DOI: 10.14260/jemds/2014/1920

REVIEW ARTICLE

CARDIOVASCULAR IMPACT OF GLYCEMIC CONTROL IN DIABETES

Biswajit Das[1], Trinath Kumar Mishra[2]

HOW TO CITE THIS ARTICLE:
Biswajit Das, Trinath Kumar Mishra. "Cardiovascular Impact of Glycemic Control in Diabetes". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 04, January 27; Page: 887-894, DOI: 10.14260/jemds/2014/1920

ABSTRACT: While type 1 Diabetes Mellitus (DM) is characterized by insulin deficiency due to pancreatic beta cell destruction, type 2 DM is characterized by a state of long standing insulin resistance (IR), compensatory hyperinsulinemia and varying degrees of elevated plasma glucose (PG), associated with clustering of cardiovascular (CV) risk and development of macrovascular disease prior to diagnosis of DM. Coronary artery disease (CAD) accounts for 70% of mortality and morbidity in patients with diabetes. Studies made in diabetes care have helped prevent or reduce microvascular complications in both type 1 and 2 diabetes. However the same cannot be said about macrovascular disease. Despite all data concerning the association of diabetes and cardiovascular disease (CVD), the exact mechanism by which diabetes is linked to atherosclerosis is incompletely understood, this is especially true in case of hyperglycemia. The positive effect of intensive glucose management in comparison to non-intensive glucose control is far from proven. DCCT and UKPDS study have shown that while a glycemic control is important for reaching long term macrovascular complications, early glucose control is far more rewarding (metabolic memory).Later trials like ACCORD, ADVANCE and VADT don't advocate tight glycemic control. In fact, ACCORD trial has shown increased mortality with tight glucose control. Tight glucose control may be beneficial in selected patients with short disease duration, long life expectancy and no CVD. In critically ill patients a blood glucose target of 140-180 mg % is fairly reasonable and achievable. The ESC/EASD guidelines of October 2013, like those of ADA, AHA and ACC continue to endorse a treatment target for glucose control in diabetes of HbAlc < 7%, based predominantly on microvascular disease with acknowledged uncertainty regarding the effect of the intensive glucose control on CVD risk. Management of hyperglycemia in diabetics should not be considered in isolation, diabetes patients require multivariant intervention for hypertension, dyslipidemia and microalbuminuria besides hyperglycemia. In fact combined use of antihypertensives, aspirin and lipid lowering agent makes it difficult to discern salutary effects of anti-hyperglycemic therapy.

KEY WORDS: Diabetes, Glycemic control, Hyperglycemia.

INTRODUCTION: Diabetes mellitus is a condition defined by an elevated level of blood glucose Type 1 diabetes is characterized by deficiency of insulin due to progressive destruction of pancreatic beta cells, progressing to absolute insulin deficiency. Type 2 diabetes is a combination of insulin resistance and beta cell failure in association with obesity and sedentary life style.

The increase prevalence of diabetes worldwide has led to a situation where approximately 360 million people had diabetes in 2011, of which 95% would have type 2 DM.[1] This number is estimated to increase to 552 million by 2013 and it is presumed that half of these will be unaware of their diabetes status.

The prevalence of diabetes is increasing worldwide and more people with diabetes will die or be disabled as a consequence of vascular complications. Prospective studies have shown in

DOI: 10.14260/jemds/2014/1920

unambiguous association of blood glucose and glycated hemoglobin level with the risk of major cardiovascular events. In case of subjects with type 1 diabetes in spite of the fact that CV rate is significantly lower compared with population with type 2 diabetes, their relative risk for coronary heart mortality is 7 fold higher than in matched counterpart without disease.

In spite of all these data concerning the association of diabetes and cardiovascular diseases (CVD), the exact mechanism by which diabetes is linked to atherosclerosis remains incompletely understood. This is especially true in case of hyperglycemia. The role of non-glycemic factors accompanying vast majority of patients with diabetes such as hypertension, dyslipidemia and hemorrheological abnormality are better understood and appear to be independent of hyperglycemia. There also has been data regarding the future impacts of statins, aspirin, ACE inhibitors and aggressive control of blood pressure on progression of CV disease. In contrast, the positive effect of intensive glucose management on CV disease outcome is far from proven. Even some studies show a negative influence. In type 2 DM, it has long been debated about which would be best strategy to reduce the micro vascular complications and also the macro vascular disease. In recent years CV complication has been the center of concern.

