Newer Developments in Epidemiology and Treatment of Diabetes

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Epidemiology of Diabetes – India Scenario

Type 2 diabetes, currently affecting 5% to 10% of most populations, has become the most frequently encountered metabolic disorder in the world; its prevalence is growing more rapidly among developing nations, primarily due to the rapid demographic and epidemiological transitions occurring in these countries as a consequence of urbanization, industrialization, and globalization.[331,332] The epidemiology of diabetes in India, the second largest country with a population of over 1 billion, is of prime importance as the prevalence of diabetes is growing rapidly not only in urban but also in rural areas. According to a recent World Health Organization (WHO) report, India has the highest number of people with diabetes in the world, with an estimated 32 million in 2000 which is set to increase to a staggering 80 million i.e., an increase of 160% by the year 2030.[333] Earlier epidemiological studies conducted in India have documented a rising prevalence of diabetes in India,[334,335] and have compared data from different regions of India or different parts within a state.[336] The first authentic data on prevalence of diabetes in India came from a multicenter study (Ahmedabad, Calcutta, Cuttack, Delhi, Poona, Trivandrum) conducted by the Indian Council of Medical Research (ICMR) in the early 1970s reporting a prevalence of 2.3% in the urban and 1.5% in the rural areas.[336] Another study conducted in Orissa state, India, has also shown that diabetes prevalence was significantly higher in the urban areas compared to the rural areas.[336] The figure in the urban areas has rapidly climbed to 12-16% (Figure 3), representing a 600-800% increase in prevalence rates over a 30-year period.[337,338] Even in urban India, the prevalence in the southern part of India was found to be higher, at 13.5% in Chennai, 12.4% in Bangalore, and 16.6% in Hyderabad; this compares with eastern India (Kolkata), 11.7%; northern India (New Delhi), 11.6%; and western India (Mumbai), 9.3%.[338]

In a cross-sectional population survey conducted in Kashmir Valley, it was observed that 1.89% of the general population have known diabetes, 4.25% have undiagnosed diabetes and 8.09% have impaired glucose tolerance, taking the total load of abnormal glucose tolerance to 14.23%.[339]

In the recent Prevalence of Diabetes in India Study (PODIS), the standardized prevalence rates for diabetes in the total Indian, urban and rural populations using WHO 1999 criteria were 4.3%, 5.9% and 2.7%, respectively.[340] In the same study using ADA 1997 criteria, the age and gender standardized prevalence rate for diabetes in the total Indian population was 3.3%. The standardized prevalence of diabetes in urban areas was significantly higher (4.6%) than that for the rural population (1.9%).[341] It may not be possible to account for the differences in figures from the more experienced Chennai center and the newly found PODIS (Editor) In Another study done to determine the temporal changes in prevalence of diabetes in an Indian rural population reported that a three-fold increase in age and sex adjusted prevalence of diabetes (from 2.20% to 6.36%) was seen in 2003 when compared with a similar study done 14 years before, attributing this increase to demographic transition due to improved living conditions in rural India.[342]

Increase in the prevalence of type 2 diabetes may also result due to migration (a move from one environment to another, either external or internal), which brings with it marked social and cultural changes.[343] Many epidemiological studies of diabetes in migrant populations, mostly in people originating from developing countries, have reported a higher prevalence of diabetes,[344] and higher odds of being diabetic despite lower rate of obesity,[345] than the host populations of those countries.

In addition there also appears to be a temporal shift, with younger ages being affected more in recent

times. It is well known that Asian Indians develop diabetes 1-2 decades earlier than Europeans.[346] Among those with diabetes the age at diagnosis in CURES as of now is highest below 40-49 years (30.4% vs 292) while in the west the highest proportion is observed at 60-70 years of age.

Newer Developments In Diabetes Treatment

Prior to the 1920s, a patient with type 1 diabetes had a grave prognosis with a rapid downhill course and survival was possible only for about 6 months to 2 years. The discovery of insulin and its introduction as therapy for type 1 diabetes in the early 1920s was understandably thought to have resolved the management of this disorder. However, within a few decades, increased morbidity and mortality due to diabetes complications necessitated more appropriate management. Since then, a wide range of new pharmacologic approaches are emerging for better control of hyperglycemia and takes care of many other facts of diabetes.

