Why and When to Treat Diabetes?

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ABSTRACT

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In spite of advances in therapy, the debilitating vascular complications of diabetes continue to occur. 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), awareness and knowledge regarding diabetes is grossly inadequate in India.2 We need to clearly emphasise on two basic questions in Diabetes management. Why to treat and when to treat?

These studies have important implications for preventing complications in diabetes. DCCT and UKPDS clearly demonstrated during '90s that intensive control of blood glucose is important in both Type 1 and type 2 Diabetes patients. Their follow up has demonstrated equally significant findings suggesting that early treatment is what matters in controlling complications. Attempts at intensive control later in the course of the disease are clearly not going to provide the same benefit as early intensive control. It's high time that we take note of this important public health message and start implementing early intensive control. The sooner the better.

Keywords: Diabetes mellitus, intensive control, early treatment, complications.

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According to the data released by International Diabetes Federation 366 million people had diabetes in 2011; by 2030 this will rise to 552 million. The number of people with type 2 diabetes is increasing in every country. 80% of people with diabetes live in low- and middle-income countries. Diabetes is quite a devastating disease. It caused 4.6 million deaths in 2011. The economic burden incurred is also huge accounting for at least USD 465 billion dollars in healthcare expenditures in 2011. The magnitude of the disease in India is gigantic with the country being the second largest nation in terms of diabetes prevalence (table 1).[1]

Table 1. Top 10 : Countries/territories of number of people with diabetes (20-79 years), 2011 and 2030

	Country / Territory	2011 Millions
1	China	90.0
2	India	61.3
3	United states of America	23.7
4	Russian Federation	12.6
5	Brazil	12.4
6	Japan	10.7
7	Mexico	10.3
8	Bangladesh	8.4
9	Egypt	7.3
10	Indonesia	7.3
	Country / Territory	2030 Millions
1	China	129.7
2	India	101.2
3	United States of America	29.6
4	Brazil	19.6
5	Bangladesh	16.8
6	Mexico	16.4
7	Russian Federation	14.1
8	Egypt	12.4
9	Indonesia	11.8
10	Pakistan	11.4

In spite of advances in therapy, the debilitating vascular complications of diabetes continue to occur. 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), awareness and knowledge regarding diabetes is grossly inadequate in India.[2] We need to clearly emphasise on two basic questions in Diabetes management. Why to treat and when to treat?

Why to treat Diabetes?

This question was answered long before through two

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elegant studies the DCCT and the UKPDS.

DCCT: The Diabetes Control and Complications Trial (DCCT), a major clinical study conducted from1983 to 1993, involved 1441 volunteers, ages 13 to 39, with type 1 Diabetes. DCCT showed that Intensive blood glucose control reduces risk of retinopathy by 76%, kidney disease by 50% and nerve disease by 60%. In participants who had some eye damage at the beginning of the study, intensive management slowed the progression of the disease by 54 per cent.[3]

UKPDS: The United Kingdom Prospective Diabetes Study (UKPDS) recruited 5102 patients with newly diagnosed type 2 diabetes in 23 centers within the U.K. between 1977 and 1991. Patients were followed for an average of 10 years to determine 1) whether intensive use of pharmacological therapy to lower blood glucose levels would result in clinical benefits (i.e., reduced cardiovascular and microvascular complications) and 2) whether the use of various sulfonylurea drugs, the biguanide drug metformin, or insulin have specific therapeutic advantages or disadvantages.

The UKPDS results establish that retinopathy, nephropathy, and possibly neuropathy are benefited by lowering blood glucose levels in type 2 diabetes with intensive therapy, which achieved a median HbA_{1c} of 7.0% compared with conventional therapywith a median HbA_{1c} of 7. 9%. The overall microvascular complication rate was decreased by 25%. For every percentage point decrease in HbA_{lc} (e.g., 9 to 8%), there was a 35% reduction in the risk of complications. A 16% reduction (which was not statistically significant, P = 0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death was observed. For every percentage point decrease in HbA_{lc} (e.g., 9 to 8%), there was a 25% reduction in diabetes-related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and nonfatal myocardial infarction.[4] The results of the UKPDS thus clearly reemphasized the need for intensive control in diabetes patients.

When to treat diabetes?

There is often lethargy in initiating treatment and maintaining glycemic control during early stages of Diabetes. Does this really matter? The follow up of DCCT and UKPDS provided clear answers.

EDIC: When the DCCT ended in 1993, researchers continued to study more than 90 percent of participants. The follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), assessed the incidence and predictors of cardiovascular disease events as well as diabetic complications related to the eye, kidney, and nerves. Following the DCCT, blood glucose levels in the intensive treatment group rose, and those of the conventional treatment group declined, so that blood glucose levels were now nearly the same between treatment groups. After 10 years, in the Epidemiology of Diabetes Intervention s and Complications (EDIC) follow-up in which the A1C levels had converged, the rates of retinopathy and proliferative retinopathy remained better than in the conventional group albeit the risk reduction was somewhat lower at 10 years than the initial 4 years. Diabetic nephropathy showed reduction of microalbuminuria, clinical albuminuria, and fewer cases of hypertension and kidney transplantation after 8 years. Diabetic neuropathy also fared well with a significant reduction of both somatic and autonomic neuropathy at 8 years of follow-up. During the 17 years of follow-up of the EDIC study, intensive therapy reduced the risk of any cardiovascular disease and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease. A beneficial effect of early intensive glycemic control was also shown for coronary calcification at 7–9 years and the progression of carotid intima-media thickness.[5-9] The following were the main findings of EDIC[10]

Table 2. 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,CVD death CVD = cardiovascular disease	57

Patients received the intensive therapy for an average of 6.5 years in the DCCT. More than 10 years after the DCCT ended, when both groups began receiving similar care, the benefits to the heart of the earlier treatment emerged. Moreover, the EDIC study found the benefits of tight glucose control on eye, kidney, and

nerve problems persisted long after the DCCT ended. Researchers call the long-lasting benefit of tight control "metabolic memory."[11]

UKPDS follow up

In post-trial monitoring of 5102 from UKPDS, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. Between-group differences in glycated hemoglobin levels were lost after the first year. In the sulfonylurea-insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), and risk reductions for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time, as more events occurred. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause(27%, P=0.002). The conclusion was 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 10 years of post- trial follow-up.[12] The beneficial effect of early intensive control on subsequent development of diabetes complications has been termed as the "legacy effect" by the UKPDS group.

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.[10] Other theories on the mechanisms of metabolic memory have been reviewed recently and include the idea that oxidative stress persists after normalization 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.[13]

What do the results of the EDIC an d UKPDS follow up studies mean for people with diabetes?

These studies have important implications for preventing complications in diabetes. DCCT and UKPDS clearly demonstrated during '90s that intensive control of blood glucose is important in both Type 1 and type 2 Diabetes patients. Their follow up has demonstrated equally significant findings suggesting that early treatment is what matters in controlling complications. Attempts at intensive control later in the course of the disease are clearly not going to provide the same benefit as early intensive control. It's high time that we take note of this important public health message and start implementing early intensive control. The sooner the better.

END NOTE

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