in Japan where 110 patients were assigned to intensive insulin treatment versus conventional insulin regimen to study the effect of intensive glucose control on microvascular complications as evidenced by retinopathy or nephropathy. The results showed a lower incidence of the development or progression of retinopathy after six years (7.7 percent versus 32.0 percent) and

there was also a lower incidence of the development or progression of nephropathy after six years (7.7 percent versus 28.0 percent).

Steno 2 Study[34]

Steno 2 study tested the effect of different interventions in reducing the CVD-risks among T2DM patients with micro-albuminuria. 160 subjects with T2DM and Micro-albuminuria at baseline were randomized into conventional treatment or intensive treatment with lifestyle modifications & pharmacological interventions. Intensive group received treatment for hypertension, dyslipidemia, hyperglycemia and antithrombotic treatment. Hyperglycemia in intensive group was managed by stepwise addition of pharmacological therapy. If goal-HbA1C (<6.5%) was not reached despite dietand exercise, oral agents were started. If Hba1c was > 7% they were started on insulin (Night time). The dose and frequency changed as needed up to 4 times a day. Follow up was for 7.8 years. STENO-2 study showed the intensive group (HbA1C <6.5%) had significantly lower CVD risk, nephropathy and retinopathy compared to conventional group. It clearly demonstrated the significance of reducing all risk factors like blood pressure, lipids, cessation of smoking, and active life style, in order to realize the reduction in CVD events.

PROactive[35]

5238 subjects with T2DM with macrovascular disease were randomly selected into either pioglitazone or placebo arms and followed up over a period of 34.5 months They found that with ~0.5% difference in HbA1c decreased risk in all-cause death, stroke and nonfatal MI.

Finnish Study[36]

2301 subjects (174-T1DM, 834-T2DM & 1294-nondiabetics) without CVD in baseline were followed up for 18 years. They reported that 1% increase of HbA1c, increased CV deaths by 52% in T1DM and 7.5% in T2DM patients.

BARI 2D[37]

2368 subjects with T2DM and CHD were randomized to receive either intense glycemic control with revascularization or intense glycemic control only (With either insulin sensitizers like Metformin or TZD or with insulin provision via insulin or SU). Follow up was for 5 years. The study showed that there is no variation in survival between early revascularization vs. intense glycemic control only, between insulin-sensitization treatment and insulin provision.

Anti-diabetic Medications and Cardiovascular Outcomes

An important issue in the management of diabetes is the risk of adverse CVD effects of medication. After the initial approval of rosiglitazone in 1999, a meta-analysis in 2007 showed an alarming 43% increase in MI and 64% in CVD mortality, leading to its restricted use in the US and Europe[38,39].

Following this, in 2008 the FDA and EMA issued guidance for approval of new anti-diabetic drugs, which requires them to rule out increased CVD risk. This has resulted in many trials having simple, placebo controlled, non-inferiority designs over short periods. These short-term trials are unlikely to provide information about long-term benefits on CVD[40].

Table IV : Antidiabetic agents and cardiovascular outcomes.

Drug group	Benefits	Risks	Studies
Metformin	Reduced MI andall-cause mortality[40]		UKPDS[42]
SU's	No significant increase in MACE[41]	Tolbutamide increased mortality[41]	University Group Diabetes Program trial[41] Meta-analysis 2013[41] CAROLINA
Thiazolidinediones (TZDs)		Increased risk HF and fractures[40] Increased risk MACE with Rosiglitazone[40]	RECORD PROactive[35] TIDE
Incretins DPP4i	Non inferiority for CVD safety[40]		CAROLINA SAVOR-TIMI[43] EXAMINE
SGLT2-I	Significant Reduction in the composite outcome of MI, stroke and CVD death	Euglycaemic Ketoacidosis UTI Mycotic infections	EMPA-REG OUTCOME[44] CANVAS[45] DECLARE-TIMI 58[46]
Insulin	No difference in CVD end points		ORIGIN[47] HEART 2D BARI 2D
GLP-1 RA	CVD deaths significantly reduced	Gastrointestinal adverse effects	LEADER[48] SUSTAIN 6[49] REWIND[50] ELIXA[51]

CONCLUSION

Although there is strong epidemiological and pathophysiological evidence for the link between hyperglycaemia and cardiovascular complications, there is controversy about the benefit of intensive glycaemic control in reducing CVD complications[52]. On the other hand, there is no strong evidence about the benefits after long duration of diabetes but that early intervention is beneficial[53].

The conclusion of the evidence is that the process of CV protection is multifactorial depending on control of associated risk factors (Hypertension, obesity, dyslipidaemia etc) and individualization of HbA1c targets to avoid hyperglycaemia and hypoglycemia[54,52]. According to the ADA patients at risk of hypoglycaemia may be subjected to a less stringent glycaemic goal of HbA1c of 7-8%, but those with less risk of hypoglycemia may be subjected to a more stringent glycaemic goal of HbA1c < 6 %[55].

DISCLOSURE

The authors declared no competing interests.

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