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How Tight is Right? Debating the Issue of Optimal Diabetes Control

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WHY OPTIMAL DIABETES CONTROL?

Hyperglycemia is unequivocally associated with micro-vascular complications both in type 1 and type 2 diabetes. Large body of evidence has accumulated through studies in animal models, observational studies in humans and clinical trials corroborating these associations[1-5]. Furthermore, intervention trials have demonstrated that while microvascular risk reduction is a continuum with no lower threshold, unacceptable incidence of hypoglycemia limits the possibility of reducing the targets further than those achieved in these trials[6]. However, it clearly emerges from these data that glycemic levels should be maintained as close to the non-diabetic range as possible.

Notwithstanding the multifactorial etiology of macro-vascular disease, unequivocal relationship exists between hyperglycemia and prevalence of CVD[7,8]. Unfortunately significant macrovascular risk reduction is likely to occur at lower levels of HbA_{1C} than achieved in major intervention trials. Whether selecting agents differently than practiced in contemporary medical practice could achieve these lower targets without producing unacceptable hypoglycemia remains to be unequivocally proved. However, positive trends have been demonstrated in STOP NIDDM trial[9], dream trial[10], DPP trial,[11] etc.

Hyperglycemia is supposed to be the hallmark of metabolic abnormality in diabetes mellitus, notwithstanding abnormalities of lipid metabolism playing an equally pivotal role in the pathogenesis and perpetuation of the disease. Besides, several clearly delineated pathogenetic mechanisms are known to establish a causal relationship between acute and chronic hyperglycemia with both microvascular as well as macrovascular complications[12]. As a natural corollary optimal glycemic control mitigates these complications to a considerable extent.

Moderate to severe hyperglycemia is also responsible for a wide variety of symptoms involving almost every organ system and merits optimal control for amelioration of such symptoms in respective individuals.

Finally hyperglycemia begets hyperglycemia by inflicting glucotoxicity and glucolipotoxicity in tandem with dyslipidemias[13,14]. Persistent hyperglycemia accelerates the inexorable decline in beta cell function in conjunction with genetic and other environmental factors. Optimal glycemic control obviously could be the most important contribution towards beta cell preservation.

WHAT ARE THE MEASURES OF OPTIMAL DIABETES CONTROL?

Fasting and post-prandial blood glucose levels are extensively measured in clinical practice across the globe to assess the degree of glycemic control. Both fasting and post prandial glucose levels have shown robust association with micro-vascular as well as macro vascular endpoints. However both these parameters have certain limitations in terms of being a true reflection of optimal glycemic control.

Glycosylated Hemoglobin (HbA_{1C}) represents average glycemic control over previous 10-12 weeks and has emerged as the most acceptable marker of diabetes control. Major clinical trials have used HbA_{1C}, as the surrogate marker for optimal diabetes control. It must however be clearly understood that there are several patients with excellent HbA_{1C}, fasting plasma glucose and 2 hr PP glucose within normal limits and yet show

wide fluctuations in the plasma glucose levels when observed over 24 hr period with either continuous blood glucose monitoring or even 8 point plasma glucose profile[15]. Unfortunately logistics of doing 8 point profile or CGMS make it unacceptable for common usage in clinical practice.

WHAT ARE THE RECOMMENDED GLYCEMIC GOALS?

The upper limit of the non diabetic range is 6.1% (mean HbA1c of 5% + 2 SD) with the DCCT-standardized assay. This has been promulgated through the National Glycohemoglobin Standardization Program (NGSP) and adopted by the vast majority of commercially available assays[16]. Consensus is gradually emerging with respect to optimal glycemic goals both in type 1 and type 2 diabetes. This has been possible as a result of several well designed clinical trials and huge epidemiological data demonstrating powerful beneficial effect of decreasing glycemia in reducing micro-vascular complications. The Diabetes Control and Complication Trial (DCCT)[6] and the Stockholm Diabetes Intervention Study in type 1diabetes[17] and the UK Prospective Diabetes Study (UKPDS)[18] and Kumamoto Study[19] in type 2 diabetes have clearly shown huge benefits in achieving HbA1c below 7%.

Latest recommendations by ADA suggest that while efforts should be made to achieve this level of control, further benefit could accrue in terms of micro-vascular and macro-vascular risk reduction by achieving HbA1c levels of < 6% in individual patients, provided the regime does not produce significant hypoglycemia[20]. This is in variance with the European Union—International Diabetic Federation recommendations of an HbA_{1C} target of < 6.5%[21].

Excellent correlation has been demonstrated between fasting blood glucose levels measured several times a week with the HbA_{1C} level. In countries where self monitoring of blood glucose (SMBG) is done frequently, measures of glycemia that are initially targeted on a day to day basis are the fasting and pre-prandial glucose levels. To achieve long term glycemia in non-diabetic range efforts should be made to maintain fasting and pre-prandial levels between 70 and 130 mg/dl. In case these levels are not achieved or the HbA_{1C} remains persistently above the target then post-prandial levels usually measured 90-120 minutes after meal should be targeted. If they could be maintained at < 180 mg/dl one is likely to achieve HbA_{1C} in the target range[22].

