Importance of Controlling Diabetes Early– The Concept of Metabolic Memory, Legacy Effect and the Case for Early Insulinisation

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Abstract

Most of the microvascular complications of diabetes are related to the degree and the length of exposure to hyperglycaemia. New data from the follow-up studies of the Diabetes Control and Complications Trial- the Epidemiology of Diabetes Intervention and Complications Study (DCCT- EDIC), and the United Kingdom Prospective Diabetes Study (UKPDS) emphasize the role of glycemic control early in the course of the disorder and its value in prevention of later complications. The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to usual (often poorer) metabolic control has been described as representing "metabolic memory" by the DCCT/EDIC investigators and as a "legacy effect" by the UKPDS investigators. This article reviews these concepts and explores the role of early use of insulin as a tool to achieve good glycemic control in type 2 diabetes.

Introduction

The epidemic of type 2 diabetes is a growing public health problem that threatens to reduce life expectancy and increase morbidity as a result of its complications. Hyperglycemia, the cardinal feature of diabetes, can be controlled either by the exogenous administration of insulin or through oral anti-diabetic drugs which increase insulin secretion, improve insulin sensitivity or reduce glucose absorption from the gastrointestinal tract. In spite of advances in therapy, the debilitating vascular complications of diabetes continue to occur.[1-3] One of the major reasons for this is the lack of awareness among patients regarding the seriousness of diabetes and consequences of poor control. According to the Chennai Urban Rural Epidemiology Study (CURES) study, awareness and knowledge regarding diabetes is still grossly inadequate in India.[4] The CURES illustrates that the "rule of halves" described in hypertension is also valid for diabetes in India [4] as summarized in Figure 1.

Complications of Diabetes

The complications of diabetes represent clinically definable endpoints that seem to occur as a result of a series of complex intracellular pathways. These pathways are not fully understood at present, but may act alone or in unison to trigger adverse effects in multiple organs.[5] The clinical endpoints are long term vascular complications which are classified as being either "macrovascular" (for example, heart disease, stroke, and peripheral vascular disease [which can lead to ulcers, gangrene, and amputation]) or "microvascular" (for example, retinopathy, nephropathy and neuropathy). In spite of the availability of newer and more effective agents to treat diabetes, the various complications of diabetes continue to represent the major cause of morbidity and mortality in these patients.[1-3, 6-10]

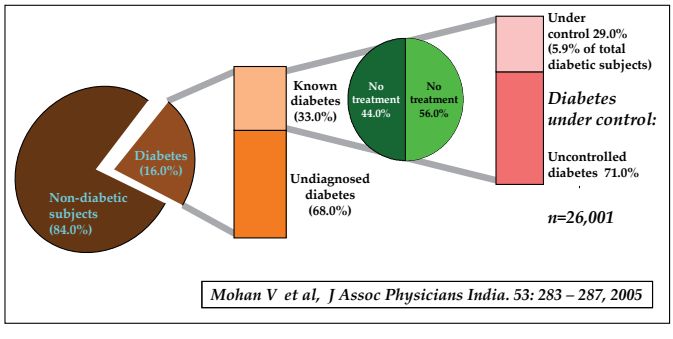

Fig. 1 : Rule of halves in diabetes

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The Diabcare-Asia observational study showed that type 2 diabetes begins at an early age amongst Indians.[11] With increasing duration of diabetes, glycemic control deteriorates, leading to late complications. Diabetes care in India leaves much to be desired and concerted efforts to increase awareness amongst health professionals to improve diabetes care are urgently needed.[12,13]

Prevention of Diabetes Complications- Clinical Evidence from Landmark Trials

The benefits of tight glycemic control in preventing chronic diabetic complications remained debated upto the mid 1990's. One of the seminal studies which confirmed the importance of optimizing glycemic control in type 1 diabetes, was the Diabetes Control and Complications Trial (DCCT),[14] and its follow-up observational study, the Epidemiology of Diabetes Intervention and Complications (EDIC) study,[15] The conclusions of the DCCT and EDIC studies were similar to those of the much smaller studies, as summarized in a meta-analysis and showed that good control of diabetes can prevent microvascular complications.[16] Other studies have explored the issue of intensive blood glucose control in patients with type 2 diabetes and have also addressed whether other therapeutic options such as blood pressure reduction and/or lipid lowering can act in concert with improved glycemic control to reduce the incidence and progression of vascular complications particularly the macrovascular complications. These studies include the Multifactorial Intervention Steno-2 study,[17] the United Kingdom Prospective Diabetes Study (UKPDS),[18] the Action in Diabetes and Vascular Disease: PreterAx and Diamicron modified release Controlled Evaluation (ADVANCE) study,[19,20] the Veterans Affairs Diabetes Trial (VADT),[21] and the Action to Control Cardiovascular Risk