Advances in Insulin Therapy

Insulin therapy has been strongly influenced by the results of the Diabetes Control and Complications Trial (DCCT)[21,22] and the United Kingdom Prospective Diabetes Study (UKPDS),[23] both of which support intensive antidiabetic therapy. Conventional insulin therapy, due to the inability of achieving tight glycemic control in people with diabetes, which is crucial to reduction of risk of long term complications associated with diabetes. In recent years, insulin analogs that simulate normal insulin secretion better have become available for better control of hyperglycemia and takes care of many other facts of diabetes.

Insulin analogues

Recombinant DNA technology has now made it possible for the production of analogues of human insulin with altered pharmacokinetic characteristics.[346] Recently three short-acting (lispro, aspart and glulisine) and two long-acting (glargine and determir) recombinant analogues of regular human insulin have been developed.[347]

Rapid-acting analogues

These are also known as rapid-onset and ultra-short-acting insulin. The first insulin analogue approved for use was insulin lispro, which became commercially available in August 1996. It has been demonstrated that when compared with regular human insulin, insulin lispro is safe and more efficient[348] and it was shown to reduce postprandial hyperglycemia in both type 1 and type 2 diabetes.

Another short acting insulin analogue Aspart, with an action profile similar to that of insulin lispro, received Food and Drug Administration (FDA) approval in 2001.[349] Studies carried out in patients with type 1 diabetes have shown that substituting insulin aspart for regular human insulin (RHI) in various insulin regimens can result in smaller postprandial glycemia excursions, lower A_{1c} levels, and fewer episodes of severe hypoglycemia.[350,351]

Insulin glulisine, a novel and recently approved rapid-acting insulin analogue, mimics the pharmacokinetic and pharmacodynamic profiles of physiological human insulin, but has a rapid onset, peak effect at 1h, and a shorter duration of action (~ 4h).[352] Compared with RHI, glulisine has a more rapid onset of action and a shorter duration of action thus requires less mealtime adjustment.[353]

Dailey et al[354] compared the safety and efficacy of glulisine with RHI in combination with Neutral Protamine Hagedorn (NPH) insulin and demonstrated that glulisine (twice-daily) associated with NPH provides small and statistically significant improvements in glycemic control compared with RHI in patients with type 2 diabetes who are already relatively well controlled on insulin alone or insulin plus oral drugs.

Long- acting analogues

Two new long-acting insulin analogues have come to the market. Long-acting analogues were created by substituting and adding amino acids to the insulin molecule (glargine) and by adding a fatty acid, which enhances binding to albumin (determir).

Insulin glargine, the first long-acting basal insulin analogue indicated for subcutaneous administration in adults with type 1 or type 2 diabetes mellitus and pediatric patients aged ≥ 6 years with type 1 diabetes, has a slower onset of action than NPH insulin and a longer duration of action with no peak in activity. In addition it also has a lower incidence of hypoglycemia, blissfully nocturnal hypoglycemia compared with NPH insulin.[355,356]

Insulin determir, a soluble long-acting human insulin analogue, provides slow absorption and a prolonged and consistent metabolic effect of upto 24 hours in patients with type 1 or type 2 diabetes mellitus. It has a more predictable, protracted, and consistent effect on blood glucose than NPH insulin,

with less intrapatient variability in glycemic control than NPH or glargine insulin.[357] A study done to investigate the pharmacodynamic profile and duration of action for five subcutaneous doses of insulin detemir and one subcutaneous dose of NPH insulin concluded that detemir showed a linear dose response over a range of clinically relevant doses and in addition provides a flat and protracted pharmacodynamic profile.[358]

The main advantages of these analogues are their long, peakless action and a lower incidence of hypoglycemia.

