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Review

Landmarks in the field of diabetes

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Many advances have occurred in field of diabetes in the past 25 years which have changed our practice of diabetes management. Changes like human insulin, insulin delivering devices, insulin pumps and glucometer along with DPP-IV inhibitors that have placebo like tolerability have revolutionized the treatment of diabetes. Studies like DCCT (Diabetes Control and Complications Trial), UKPDS (United Kingdom Prospective Diabetes Study), Finnish study and FINMONICA have changed our thinking and consequently the management of diabetes. It would be interesting to know what changes are of clinical relevance in the modern practice of diabetes.

Key words: DCCT (Diabetes Control and Complications Trial), UKPDS (United Kingdom Prospective Diabetes Study), FINNISH diabetic studies.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease; in 2002, the per-capita cost of health care was $13,243 for people with diabetes, while it was $2560 for those without diabetes. Rates of diabetes are increasing worldwide. At least 171 million people currently have diabetes, and this figure is likely to more than double to 366 million by 2030 (Laditka et al., 2001). The top 10 countries, in numbers of people with diabetes, are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh. The greatest percentage increase in rates of diabetes will occur in Africa over the next 20 years. However, at least 50% of people in Africa with diabetes are undiagnosed, and many in their 30s to 60s will die from diabetes.

The past 25 years have seen many developments in diabetes that have changed the concept and management of diabetes. It would be interesting to know what changes have profoundly altered the management of diabetes. Changes of great importance are:

1. DCCT: The Study That Forever Changed the Nature of Treatment of Type 1 Diabetes (1993).
2. United Kingdom Prospective Diabetes Study (UKPDS, 1996).
3. Epidemiology of Diabetes Interventions and Complications (EDIC, 2003).
4. Diabetes as a cardiovascular disease equivalent. (1998) Thiazolidinedione - A promise unfulfilled GLP I analogues and DPP-IV inhibitors.
5. Advent of human insulin, insulin analogues and insulin delivering devices and portable glucometers.

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DCCT: THE STUDY THAT FOREVER CHANGED THE NATURE OF TREATMENT OF TYPE 1 DIABETES (1993) {IMPLICATIONS OF THE UKPDS, 2002}

DCCT was designed as a carefully conducted, prospective, randomized controlled clinical trial - with sufficient statistical power - to determine whether intensive treatment, with the goal of maintaining blood glucose concentrations close to the normal range, could decrease the frequency and severity of diabetic microvascular complication.

A total of 1,441 subjects with type 1 diabetes were enrolled. The results show unequivocally that intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy in patients with type 1 diabetes. Importantly, in the DCCT, there was not a "glycaemic threshold;" rather, there was a continuous relationship between glycaemic exposure and risk of complications.

Therefore, intensive therapy, with the goal of achieving glucose levels as close to the nondiabetic range as possible, should be employed in most patients with type 1 diabetes. As this study was carried out in type 1 DM and for microvascular complication of DM there was a need to study further for type 2 DM and macrovasucular complication.

UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS) (DCCT, 1987)

The United Kingdom Prospective Diabetes Study (UKPDS) recruited 5,102 patients with newly diagnosed type 2 diabetes in 23 centers within the U.K. The UKPDS was originally designed as a straightforward randomized clinical trial comparing the effects of an “intensive treatment policy” with four pharmacological monotherapies, versus a diet control group, on the cardiovascular and microvascular complications of type 2 diabetes.

The UKPDS results confirm and extend previous evidence supporting the hypothesis that hyperglycemia and its squeals are a major cause of the microvascular complications of diabetes. The risk gradient in the UKPDS for late microvascular events was very similar to that seen in the DCCT for early microvascular events. This indicates that the presence of hyperglycemia is a toxic state whether it occurs early or late in life and irrespective of its underlying cause.