Optimal target for post prandial glycemic control is currently under intense debate. European Diabetes Policy Group have suggested that post prandial glycemic peak should not exceed 135 mg/dl to reduce arterial risk and should not exceed160 mg/dl to reduce micro-vascular risk[23]. Besides there is emerging data suggesting 1 hr 15 mts post meal as the optimum time to measure post prandial glycemia[24]. Stronger evidence linking post prandial glycemia and cardio vascular risk has led to suggestions pertaining to targeting PPG as well as HbA1c and fasting plasma glucose. It has been recently demonstrated that PPG values > 160 mg/dl was recorded at least in 84% patients suggesting this as a frequent phenomenon in patients with apparently good metabolic control as reflected by HbA_{1C}[25].

One should expect significant incidence of hypoglycemia while trying to achieve these glycemic targets, particularly with regimes using sulfonylureas or insulin. This should not deter one from achieving the defined glycemic targets as these episodes are generally well tolerated, easily treated with oral carbohydrate and rarely if ever progress to more severe hypoglycemia, loss of consciousness or seizures. The wisdom lies in empowering the patient with the knowledge to diagnose and treat hypoglycemia promptly rather than compromise with poor glycemic control.

WHAT IS THE DEBATE?

Type 1 Diabetes

Risk reduction for micro-vascular complications including retinopathy, nephropathy and neuropathy has a consistent relationship with decreasing levels of HbA1c even into the near non-diabetic range. As the lower level for the beneficial effect has not been defined, the overriding consideration is the issue of hypoglycemia. In type 1 diabetes data from DCCT clearly shows an approximately threefold increase in the incidence of severe hypoglycemia even though intensive therapy did not lower mean HbA_{1C} to the non-diabetic range[26].

Although majority of these events were benign, there was a significant increase in the incidence of events resulting in seizure or coma requiring hospitalization or emergency department treatment. However it should also be noted that there was not a single incident of fatal hypoglycemia or macro-vascular event that could be ascribed to hypoglycemia. Similarly, these adverse events did not result in any impairment either of the neurocognitive function or quality of life measures[27]. Moreover 99% of the randomized subjects completed the study with a mean follow-up for 6.5 years.

It could be worthwhile assessing as to what is achievable in clinical practice. In DCCT the target goals

for glycemic control were pre-meal blood glucose levels between 70-120 mg / dl, peak postprandial levels below 180 mg / dl and HbA_{1C} levels < 6.05%. Intensive therapy and intensive monitoring with three or more insulin injections per day, insulin pump and SMBG could achieve an impressive reduction in the HbA1c by approximately 2% (7.2% vs. 9.1%). However, intensive therapy could not achieve the HbA_{1C} level of non-diabetic subjects (< 6.05%). Furthermore, after 5 to 7 years of the completion of the trial the HbA_{1C} of the intensively treated patients drifted up to the HbA_{1C} levels of conventionally treated subjects.

On the flip side even with identical HbA1c levels after 5 to 7 years, the differences in the rate of retinopathy and nephropathy continued to expand between the two treatment groups[28]. It appears from this observation that tight glycemic control creates an 'imprinting' leading to a metabolic memory with respect to complications.

Another landmark study Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) showed excellent correlation between HbA_{1C} levels at baseline with incidence of retinopathy, progression to proliferative retinopathy, macular edema and vision loss with no threshold within the diabetic range[29]. Combining epidemiological observation from WESDR[29] and astounding results from DCCT / EDIC[28], one can safely conclude that efforts should be made to achieve HbA1c level in the non-diabetic range, albeit with comprehensive counseling towards identification and prompt treatment of hyperglycemia.

Until recently it was perceived that **Macro-vascular risk reduction** in type 1 diabetes has not been as impressive as the micro-vascular risk reduction. In DCCT even though intensive treatment reduced combined major cardiovascular endpoints by 41%, it did not reach statistical significance (p=0.06). However EDIC study following DCCT cohort has clearly shown beneficial effect of intensive therapy on carotid intima-media thickness, a surrogate marker of atherosclerosis[30].