Table 1 : Epidemiology of Diabetes Intervention and Complications (EDIC) study: Key findings

Complication (years of follow up)	% reduction in former intensive treatment group
Retinopathy (10 years EDIC)	
Progression of retinopathy	24
Progression to Proliferative retinopathy	59
Nephropathy (8 years EDIC)	
New microalbuminuria	59
Clinical albuminuria	84
Neuropathy (8 years EDIC)	
Symptoms	51
Signs	43
Cardiovascular disease (17 years DCCT+EDIC)	
Any	42
Non-fatal myocardial infarct, stroke or CVD death	57

CVD = cardiovascular disease;
DCCT = Diabetes Control and Complications Trial

in Diabetes (ACCORD) study.[22] The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control followed by a return to usual (often poorer) metabolic control was described as representing "metabolic memory" by the DCCT/EDIC investigators and as the "legacy effect" by the UKPDS investigators.[23]

In the DCCT, type 1 diabetes patients were either placed on standard or intensive treatment regimens to normalize their glucose levels. Because the occurrence as well as progression of microvascular complications viz, retinopathy, nephropathy and neuropathy was profoundly reduced in patients with tight glucose control, the DCCT was prematurely terminated after a mean time of 6.5 years with a recommendation that all patients be given intensive therapy.[14]

Epidemiology of Diabetes Intervention and Complications (EDIC) study

The EDIC trial, a follow-up to the DCCT, showed that compared to their counterparts who had earlier received intensive therapy, patients on the standard treatment regimen during the DCCT continued to have a higher incidence of complications several years later, although the glycated hemoglobin of both groups had now become similar. This suggests that the benefits of early tight control persist for several years even if the control is relaxed. Besides, new data from EDIC also suggests that the influence of early glycemic control on the progression to macrovascular events also may become more evident on longer follow-up.[24-27]

The first DCCT follow-up showed that the risk of retinopathy remained significantly reduced in the intensive group compared to the conventional treatment group in the first four years after the end of the trial, despite similar HbA_1C levels over this period.[28] More convincing results were obtained after 10 years of EDIC follow-up, in which the HbA_1C levels had converged completely and the follow-up was longer. The intensive treatment group had lower rates of progression of retinopathy and proliferative retinopathy but the risk reductions at 10 years were lower compared to the first 4 years of follow-up.[29] Diabetic nephropathy was reported during the 8 years' follow-up and showed a reduction in new microalbuminuria and clinical albuminuria, with fewer cases of hypertension and patients needing renal replacement therapy, in the former intensively treated group.[30]

Diabetic neuropathy was also reported at 8 years' follow-up with a reduction in neuropathic symptoms and signs in the former intensively treated group.[31] During the 17 years of follow-up in DCCT and EDIC, intensive therapy reduced the risk of any cardiovascular disease and the risk of non-fatal myocardial infarction, stroke, or death from cardiovascular disease.[32] A beneficial effect of former intensive diabetic control was noted on coronary artery calcification at 7 to 9 years' follow-up. In the EDIC study after 6 years of follow up the progression of carotid artery intima–media thickening was less in the former intensively treated group.[33]

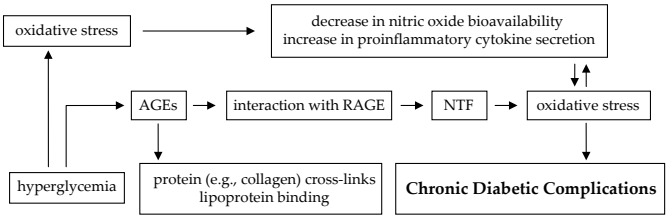
Table 1 shows the reduction in various complications in the former intensive treatment group in the EDIC study.

Collectively, these observations support the concept that early glycemic environment is imprinted on the tissues and vascular cells and the authors of the DCCT/EDIC have referred to this phenomenon as "metabolic memory".[26]

Clinical Evidence from the UKPDS

Data from the United Kingdom Prospective Diabetes Study (UKPDS) ratifies this evidence in subjects with type 2 diabetes. Specifically, people with lower fasting plasma glucose values at the time of diagnosis had fewer vascular complications and fewer adverse clinical outcomes over time as compared to people with higher fasting plasma glucose values, despite similar rates of glycemia later,[25] suggesting that early metabolic control has enduring beneficial effects even in type 2 diabetes.