Advances in Oral Medication

Earlier selecting on oral agent for the treatment of type 2 DM was as simple as choosing which sulfonylurea (SU) to use. Presently, a variety of newer agents with unique mechanisms of action and several combinations have been available for use as monotherapy or in combination regimens with insulin. Three ways in which these agents work toward improving glycemic control include, increasing insulin secretion (insulin secretagogues), increasing insulin action (insulin sensitizers), and decreasing carbohydrate adsorption (inhibitors of glucose absorption).[363]

Insulin secretagogues

Sulfonylurea compounds (SUs) were the first available oral antidiabetic agents and they remain an important tool in the pursuit for optimal glycemic control. Second generation SUs (glyburide, glipzide and glimepiride) are considered more potent and safer than the first generation SUs.[364] Non-SU Secretagogues include repaglinide and nateglinide released in 1999 and 2001 respectively and they are a different class from SUs. Repaglinide is a member of the meglitinide family and nateglinide, a derivative of phenylalanine. Repaglinide is a short-acting drug that increases insulin secretion and its advantages include shorter half-life, less episodes of hypoglycemia, however ,multiple dosing and costs are the disadvantages for general use. Nateglinide is a rapidly acting short-duration insulinotropic agent that stimulates insulin release in a glucose-dependent manner.[365] The main difference between Non-SUs and the SUs is the rapidity and duration of stimulation of insulin secretion.

The drugs on the horizon under this category include the gut-derived hormones (incretins), which are released after meal ingestion and stimulate insulin secretion postprandially. In humans, glucose-dependent insulinotropic polypeptide (GIP) and glucagons-like peptide-1 (GLP-1) are the most important incretins. The potential use of these insulinotropic gut peptides for the treatment of diabetes has been considered and among these GLP-1 has been most successful, which exerts antidiabetogenic properties in subjects with type 2 diabetes.[366] Under hyperglycemic conditions in humans, GLP-1 stimulates insulin secretion and normalizes blood glucose levels. GLP-1 does not cause hypoglycemia as it does not stimulate insulin secretion at normal glucose levels. Furthermore, it inhibits glucagon secretion and delays gastric emptying. In vitro and animal data have demonstrated that GLP-1 increases beta-cell mass by stimulating islet cell neogenesis and by inhibiting the apoptosis of islet cells. In addition, GLP-1 simulates satiety by acting as a transmitter or by crossing the blood brain barrier to act on the hypothalamus.[367]

The hormonal action of GLP-1 is rapidly terminated as a consequence of enzymatic cleavage by dipeptidyl peptidase IV (DPP IV), making it unattractive as a therapeutic agent because of the very short half-life. Recent clinical evidence has shown that either infusion of GLP-1 or inhibition of DPP IV can result in dramatic reductions in plasma glucose concentrations, reductions in HbA_{1c} and improvement in pancreatic β-cell function. Thus, both represent potential targets for the prevention of the hyperglycemia associated with diabetes and impaired insulin function. Thus, the use of inhibitors DPP IV-resistant GLP-1 receptor agonists, such as liraglutide (NN2211) or exendin-4 (exenatide), that are resistant to degradation, called 'incretin mimetics', and the use of inhibitors of DPP IV, such as NVP DPP728, P32/98 and K579 are being investigated in clinical trials. A second generation DPP IV inhibitor viladagliptin (LAF237), sitagliptin (MK-0431) and saxagliptin (BMS- 477118) are also currently explored in clinical investigations.[366,367]

Insulin sensitizers

The insulin-sensitizing biguanides and thiazolidinediones (TZDs or glitazones) are used to combat insulin resistance and are indicated for type 2 diabetes.[368] The agents currently available in the class of insulin sensitizers are rosiglitazone and pioglitazone. They are used in monotherapy or in combination with metformin, sulfonylurea, or insulin. Metformin is likely the initial treatment of choice for most patients with type 2 diabetes for a variety of

reasons. By improving insulin sensitivity, it also improves a variety of other factors related to increased cardiovascular risk.[369] The actual mechanism of action is not fully known, but its main effect is to decrease hepatic gluconeogenesis, thus improving fasting hyperglycemia.[370] The main side effect of metformin is gastrointestinal intolerance, which occurs in approximately 30% of patients.[371]