The most gratifying results have come from EDIC cohort after 11 years of follow-up showing 42% risk reduction for any cardio-vascular disease and 57% risk reduction for non-fatal MI, Stroke or death from cardio vascular diseases[31]. On its face value it would immediately require reduction in the currently recommended HbA1c target for children and adolescents i.e., less than 8% for children 6 to 12 years of age and less than 7.5% for those 13 through 19 years of age[22]. In real life situation even the currently recommended age specific goals for children and adolescents with type 1 diabetes are extremely difficult to reach and that too with unacceptable incidence of hypoglycemia. Notwithstanding the unique risk of hypoglycemia in this age group, low risk of complications before puberty, developmental issues and psychological issues surrounding adherence to medication and dietary regimens, efforts to achieve HbA1c target in the non-diabetic range would clearly make an unimaginable impact on the macro-vascular risk reduction. This stand to reason as data clearly suggests that atherosclerosis begins early in patients with type 1 diabetes and that the progression of CVD is much more aggressive in this group[32]. Unfortunately until the availability of new therapies and innovative approaches the results of the landmark DCCT / EDIC trial can not be translated into clinical practice.

Type 2 Diabetes

Micro-vascular risk reduction in type 2 diabetes has been unequivocally demonstrated in UKPDS[18]. Similar to the results of DCCT in type 1 patients, this impressive risk reduction was associated with a substantial increase in the incidence of hypoglycemia. Furthermore majority of the patient could not achieve the glycemic target in the intensively treated group. However, there was no lower threshold of HbA1c for micro-vascular risk reduction.

UKPDS unfortunately failed to show any significant benefit in terms of **macro-vascular risk reduction,** even though there was a trend towards the same. Extrapolating data from DCCT / EDIC study, it could be argued that further reduction of Hba1c could have resulted in significant macro-vascular benefits. However, targeting the same with the treatment regimens used in the trial and that usually followed in contemporary practice would have further escalated the incidence of hypoglycemia.

In type 2 diabetes achieving lower Hba1c targets may not be that difficult as that in type 1 diabetes as there are several anti hyperglycemic agents that can be safely used at much lower levels of glycemia without incurring extra risk of hypoglycemia. Recent results from prevention trials have clearly demonstrated that lower levels of Hba1c could be achieved by selecting agents like Metformin or Rosiglitazone without increasing the risk of hypoglycemia. In DPP Metformin use could reduce the rate of conversion from IGT to diabetes by 31% without any increased incidence of hypoglycemia[11]. The DREAM trial has shown even more impressive reduction in the conversion rate (62%) without increasing the risk of hypoglycemia. However there was marginal increase in the incidence of edema, weight gain and heart failure[10]. Substantial evidence is likely to come

from few of the on-going studies looking at the relationship of intensive glycemic control and CVD in type 2 diabetes[33,34].

CONCLUSION

Results of DCCT/EDIC in type 1 diabetes and those of DREAM and other primary prevention trials in type 2 diabetes have opened new debate regarding timing (primary prevention or secondary prevention) and modality of intervention towards treat to target approach. Results of DCCT/EDIC lay the foundation of aggressive reduction of glycemic target to non-diabetic range. Similarly, primary prevention trials in type 2 diabetes like DREAM, DPP etc confirm feasibility of achieving glycemic targets in the non-diabetic range without increasing the risk of hypoglycemia.

These results could herald a new era of aggressive approach towards achieving glycemic targets in the non-diabetic range. However, it should be clearly understood that these trials demonstrated reduced conversion of IGT to type 2 diabetes and one can argue that they should not be extrapolated in terms of achieving reduction in micro-vascular or macro-vascular complications. Furthermore we are not sure if aggressive intervention with an objective to treat to target should be implemented in patients of all ages. It goes without saying that targets are different in pregnancy.

What clearly emerges from these studies is the fact that the currently recommended targets are generally adequate in clinical practice. Even at this level of glycemic control there is significant incidence of hypoglycemia, which is not only agonizing and frightening experience for the patient but also a deterrent and demotivation for further optimal glycemic control. It should not be forgotten that neither DCCT nor UKPDS study subjects could achieve the glycemic levels in the non diabetic range in their intensive-treatment groups. Even in a well controlled trial scenario the achieved mean level of HbA_{1C} was ~7%, 4 SD above the non-diabetic range. Yet the incidence of hypoglycemia was % in DCCT and % in UKPDS. In real life scenario achieving such targets will not only be daunting but also likely to produce higher incidence of hypoglycemia. Furthermore the financial logistics involved in achieving these targets are beyond the reach of majority of patients. What is imperative is to change the lackadaisical attitude to a more vigilant one in presence of HbA_{1C} of > 7% by prompt initiation or change in therapy with a goal of achieving HbA_{1C} as close to non-diabetic range as possible without increasing the risk of hypoglycemia and giving due consideration to the life expectancy of the individual patient.

Therefore, prudence lies in targeting currently recommended levels of glycemic control and effectively targeting other metabolic parameters like hypertension, dyslipidemias, obesity, insulin resistance, inflammation, hypercoagulability etc, which have been rather neglected hitherto in clinical practice. This paradigm could change with availability of better molecules and better delivery systems which could ensure lower glycemic levels without increased risk of hypoglycemia.

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