The UKPDS also demonstrated by epidemiological analysis that cardiovascular outcomes were consistently associated with hyperglycemia in a manner similar to the relationship between microvascular complications and hyperglycemia. Nonetheless, the UKPDS did not prove definitively that intensive therapy that lowered blood glucose levels reduced the risk of cardiovascular complications compared with conventional therapy. Thus, the role of hyperglycemia in cardiovascular complications was still unclear. The results of the UKPDS blood pressure study also indicate that aggressive treatment of even mild-to-moderate hypertension is beneficial. Moreover, continued reduction of blood pressure into the normal range resulted in fewer complications. Hence, blood pressure should be kept below 130/85 mmHg, as previously recommended by the American Diabetes Association and others. Initially this appears to be strange conclusion; why should a metabolic disorder affecting CHO, proteins and fat metabolism have complications decreased by tight blood pressure control? But when you realize that macrovascular disease is due to accelerated atherosclerosis brought about by, it is no longer surprising that reduction of blood pressure controls macrovascular disease.

The results of UKPDS were notable for two things: The first mentioned that UKPDS results established that retinopathy, nephropathy, and neuropathy are benefited by lowering blood glucose levels in type 2 diabetes with intensive therapy; the overall microvascular complication rate was decreased by 25%. The second showed that aggressive control of even mild hypertension is beneficial and easier to achieve than control of hyperglycemia which tends to slip over time.

Neither UKPDS nor DCCT gave a definitive answer to the question of whether glucose control reduces the risk of cardiovascular disease.

EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC, 1999)

At the end of the DCCT, although the care of all patients was transferred to their own physicians, most were also enrolled in EDIC study, an observational study to assess the long-term outcomes in subjects who had participated in the DCCT. The main conclusions were as follows:

1. Intensive therapy aimed at achieving glycemic levels as close to the non-diabetic range as safely possible reduces the development and progression of all diabetes-specific complications by as much as 76%.
2. Intensive therapy reduces measures of atherosclerosis over time, and probably reduces cardio-vascular diseases (CVD) events as well.
3. Intensive intervention is most effective when implemented early in the course of diabetes; if intensive intervention is delayed, the momentum of complications is harder to slow, as shown by the results of the secondary intervention group.
4. The salutary effects of a 6.5-year mean period of intensive therapy persist for at least 10 years after differences in glycemia between the original intensive and conventional therapy groups have disappeared (metabolic memory).
5. Chronic glycemia and duration of diabetes are the major factors in the pathogenesis of microvascular complications in type 1 diabetes and play a role in the development of atherosclerosis.

The EDIC follow-up study showed the perhaps somewhat surprising result that the beneficial effects of improved glycaemic control are sustained even after there is some slippage in the degree of control attained, and that the adverse effects of hyperglycaemia continue even when there is subsequent improvement in glycaemic control. These observations suggest either that there is some sort of 'metabolic memory' or that once the processes leading to microvascular complications are initiated, then they are self-perpetuating. The lesson is that patients should strive for the best possible control as early as possible in the course of the disease, ideally from the time of diagnosis of their diabetes.

DIABETES AS A CARDIOVASCULAR DISEASE EQUIVALENT: FINNISH STUDY (Steven et al., 1998) AND FINMONICA (Miettinen et al., 1998)

Nearly 65% of deaths among diabetics are directly attributable to vascular disease, and type 2 diabetes is associated with a two- to fourfold increased risk of CHD. In 1998 seminal work done by Steven (Finnish study) stated that the impact of heart disease on people with diabetes is significant. The results showed the seven year incidence rates of myocardial infarction in non-diabetic subjects with and without prior myocardial infarction at base line were 18.8 and 3.5 percent, respectively (P<0.001).The seven-year incidence rates of myocardial infarction in diabetic subjects with and without prior myocardial infarction at base line were 45.0 and 20.2 percent, respectively (P<0.001). Put simply diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as non-diabetic patients with previous myocardial infarction.

In addition it was recently shown that the one-year case fatality rate for a first myocardial infarction (from the onset of symptoms, thus including prehospitalization mortality) in the population studied in the Finnish. Monitoring International Cardiovascular Disease (FINMONICA) trial was 45 percent in diabetic men and 39 percent in diabetic women. These case fatality rates were significantly higher than the rates in non-diabetic subjects (38 percent for men and 25 percent for women). Of the diabetic subjects who died, 50 percent of men and 25 percent of women died before hospitalization. These patients, by definition, could not benefit from secondary prevention strategies, indicating (especially in diabetic men) that aggressive management of cardiovascular risk factors in diabetic subjects should precede the onset of clinical coronary heart disease.