In the UKPDS, patients with type 2 diabetes mellitus who were on intensive glycemic control had a lower risk of microvascular complications than those receiving conventional dietary therapy. A post-trial monitoring was done to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.[27] In this Outcomes Study, of 5102 patients with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control. In the post-trial monitoring, 3277 patients were asked to attend the UKPDS clinics annually for 5 years, but no attempts were made to maintain their previously assigned therapies. Annual questionnaires were used to follow patients who were unable to attend the clinics. All patients in years 6 to 10 of follow up were also assessed through questionnaires. Seven prespecified aggregate clinical outcomes from the UKPDS were examined on an intention-to-treat basis, according to previous randomization categories. After the first year, between-group differences in glycated hemoglobin levels were lost. In the sulfonylurea–insulin group, relative reductions in risk persisted at 10 years, for any diabetes-related endpoint (9%, $p = 0.04$), for microvascular disease (24%, $p = 0.001$), for myocardial infarction (15%, $p = 0.01$) and for death from any cause (13%, $p = 0.007$). In the metformin group, significant risk reductions persisted for any diabetes-related endpoint (21%, $p = 0.01$), myocardial infarction (33%, $p = 0.005$), and death from any cause (27%, $p = 0.002$). Thus it was concluded that despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during the 10



Adapted from Drzewoski J, et al. Pol Arch Med Wewn. 2009; 119: 493-500

AGE – advanced glycation end product, NTF – neurotrophic factors, RAGE – advanced glycation end product receptor

Fig. 2 : The vicious circle of metabolic memory

years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients. The beneficial effect of early intensive control on subsequent development of diabetes complications has been termed as the "legacy effect" by the UKPDS group.

Mechanisms for "Metabolic Memory" and "Legacy Effect"

Two current hypotheses suggest that poor control of diabetes results in some irreversible mitochondrial or vascular change which then predisposes or progresses to overt long-term complications. To what extent the cause of the damage is glucotoxicity or lipotoxicity or a combination of these factors is unknown and no doubt these toxic effects are modified by other inherited or acquired metabolic processes. The well-established time relationship of duration of diabetes and incidence of long-term complications is therefore shifted to the left by poor metabolic control. For most patients with type 1 diabetes, HbA_1C measurements are the only evidence available of their overall control as mitochondrial function or detailed vascular health are not easily or routinely assessed – and indeed, if irreversible, not particularly helpful for the individual. Perhaps, carotid artery intimal thickness or vascular reactivity and resistance should be measured and followed to help identify vascular risk in patients. The accumulation of AGEs, which are formed during periods of hyperglycemia and persist for many years, may be one of the important factors in metabolic memory. AGEs are a heterogenous group of chemical moieties occurring as a result of a nonenzymatic reaction of glucose with proteins, lipids, and nucleic acids. The role of AGEs in the progression and complications of diabetes has been reviewed recently [34]. AGEs act directly to induce cross-linking of long-lived proteins such as collagen to promote vascular stiffness, and, thus, alter vascular structure and function. AGEs can also interact with certain receptors, to induce intracellular signalling that leads to enhanced oxidative stress and elaboration of key proinflammatory and prosclerotic cytokines. AGE modification of mitochondrial proteins may be irreversible and may result in decline of mitochondrial function with excess formation of reactive oxygen species. Support for the concept of the deleterious effects of the accumulation of AGEs (glycated collagen and carboxymethyllysine) has been obtained from skin biopsies in the DCCT and the EDIC study with the prediction of risk of progression of retinopathy and nephropathy, even after adjustments for mean HbA_1C. Indeed the predictive effect of HbA_1C was abolished after adjustment for the two AGEs measured.[35, 36]

Other theories on the mechanisms of metabolic memory have been reviewed recently and include the idea that oxidative stress persists after normalisation of glucose levels and that there is long-lasting activation of epigenetic changes in the promoter region of a key inflammatory marker by transient spikes of hyperglycemia in mice. Another theory holds that insulin in addition to suppressing glucotoxicity and lipotoxicity also has important anti-inflammatory effects. Figure 2 summarizes the vicious cycle of metabolic memory.[37]

"Clinical Inertia" in Diabetes – Failure to Achieve Tight Control and the Concept of "Avoidable Glycemic Burden"

Type 2 diabetes is a progressive disease. The two main pathophysiologies in type 2 diabetes are insulin resistance and beta-cell secretory defect. Although IR has long been considered to be the initial pathophysiological derangement in type 2 diabetes, evidence is accumulating that beta-cell dysfunction may start earlier in the course of the disease than was initially believed. The UKPDS showed that by the time diabetes was diagnosed, patients had already lost more than 50% of their beta-cell secretory capacity, and this beta cell loss continues inexorably as time passes.

