Introduction

Diabetes is a disease characterized by chronic hyperglycemia. Thus, it is logical to presume that tight control of blood glucose levels could tackle diabetes-related vascular complications. However, this remained a presumption till the publication of two landmark studies: the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). These two studies provided compelling evidence that glycemic control can prevent the onset and progression of diabetic microvascular complications like neuropathy, nephropathy and retinopathy. This article will focus on important research into the issue of glycemic control in diabetes, as diabetes is a disease characterized by hyperglycemia. Recently, the results of the follow up arm of the DCCT and the UKPDS have been published, and that too will be featured in this article.

Revisiting the UKPDS and the DCCT Studies

The DCCT studied type 1 diabetes, while the UKPDS was carried out in type 2 diabetes. Thus the DCCT randomized patients into intensive or conventional insulin therapy, while the UKPDS used oral drugs and insulin in a stepwise manner in conventional as well as intensive treatment arms. The DCCT studied 1441 subjects with type1 diabetes, randomized patients to receive either intensive or conventional glucose control, and followed them up for about 6.5 years. The UKPDS randomized 3867 patients to receive either intensive or conventional glucose control, and followed them up for 10 years. The reduction in hyperglycemia, as measured by the HbA1c was different in the two studies. In the DCCT, the HbA1c was 7.2 % in the intensive arm and 9.1% in the conventional arm. In the UKPDS, these values were 7% and 7.9% respectively. Thus the UKPDS studied a larger number of patients for a longer duration. However, intensive therapy could reduce the HbA1c better in the DCCT study.

How much did intensive glycemic control improve microvascular disease?

Both the UKPDS and the DCCT showed that tight glucose control can prevent the onset and progression of microvascular complications like neuropathy, nephropathy and retinopathy to a very significant extent. For example, here is a discussion on diabetic retinopathy: in the DCCT, intensive therapy prevented onset of retinopathy by 76%. In addition, the progression of retinopathy was prevented by 54%, risk of maculopathy was reduced by 23% and the risk of severe non-proliferative diabetic retinopathy (non-PDR) and PDR was reduced by 47%. As noted above, the HbA1c reductions in the UKPDS were less substantial than those in the DCCT. However, the UKPDS too showed that glycemic control would reduce the onset and progression of diabetic retinopathy in type 2 diabetes. In the UKPDS, all microvascular events were reduced by 25%, risk of retinal photocoagulation was reduced by 29%, vitreous hemorrhage was reduced by 23% and the occurrence of legal blindness reduced by 16%. Interestingly, in the UKPDS Study, intensive therapy even reduced the need for cataract extraction.

Does intensive insulin therapy result in side effects?

In both the UKPDS and the DCCT, intensive glucose control resulted in greater hypoglycemia. For instance, there were 43 extra episodes of hypoglycemia requiring assistance per 100

Table. Summarizing the UKPDS and the DCCT Studies

<table>
<thead>
<tr>
<th>Study Feature</th>
<th>DCCT</th>
<th>UKPDS</th>
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</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Type 1 diabetes</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Number</td>
<td>1441</td>
<td>3867</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>Intensive vs. conventional</td>
<td>Intensive vs. conventional</td>
</tr>
<tr>
<td>Medications used</td>
<td>Insulin only</td>
<td>Oral drugs and insulin</td>
</tr>
<tr>
<td>HbA1c difference</td>
<td>9.1 vs. 7.2%</td>
<td>7.9 vs. 7%</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>No change in short term*</td>
<td>No change in short term*</td>
</tr>
<tr>
<td>Microvascular Disease</td>
<td>Reduced in intensive arm</td>
<td>Reduced in intensive arm</td>
</tr>
</tbody>
</table>

*Note that in the follow up arm of the DCCT and UKPDS, macrovascular complications / cardiovascular event rates improved, showing a long term benefit of glucose control.
Does glucose control initially worsen retinopathy?

The DCCT clearly suggested that an “early worsening” of diabetic retinopathy can occur in subjects instituted on tight glycemic control. This early worsening of retinopathy was defined as a minimum 3-step progression of the severity of retinopathy, the new occurrence of cotton wool spots and/or intraretinal microvascular abnormalities, and retinopathy was termed as “clinically important retinopathy” in the DCCT if it occurred between baseline and the 12-month follow-up visit. In the intensive arm, early worsening of retinopathy was documented in 13.1% of 711 patients, while only 7.6% of 728 patients assigned to conventional treatment developed this deterioration. Remarkably, after 18 months, this early worsening in retinopathy reversed significantly. Eventually patients in the intensive-therapy arm fared better than those on conventional therapy. Importantly, identifiable risk factors for early worsening were higher baseline HbA1c levels and reduction of this level during the first 6 months following randomization.