GLYCEMIC CONTINUUM AND CVD: Type 2 DM develops following a prolonged period of euglycemic insulin resistance(IR) which progresses with development of beta cell failure to frank diabetes with increased risk of vascular complications. While microvascular complications like retinopathy, nephropathy and neuropathy develop with overt hyperglycemia, macrovascular complications like coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD) appear earlier during the stage of IFG and IGT. Thus these complications are already established when type2 DM is diagnosed. Over 60% pts. with type 2 DM develop CVD which is a more severe and costly complications than retinopathy.

MOLECULAR BASIS OF CVD: In diabetes insulin resistance has an important role in the pathophysiology of diabetes and CVD. Both genetic and environmental factors facilitate its development. The development of CVD in people with IR is characterized by early endothelial dysfunction and vascular inflammation leading to monocyte recruitment, foam cell formation and subsequent development of fatty streaks.[1] Over many years this leads to atherosclerotic plaque which in presence of enhanced inflammation becomes unstable and rupture to promote occlusive thrombus production. Atheroma from people of diabetes has more lipid, inflammatory change and thrombus than those free from DM. These changes occur over a 20-30 year period and are mirrored by the molecular abnormalities seen in untreated insulin resistance and DM.

Type 2 DM patients are obese and the release of free fatty acids (FFA) & cytokines from adipose tissue directly impairs insulin sensitivity in skeletal muscle and adipose tissue. FFA induces reactive oxygen species production, blunts activation of IRS 1 and P13K – AKT signaling leading to down regulation of insulin responsive GLUT 4.

Hyperglycemia decreases nitric oxide bioavailability and affects vascular function involving over production of reactive oxygen species. [1] The mitochondrial electron transport chain is one of the first targets of high glucose with a direct increase in super oxide anion formation. A further increase in super oxide anion formation is driven by a vicious cycle involving ROS induced activation of PKC. Mitochondrial ROS in tern activates cascades involved in the pathogenesis of the CV complications

DOI: 10.14260/jemds/2014/1920

including polyol flux, AGE and RAGE. Hyperglycemia induced ROS generation is involved in the persistence of vascular dysfunction despite normalization of blood glucose levels. This phenomenon is called metabolic memory which explains why vascular complication progresses despite intensive glycemic control.

Insulin resistance macrophage increases expression of oxidized LDL scavenger receptor-B, promoting foam cell formation and atherosclerosis. Macrophage dysfunction provide a crucial link between diabetes and CVD by both enhancing it and by contributing to the development of fatty streaks and vascular damage.

IMPACT OF GLUCOSE CONTROL ON CVD AND ITS COMPLICATION$: Randomized controlled trials provide compelling evidence that microvascular complications of DM are reduced by tight glycemic control. However the same cannot be said about macrovascular disease. Several prospective trials have been conducted which have so far failed to provide any conclusive evidence of the superiority of glycemic control in reducing macrovascular complications, or death rates in people with advance disease or those with long duration of diabetes.

LONG TERM EFFECT OF GLYCEMIC CONTROL

A. **Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC):** In DCCT the rate of CV events was not significantly altered in the intensive treatment group of patients with type 1 DM.[2] After termination of study, 93% of the cohort were followed for additional 11 years under EDIC, during which the differences in HbA1C disappeared. During the combined l7 years follow up, the risk of any CV event was reduced significantly in the intensive group by 42% (9.63% $p < 0.1$).

B. **United Kingdom Prospective Diabetes Study:(UKPDS)** [3] **:** In the UKPDS trial, 3867 newly diagnosed subjects with type 2 DM were randomized to an intensive glucose control arm involving use of sulfonylurea or insulin and a conventional arm employing life style management. A subgroup of overweight subjects were included in the study that compared intensive glucose control with metformin (n=343) against conventional therapy (n=411). In the insulin and sulfonylurea group, a mean HbA1C level of 7% was achieved versus 7.9% in the control arm over 10 years. Intensive control decreased risk for a composite end point of all diabetes related complications (RRR=12%, p=0.029), and significantly improved microvascular disease risk (RRR=25%, p=0.01), whereas a trend towards decreased risk of Ml was observed with intensive control (14.8 % vs. 16.8%, p=0.052, statistically not significant). Stroke was numerically increased (5.6% vs. 5.2%, p=0.05). In over weight subjects, metformin had better glucose control (Alc > 7.4% vs. 8%) as well as significantly improved risk for MI (RRR=39%, p=0.01) and for all-cause mortality (RRR=26% p=0.011). In extension phase UKPDS study, the patients were followed up for additional l0 years after completion of the trial, during which difference between HbA1c levels in both the groups disappeared. The follow up showed significantly reduced risk for MI in those originally randomized to intensive glycemic control both in insulin and sulfonylurea groups (RRR=15%, p-0.01) and in the metformin group (RRR=33%, p=0.05).