The conventional approach to treatment of type 2 diabetes follows a step-wise strategy. This involves sequential introduction of lifestyle modification, single oral antidiabetic agents then, oral antidiabetic agents in combination and finally insulin therapy. Often there is a long delay before a new agent is introduced, even though the HbA_1C levels are way above target. This failure to initiate or intensify treatment even when indicated is termed "clinical inertia". As a result of clinical inertia, patients accumulate several years of hyperglycemia before therapy is intensified or changed- the so-called "avoidable glycemic burden". It has been estimated that an average patient accumulates 5 years of HbA_1C more than 8%, and 10 years of HbA_1C more than 7% before insulin therapy is initiated.[38]

Clinical inertia in achieving glycemic targets in Indian diabetic subjects could be expected to be even more due to the low rates of awareness of diabetes and its complications in India.[12] Moreover, other factors like non-affordability, lack of accessibility to health care services, and inadequate follow-up are additional factors contributing to this problem in developing countries like India.

Benefits of Early Insulin Therapy

The currently available oral antidiabetic agents have different mechanisms of action. However, all of them exert their antihyperglycemic effects only if some degree of endogenous insulin is present. As beta cell function declines with increasing duration of diabetes, these agents ultimately become ineffective, even in combination. To date, no antidiabetic agent has been shown to arrest or reverse beta cell decline indefinitely in type 2 diabetes. Therefore, most patients with type 2 diabetes will ultimately need insulin to achieve their glycemic targets.

Insulin is the antidiabetic agent par excellence. It has a proven safety record stretching back to the 1920s. The dosage of insulin is limited only by hypoglycemia; it is safe in renal, hepatic and cardiac disease and in pregnancy. Used correctly, it can bring any level of elevated HbA_1C to target.

In addition to its beneficial effects on cardiovascular risk factors such as cholesterol, triglycerides and waist-hip ratios,

insulin therapy also appears to partially restore insulin-mediated endothelial function,[40] improve vasodilatation[41] and fibrinolytic profiles.[42]

Insulin therapy also has the ability to reverse glucotoxicity- the temporary decline in beta cell function following chronic exposure to high glucose concentrations. Intensive insulin therapy has been shown to significantly improve beta cell function in patients who have failed maximal doses of oral antidiabetic agents. Also, short courses of insulin therapy administered early in the course of type 2 diabetes have been shown to induce temporary "remission" of diabetes, during which time diabetes can be controlled with diet alone.[39] Such early use of insulin has also been shown to improve beta cell function.[43]

There are numerous barriers to initiating insulin in clinical practice. Patients as well as physicians have several misconceptions regarding insulin, most of which are not supported by hard evidence. The most common concerns relate to weight gain, hypoglycemia and the fear of injections. While weight gain is frequent with insulin injections, the long-term benefits of tight glycemic control far outweigh the minor risks associated with this. Moreover, many of the currently available oral antidiabetic agents are also not free of this side-effect. Newer insulin preparations have less tendency to cause weight gain compared to conventional insulins.[44]

Hypoglycemia is the major factor preventing patients with diabetes from achieving glycemic targets. The incidence of severe hypoglycemia is thankfully low in type 2 diabetes patients, even if they are on insulin. The risk of hypoglycemia can be minimized by using proper insulin regimens, patient education, regular monitoring and by the use of newer insulin analogues, which have a more physiological time-action profile.

The advent of newer insulin delivery devices like insulin pens and finer needles has made the administration of insulin a less painful affair. Proper attention to injection technique can also minimize the pain associated with insulin injections. Use of Continuous Subcutaneous Insulin Infusion pump enables the patient to derive the full benefits from intensive insulin therapy with minimum disruption to his lifestyle and achieve excellent control, although it is currently quite expensive.

In spite of the advances in insulin pharmacology and delivery systems, insulin use is often delayed until it is absolutely necessary. To improve diabetes management and glycemic control nationwide, physicians must learn to overcome clinical inertia, to intensify therapy when appropriate, and to use insulin when clinically indicated. From an intervention point of view, many strategies might be developed to reduce clinical inertia and its determinants. Educational or learning interventions that target cognitive barriers to medication initiation or intensification for patients with chronic disease have received some attention and initial reports show some positive effects on clinical inertia. Patient empowerment might also decrease clinical inertia, and some previous studies have demonstrated that patient empowerment leads to better diabetes care.[45]

Conclusions

Early, intensive treatment of new onset diabetes mellitus aimed at tight glucose control reduces the risk of microvascular complications and probably, macrovascular disease as well. "Metabolic memory" and "legacy effect" are terms that have been used to describe the fact that glucose control early in the natural history of diabetes profoundly influences the prognosis later on in life. Most patients with type 2 diabetes ultimately require insulin to attain glycemic targets. Early use of insulin therapy can help normalize blood sugar and HbA_1C levels and thus enable patients to benefit from a favourable "metabolic memory" or "legacy effect". While there are several barriers to initiation of insulin therapy, most of these can be overcome by patient education and judicious use of new technology like newer insulins and insulin delivery devices.

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