What are the recent follow up DCCT/ UKPDS cohort results?

After the DCCT study was completed, this cohort was followed up in what was termed the EDIC Study (Epidemiology of Diabetes Complications and its Interventions). The follow up showed that the glucose control in the intensive group had worsened somewhat. Also, glucose control in the conventional therapy had improved. As a result the HbA1c values were comparable in the two groups after the study was stopped. However, subjects who had been randomized to receive intensive insulin therapy (in the past) had lower prevalence of retinopathy as well as other diabetic complications (including, macrovascular disease/cardiovascular events). This suggested that even a transient period of intensive glucose control (in the distant past) might still have benefits on diabetic complications even if such an intensive therapy is stepped down.

The follow up results of the UKPDS have been published recently. The results show that intensive glucose control became more lax after the study ended, while the treatment of the conventional group became more intense after the end of the study period. In other words, after this study on type 2 diabetes ended, the intensive group slowly increased its A1C levels and the conventional group slowly reduced its A1C levels. But remarkably, people who had been on intensive therapy still did better even 10 years after the study ended. The authors attribute this to the “legacy effect” of hyperglycemia. The term “legacy effect” signifies that even a short period of glucose control (in the distant past) will have benefits in the remote future, even if glucose control has become a little lax after the period of tight control. Unlike glycemic control, blood pressure control does not seem to have a legacy effect, but rather a more immediate/short term benefit in type 2 diabetes. Indeed, glycemic control started early and continued can, in the long term, even prevent cardiovascular events, as shown by the new UKPDS data.

Did the UKPDS studies give any insight into the natural history of diabetes?

The UKPDS showed that type 2 diabetes is a progressive disease. Over a period of time i.e. the 10-year study duration, the HbA1c levels tended to rise. This progression in the diabetic state was also attributable to failing beta cell function. The clinical implication is that a stepwise escalation of oral drugs and eventually insulin will be required to prevent unnecessary exposure of the patient’s tissues to hyperglycemia.

What was the effect of blood pressure lowering on diabetic complications?

The UKPDS showed that blood pressure control can favorably impact microvascular and macrovascular complications. The UKPDS randomized 1,148 subjects with hypertension in addition to their type 2 diabetes to receive either of the following 2 regimens: a less tight blood pressure (BP) control regimen or a tight blood pressure control regimen. The less-tight BP control and the tight group achieved mean blood pressure readings of 154/87 mm Hg and 144/82 mm Hg respectively over a median duration of 8.4 years. The tight BP control regimen reduced microvascular endpoints by 37% (p=0.0092), risk of any diabetes-related endpoint by 24% (p=0.0046), and stroke by 44% (p=0.0013). Tight BP control even reduced the prevalence of deterioration of visual acuity by 47% (p=0.0036). This suggested that tight BP control resulted in less diabetic maculopathy. Thus the UKPDS study definitely suggests that blood pressure control is important in tackling diabetic retinopathy.

What is the recent controversy on target HbA1c?

The last year saw the publication of the ACCORD study, which showed an increase in cardiovascular death in subjects on intensive control. While a similar study called ADVANCE (with significant differences too) study showed no significant cardiovascular risk, the issue of glucose control has become a matter of debate. This is especially true after a third study, called the VADT study showed that very intensive glucose control can have no significant benefits on cardiovascular mortality. It is increasingly being known that hypoglycemia can adversely affect cardiac events, and it is obvious that tighter the control is, more is the risk of hypoglycemia. Thus, it is the author’s opinion that in subjects who are older, have longstanding diabetes and significant risk factors for cardiovascular risk, very aggressive glucose control may
not benefit, and may even increase cardiovascular risk. In younger subjects, with recent onset diabetes and few or no cardiovascular risk factors, strict glucose control started early on could prove beneficial in the long run. What then, is the ideal A1C to aim for? Again, in the author’s opinion, the American Diabetes Association-recommended target of <7% seems more reasonable compared with the stricter recommended by other reports.

References


10. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research, G., Retinopathy and Nephropathy in Patients with Type 1 Diabetes Four Years after a Trial of Intensive Therapy. NEJM 2000:381-389.