DOI: 10.14260/jemds/2014/1920

There was also significantly 13% reduction in all-cause mortality in the intensively treated group. This persistent benefit generated from early strict glycemic control is known as legacy effect, which outlies the original reduction of HbA1c and subsequent loss of glycemic control. These observations are similar to those seen in DCCT follow up EDIC study where CV events, non-fatal MI, stroke and CV death were reduced by 57% despite loss of glycemic separation. [2]

Combined UKPDS and DCCT / EDIC study show that

1. Glycemic control is important for reducing long term macrovascular complications.
2. Very long follow up period is necessary to demonstrate any benefit.
3. Early glucose control is important (metabolic memory).

MEDIUM TERM EFFECTS OF GLYCEMIC CONTROL:

1. **Action to Control Cardiovascular Risk in Diabetes (ACCORD)** [4]**:** The land mark study was designed to determine whether CV disease event rate could be reduced by intensively treating hyperglycemic hypertensive and dyslipidemia in a double 2x2 factorial design. The trial was based on the hypothesis that a 1.5% difference in HbAlc would result in 15% difference in a population of high risk diabetic individuals having a 3% annual CVD event rate.

   The study included 10, 251 patients with established type 2 DM and 1/3rd having a CV event. Patients were randomized to intensive glucose (targeting HbAlc < 6% and achieving a level of 6.4%) or standard therapy (targeting HbAlc of 7.0 - 7.9 % and achieving level of 7.5%). A variety of glucose lowering therapy was used. There was non-significant trend towards reduction in primary outcome of trial (a composite of non-fatal Ml, stroke or CV death) with intensive control. However, unexpectedly there was higher all-cause mortality (CR-1.22, 95 % Cl-1.01-1.46, p=0.04). Higher rate of severe hypoglycemia and weight gain were reported in intensive glycemic control group. Patients with high HbAlc level at base line were at higher rate of hypoglycemia as were those who did not respond properly with a fall of HbAlc in intensive control group. The explanation for incremental mortality remains unresolved: possible explanations include hypoglycemia precipitating CV death, pernicious effects of specific drug or combinations and a chance finding.

2. **ADVANCE TRIAL** [5]**:** The study was conducted to determine whether intensive lowering would reduce risk of microvascular and macrovascular events in individuals with type 2 DM and vascular risk factors compared to standard conventional case. The study involved 11, 140 subjects. The mean duration of follow up was 5 years. The patients were randomized to intensive versus standard glucose control with gliclazide plus other drugs in the intensive arm compared with other drugs in the standard control group. Mean HbAlc achieved was 6.5% in the intensive group compared with 7% in the standard group. The incidence of combined major macrovascular and microvascular events was significantly reduced (HR-0.9, 95% CI 0.82-0.98, p=0.01) in the intensive control group. This was primarily driven by reduction in progression of albuminuria or emergence of new nephropathy. The CV component of the primary event was not significantly reduced by intensive glucose control. There was no evidence of increase in all-

DOI: 10.14260/jemds/2014/1920

cause mortality. Actually there is a non-significant trend towards reduction in all-cause mortality.

3. **The VADT study[6]:** The trial included American veterans, and 90% were males. A variety of glucose lowering agents was used including metformin, glimepride, rosiglitazone and insulin. An HbAlc of 6.9% was achieved in the intensified control arm compared with HbA1c of 8.4% in the standard treatment arm. After a median follow up of 6.5 years, no significant lowering of composite CV outcomes was noted in the intensive control group. Severe hypoglycemia was more prevalent in the intensive control group. Benefits of intensive control were apparent only in individuals with shorter duration of diabetes, lower HbAlc and absence of CVD at base line.

Insights from ACCORD, ADVANCE and VADT trial:

1. Striking finding of all 3 studies is the suggestion that a beneficial effect of glycemic control intervention is more likely in association with less disease duration.