This led to the concept that if you want to prevent death in diabetes you would have to institute the same measures as of a patient suffering from heart attack .This contributed to the use of aspirin, ACE inhibitors and statins in the management of diabetes and the slogan--Having diabetes is like having a heart attack.

THIAZOLIDINEDIONE - A PROMISE UNFULFILLED

Both, impaired beta-cell function and insulin resistance, predominantly of the skeletal muscle, are considered to be the key factors in the pathogenesis of type-2 diabetes (non-insulin-dependent diabetes; NIDDM). In the early stage of the disease, impaired insulin-mediated glucose disposal is accompanied by increased insulin secretion and hyperinsulinaemia. The thiazolidinediones, by improving insulin sensitivity of target tissues, appear to be a novel pathophysiologically interesting approach for the treatment of patients with NIDDM or impaired glucose tolerance. Thiazolidinediones mainly elicit the following actions: Enhancement of insulin-mediated glucose disposal in patients with insulin resistance, impaired glucose tolerance and NIDDM, reduction of hyperglycaemia (blood glucose; HbA1c) and concomitant hyperinsulinaemia, improvement of dyslipidaemia in NIDDM.

Troglitazone, the first approved drug in this class, has been shown to decrease plasma glucose levels as monotherapy but is more effective in combination with sulphonylureas, metformin, or insulin. However, despite its generally good safety profile, troglitazone has been associated with severe idiosyncratic hepatocellular injury. There have been more than 150 spontaneous reports of serious hepatic events, including at least 25 instances in which patients died or required a liver transplant. The drug has therefore been banned.

Rosiglitazone the second approved drug has also been banned because of unacceptable cardiovascular mortality (The Rosiglitazone Controversy, 2007). At present only pioglitazone remains on the scene-for how long anybody's guess .It is is reported to be safe and well tolerated, though it is being investigated by the US FDA for renal carcinoma.

Since combination therapy is increasingly important in type 2 diabetes management following failure of monotherapy because complementary mechanisms of action of the different classes of oral agents demonstrate synergistic effects when used in combination. Oral agents may also be used as adjuncts to insulin for achieving glycaemic control. The overall reduction in HbA1c is modest about 1. It is moderately effective in controlling hyperglycemia with side effect like fluid retention, anemia and redistribution of adipocyte mass.

Chances are that glitazones would be confined to the footnotes of history unless more potent and less toxic drugs are produced.

GLP I ANALOUGES AND DPP-IV INHIBITORS (Ahrén et al., 2004)

Glucagon-like peptide (GLP-1) is a potent glucoregulatory hormone that is released from intestinal L cells into the circulation in response to nutrient ingestion and neural and endocrine stimuli. GLP-1 modifies glucose homeostasis through actions that include potentiating of glucose-stimulated insulin secretion and biosynthesis and suppression of glucagon secretion, gastric emptying, and food intake. GLP-1 may also enhance insulin-independent glucose disposal in the peripheral tissues. The abilities of GLP-1 to stimulate insulin secretion and inhibit glucagon release are glucose-dependent; thus, the risk of hypoglycemia with GLP-1 administration is low. GLP-1 also increases beta-cell mass in preclinical models of diabetes through mechanisms that include stimulation of beta-cell proliferation and neogenesis and inhibition of beta-cell apoptosis. More recent studies in both animals

and humans indicate that GLP-1 may also play a protective role in the cardiovascular system.

The actions of GLP-1 have generated substantial interest in using this peptide as a therapeutic agent for the treatment of type 2 diabetes (Marre et al., 2009). However, the therapeutic potential of native GLP-1 is limited by its very short plasma half-life (approximately 90 seconds). This is due to both rapid inactivation by the ubiquitous proteolytic enzyme dipeptidyl peptidase (DPP-IV) and renal clearance. Consequently, long-acting, DPP-IV-resistant GLP-1 analogs have been developed for clinical use, including exenatide (*Byetta*), liraglutide, CJC-1131, AVE010, and LY548806. These drugs are GLP-1 mimetics that bind to GLP-1 receptors with similar affinity and produce biological actions identical to those of native GLP-1 but are resistant to DPP-IV-mediated inactivation and renal clearance. These compounds are able to exert more sustained GLP-1-like activity for longer periods of time in vivo.