The TZDs, a relatively newer class of antidiabetic agents, have been shown to be efficacious in reducing glucose concentrations, maintaining glycemic control, and improving other cardiovascular risk factors including reduction of visceral adiposity, alteration of lipoprotein concentrations with a favorable distribution of cholesterol subfractions, and decreasing markers of inflammation and endothelial dysfunction.[372] It has been well-documented that TZDs improves insulin sensitivity and beta-cell function, both in monotherapy and in combination with other oral antidiabetic agents.[373] In addition to clinically approved TZDs, new agonists of the peroxisome proliferators activator receptor gamma (PPAR gamma) are being identified to selectively improve insulin actions, and dual agonists of PPAR gamma and PPAR alpha are being evaluated for enhanced control of hyperglycemia and dyslipidemia.[374]

Inhibitors of glucose absorption

The alpha-glucosidase inhibitors including acarbose or miglitol delay intestinal absorption of ingested carbohydrates and have the potential to improve glycemic control in type 2 diabetes mellitus.[375] Another drug for inhibition of glucose absorption is voglibose. Vichayanrat et al[376] studying the efficacy and safety of voglibose and acarbose in type 2 diabetes patients demonstrated that both of these significantly decreased HbA_{1c}, PPBG and postprandial insulin levels while voglibose was associated with less gastrointestinal side effects with slightly less efficacy for postprandial glucose reduction.

Glucagon suppressor

Amylin, a peptide neurohormone that is co-secreted with insulin from the pancreatic beta cells in response to meals suppresses glucagons secretion, slows gastric emptying, and decreases food intake.[377] In particular, amylin appears to have important actions in controlling prandial glucose homeostasis. It inhibits postprandial glucagons secretion and delays gastric emptying thereby modifying postprandial hyperglycemia in diabetic individuals which apparently leads to overall glycemic control without a concomitant increase in the number of severe hypoglycemic episodes. Moreover, it also acts as a satiety agent. Amylin replacement may therefore improve glycemic control in diabetes mellitus. However, human amylin exhibits physicochemical properties predisposing the peptide hormone to aggregate and form amyloid fibres, which makes it unsuitable for pharmacological use. A stable amylin analogue, pramlintide, with actions and pharmacokinetic and pharmacodynamic properties similar to the native peptide is in advanced clinical trial.[378]

Combination therapy

For type 2 diabetes patients, oral monotherapy may be initially effective for controlling blood glucose, but it is associated with a high secondary failure rate. By taking advantage of differing mechanisms of action, combination therapy (eg. sulfonylurea plus metformin, a thiazolidinedione, or acarbose, metformin plus a thiazolidinedione or acarbose) is evolving as a means of optimizing glycemic control in patients in whom a single agent or insulin is inadequate.[379-381] A single-tablet insulin resistance minimizing hyperglycemia and vascular risk in type 2 diabetes.[382] Currently triple combination therapy is being closely studied. Kaye et al[383] evaluated the efficacy of addition of a TZD as a third agent to sulfonylureas in diabetic patients not adequately controlled on two drug combinations, resulting in 1.4% decrease in HbA_{1c}. The addition of a TZD as a third agent to sulfonylureas plus metformin was reported to be beneficial in about 60% of type 2 diabetic patients.[384] In another study conducted in 38 Greek diabetic patients who were inadequately controlled on maximum doses of glimepiride and metformin, rosiglitazone was added, which led to a 1.4% reduction in HbA_{1c}.[385] Although triple combination therapy has the potential to enhance glycemic control, it is not without limitation and the strategy needs further investigations.

In summary, diabetes having reached epidemic proportions is contributing to considerable morbidity and mortality due to microvascular and macrovascular complications. The pharmacologic tools currently available and capable of allowing most patients with type 2 diabetes to achieve good metabolic control thereby reducing the risk of developing diabetes associated complications.

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