   In the ACCORD study trial participants entering with base line A1c < 8% rather than having adverse effects of intensive glycemic treatment on mortality, showed a significant reduction in primary outcome favoring such treatment. Similarly in ADVANCE trial, the combined macro and microvascular primary outcome benefit of glycemic control intervention was seen in participants without a baseline history of macrovascular disease. Similarly in the VADT trial, patients who had composite outcome event had longer diabetes duration, higher HbAlc and coronary arterial calcification.
2. Effect of hypoglycemia may be of importance. In the ACCORD study, although investigators stated that this was not a mediator of increased mortality associated with intensive therapy, intensive interventions was associated with significant severe hypoglycemia. The ADVANCE and VADT study group similarly have reported high incidence of severe hypoglycemia.
3. A meta-analysis of these 3 trials suggests that HbA1c reduction of 1% is associated with 15% of RRR in non-fatal Ml, but without benefit on stroke or all-cause mortality.
4. Conclusion from these 3 trials is that intensive glycemic control should be appropriately applied in an individualized manner taking into account age, duration of diabetes and h/o CVD.

GLUCOSE CONTROL IN ACS

Elevated plasma glucose during an ACS is associated with a serious prognosis in patients with DM than without diabetes. Hyperglycemia may relate to previously undetected glucose perturbations but also to stress induced catecholamine release increasing FFA concentration, decreased insulin production and increasing insulin resistance and glycogenolysis with a negative impact on myocardial metabolism and function.

Two strategies have been tasted in an attempt to improve prognosis in patients with ACS

1. **Metabolic modulation:** Metabolic modulation by means of glucose-insulin-potassium infusion regardless of presence of DM or elevated PG is based on the assumption that increase in intracellular potassium stabilises the cardiac myocytes and facilitates glucose transport into the cell. Other potential benefit includes decreased production of FFA, improved use of glucose for energy production and improved endothelial function and fibrinolysis. Despite

DOI: 10.14260/jemds/2014/1920

these proposed mechanistic benefits of G&K therapy and, the strategy has been proven futile in CREATE trial which enrolled more than 20000 patients with Ml who randomised to G&K therapy versus usual care. No benefit of G&K therapy was demonstrated. This lack of effect may be due to increased PG or negative effect of fluid load induced by G&K infusion.

The DIGAMI trial, which is often misinterpreted as a trial of intensive glucose control is actually a glucose insulin infusion therapy trial. The first DIGAMI trial randomized 620 patients with DM and AMI to > 24 hrs. for insulin-glucose infusion followed by multi-dose insulin or routine glucose lowering therapy. Mortality after 3-4 yrs. was significantly reduced in the intervention group[7]. However DIGAMI-2 failed to replicate this prognostic benefit. The plausible reason for this discrepancy was that in DIGAMI-l admission HbAlc decreased more (1.5%) from a higher level (9.1%) compared with 0.5% from 8.3% in DIGAMI-2. Since DIGAMI-2 trial did not achieve a difference in glucose control between intensively treated and control groups, it is still an open question as to whether glucose lowering is beneficial.

2. **Glucose control in ICU setting:** In 2001 Van den Berghe published a randomised controlled trial of critically ill surgical pts. showing that tight glucose control reduced hospital mortality[8]. Since the greatest decrease in death occurred in subgroup of pts. with multi system organ failure, it was speculated that benefits of tight glucose control might extend to medical ICU patients as well. However subsequent trials by the same group couldn't demonstrate any benefit with tight glycemic control. Further recent trial like VISEP and European glucontrol showed trend for increased rate with tight glucose control. The NICE SUGAR trial in fact demonstrated an actual 14% increase in mortality rate with intensive glucose regimen[9].

   Few of these trials assessing glucose control in ICU settings included ACS patients. Therefore, general applicability of the observation remains uncertain. Because of paucity of data on tight glycemic control a glucose target of < l80 mg % is a reasonable approach in ACS pts.

WHY LOWER IS NOT NECESSARILY BETTER?

The UKPDS study was the first to provide evidence that in newly diagnosed type2 DM pts. intensive glucose control may reduce the risk of microvascular complications, also with modest effect on CV outcomes. Thus the concept 'the lower, the better' (glucose level) was proposed by all diabetology guidelines as a paradigm for type2 DM patients. However, this concept has been challenged by 3 landmark trials: ACCORD, ADVANCE and VADT.

Numerous potential reasons have been put forth to explain the lack of benefits with intensive glucose control therapy. These include pernicious effects of specific drugs or drug combinations, increased incidence of hypoglycemia precipitating CV death and a mere chance finding.