An alternative therapeutic approach for prolonging the action of native GLP-1 is to inhibit DPP-IV activity, thereby preventing GLP-1 degradation. Several orally active agents like sitagliptin, vildagliptin and saxagliptin that inhibit DPP-IV activity are being marketed for the treatment of type 2 diabetes and many more are in the pipeline. These hypoglycemic agents not only efficient in reducing hyperglycemia but also have the ability to preserve the beta cells. When combined with metformin this agent becomes a formidable weapon in controlling diabetes. It will not be an exaggeration to say that in time to come DPP-IV inhibitors alone or in combination would be the drug of first choice in diabetes.

ADVENT OF HUMAN INSULIN, INSULIN ANALOGUES AND INSULIN DELIVERING DEVICES

As regard human insulin, we were injecting bovine and porcine insulin for well nigh 60 years from 1924-1984. No major complications have ever ensued other than a progressively increasing dose and increasing anti-insulin antibody titer. No trial has ever shown that human insulin has increased longevity of life over bovine and porcine insulin. Other than the argument that humans should be injected with human insulin if available, this development of human insulin does not appear to be a real advance.

Insulin analogues have not really benefited the vast majority of humans because of their cost. No trial has ever shown their supremacy over conventional human insulin in reducing microvascular or macrovascular complications of diabetes. All that has ever been shown is a better control with less side effects (hypoglycemia and lipodystrophy). But whether it translates into a reduced mortality is a million dollar question that will take not less than 20 years to be answered.

However, advent of 30 gauge plastic disposable syringe with fixed needle (B.D) has been a boon for people who were on injection with glass syringe and 26 gauge needle. Fixed needle syringe allowed the manufacturer to give a 30 gauge needle so that pain became less. This needle also prevents infection occurring over needle prick sites because of its disposable nature. Further advance resulted in the development of insulin pens over the standard syringe and vial because pens are more convenient and more accurate. Pre-filled disposable pens are easiest of them all, because one does not install a new cartridge when the pen is empty– just toss it out .Pens can be carried in the pockets and used when required. Finally Insulin pumps were developed to avoid repetitive subcutaneous injections. The pump itself is essentially a device that holds a syringe filled with insulin. Insulin delivery is exquisitely controlled by a mechanism that pushes the plunger of a syringe down to infuse insulin into the subject *via* an infusion set. The infusion set is attached to a straight or bent needle or a Teflon catheter that has been designed for optimal function and comfort. This is inserted into the subcutaneous tissue, most often of the abdomen, but potentially of the upper legs or arms, or of the buttocks.

ADVANTAGES OF PUMP THERAPY

i. More physiologic
ii. Less variable insulin absorption
iii. Better match between insulin and food
iv. Greater lifestyle flexibility
v. Easier to travel - improved portability

The insulin pump is an open-loop system that has two concurrent modes of insulin delivery continuously through basal infusion and intermittently through bolus insulin delivery. Insulin replacement can be provided in a near physiologic fashion, integrating both lower basal insulin secretion and higher postprandial requirements. Insulin pumps have provided additional flexibility of modifying basal insulin replacement in response to circadian rhythms. Moreover, it can be preprogrammed to decrease during exercise and increase during times of inactivity**.**

Glucometer

Since approximately 1980, a primary goal of the management of type 1 diabetes and type 2 diabetes mellitus has been achieving closer-to-normal levels of glucose in the blood for as much of the time as possible, guided by SMBG (Self monitoring blood glucose levels) several times a day. The benefits include a reduction in the occurrence rate and severity of long-term complications from hyperglycemia as well as a reduction in the short-term, potentially life-threatening complications of hypoglycemia. Portable, economical meters with economical glucose strips have saved many lives besides

besides reducing the drudgery of repeated laboratory investigations.

What is the author's wish for good diabetes control? A simple, safe, single drug that controls hyperglycemia, microvascular and macrovascular complication.

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