HYPOGLYCEMIA AND ADVERSE CV EVENTS

In the ACCORD trial, which included diabetic patients with CV disease or high CV risk, symptomatic, severe hypoglycemia was associated with higher mortality in pts. in both study arms[4]. ADVANCE trial also showed that occurrence of severe hypoglycaemic episodes has a detrimental effect on CV outcome.

The ORIGIN trial also showed evidence corroborating hypoglycemia with adverse CV outcomes. The trial randomized 12, 537 people at high risk of CVD plus IGF, IGT or type2 DM to receive insulin glargine (with a target FBS level of < 95mg %) versus standard care. After a median follow up of 6.2 years, the rates of incident CV outcome were similar in both the groups. In this population of ORIGIN trial, severe hypoglycemia occurred in 5.7% & 1.8% patients assigned for insulin glargine and standard therapy groups respectively. Severe hypoglycemia was associated with a greater risk for primary outcome, mortality, CV deaths and arrhythmic deaths.

Compensatory mechanisms induced by hypoglycemia, such as enhanced catecholamine release, may aggravate myocardial ischemia and provoke arrhythmia. Still then, it remains unclear whether hypoglycemia is simply a marker of disease severity or contributes to adverse outcomes. Hypoglycemic episodes probably identify patients at risk for other reasons like malnutrition, HF, and renal dysfunction.

CURRENT GLYCEMIC TARGETS (ESC/EASD guidelines) [1]

1. While an HbA1 c target of less than 7% to reduce microvascular disease is a generally accepted level, the evidence for an HbA1c target in relation to macrovascular risk is less compelling
2. Consensus indicates that an HbA1c of less than 7% should be targeted but with acknowledgement of need to pay attention to the individual requirement of the patient.
3. Fasting plasma glucose should be less than 120mg % (7.2mmol/l) and postprandial less than 160-180mg % (9-10mmol/l) on an individualized basis.
4. Ideally tight glycemic control should be started early in the course of the disease in younger people and without attendant comorbidities.
5. Stringent targets like HbAlc 6-6.5% may be considered in selected patients with short disease duration, long life expectancy & no CVD, if it can be achieved without hypoglycemia or other adverse effect.
6. For critically ill indoor patients insulin therapy is indicated at a threshold of no greater than 180mg %(l0mmol/l) (ADA2008)
7. Once insulin therapy has been started in critically ill patients a glucose range of 140-180 mg% is recommended.
8. With the preferred method of intravenous insulin infusion, frequent glucose monitoring is essential to minimize occurrence of hypoglycemia and to achieve optimal glucose control.
9. Tight glucose control (80 – 110 mg %) has not been associated with mortality benefit in many trials. In past some trials so increase mortality.

REFERENCES:

1. Ryden L, Grant P J, Anker S T, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2013; 34:3035-3087.
2. The effect of intensive treatment of diabetes on the development & progression of long term complications in Insulin dependent diabetes mellitus. The Diabetes Control & Complications Trial Research Group. N Engl J Med 1993; 329:977-986.
3. Holman R R, Paul S K, Bethel M A, et al, 10 years follow-up of intensive glycemic control in Type 2 diabetes. N Engl J Med 2008; 359; 1577-1589.

REVIEW ARTICLE

4. Gerstein HC, Miller ME, Brington R, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545-2559.
5. Patel A, Mac Mohan S, Chalmes J, et al. Intensive blood glucose control & vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560.
6. Duckworth W, Abraira C, Moritz J, et al. Glucose control & vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360:129-139.
7. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction(DIGAMI Study);Effects on mortality at 1 year. J Am Coll Cardiol 1995; 26:57-65.
8. Van den berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359.
9. Finfer S, Chittock DR, Susy, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283.

AUTHORS:

1. Biswajit Das
2. Trinath Kumar Mishra

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Cardiology, SCB Medical College, Cuttack, Odisha.
2. Professor and HOD, Department of Cardiology, SCB Medical College, Cuttack, Odisha.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Trinath Kumar Mishra,
Professor and HOD,
Department of Cardiology,
SCB Medical College,
Cuttack - 753007, Odisha.
E-mail: drtkmishra@yahoo.com

Date of Submission: 26/12/2013.
Date of Peer Review: 27/12/2013.
Date of Acceptance: 10/01/2014.
Date of Publishing: 22/01/2014.