

Recent Advances in Management of Diabetes Mellitus

Mohammad Ashraf Ganie, Suman Kotwal

Department of Endocrinology,
Sher-i-Kashmir Institute Medical Sciences, Srinagar, J&K, India

Abstract: Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. There is an increase in the prevalence of type 1 diabetes also, but main cause of diabetic epidemic is type 2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. Future drug therapy of T1DM will depend on the success of ongoing and planned intervention trials. Immunomodulation alone, or possibly combined with immunosuppressive therapy, seems to be promising in reducing the loss of C-peptides after diagnosis. Studies of the function of the human immune system lag behind that of the mouse and rat. Since 2001, Trial Net, an international network of clinical research groups supported by the National Institutes of Health, has established an infrastructure for trials for predicting and preventing T1DM.

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. There is an increase in the prevalence of type 1 diabetes also, but main cause of diabetic epidemic is type 2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. According to World Health Organization (WHO) reports, India had 32 million diabetic people in the year 2000¹. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025². The majority of cases of diabetes fall into two broad etiopathogenetic categories now called type 1 and T2 DM.

The etiologic classification of diabetes mellitus currently recommended by WHO and the ADA in 1997.

DIAGNOSIS AND CLINICAL PRESENTATION

Type 1 DM: Type 1 diabetes mellitus, results from insulin deficiency following destruction of the insulin-producing pancreatic beta cells. It most commonly presents in childhood but one-fourth of cases are diagnosed in adults. The incidence of type 1 diabetes varies depending upon various factors like age, family history, environmental factors etc. Incidence rates in children <14 years ranging from 0.1/100,000 per year in China to 37/100,000 per year in Finland³. The incidence of childhood type 1 disease is rising worldwide, with reported annual increases of 2 to 5 percent in Europe, the Middle East, and Australia⁴. Type 1A diabetes mellitus results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. In genetically susceptible subject, this process is probably triggered by one or more environmental agents. Type 1B diabetes mellitus refers to non-autoimmune islet destruction.

Type 1 diabetes can present in several different ways⁵. Classic new onset, diabetic ketoacidosis or as asymptomatic incidentally discovered diabetes. Classic new onset presents as hyperglycemia without acidosis. Symptoms are caused by hyperglycemia and include polyuria, polydipsia, and weight loss despite increased appetite initially. Children with type 1 diabetes often present with diabetic ketoacidosis (hyperglycemia and ketoacidosis). The International Society for Pediatric and Adolescent Diabetes (ISPAD) in 2007 defined the following biochemical criteria for the diagnosis of DKA⁶; Hyperglycemia, blood glucose of >200 mg/dL (11 mmol/L) a metabolic acidosis, defined as a venous pH <7.3 and/or plasma bicarbonate <15 meq/L (15 mmol/L). These abnormalities are accompanied by hyperketosis

(concentration of total ketone bodies >5 mmol/L) and hyperosmolality. Some children will be diagnosed with type 1 diabetes before the onset of clinical symptoms.

Type 2 DM: T2 DM mellitus (T2DM) is the most common form of diabetes. It is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. The risk of developing T2 DM increases with age, obesity, and physical inactivity. T2DM shows strong familial aggregation, so that persons with a parent or sibling with the disease are at increased risk, other individuals with obesity, hypertension, or dyslipidemia and women with a history of gestational diabetes are also at increased risk of developing T2 DM. T2 DM is now considered to be a facet of Syndrome X (Reaven's syndrome) comprising of hyperinsulinemia, dyslipidemia, hypertension and hyperglycemia.

T2DM frequently goes undiagnosed for many years because the hyperglycemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes; however, such patients are at increased risk of developing macrovascular and microvascular complications. The classic symptoms of polyuria, thirst, recurrent blurred vision, paresthesias, and fatigue are manifestations of hyperglycemia and osmotic diuresis and are present late in the course of disease. Diabetes should be suspected in women with chronic candidal vulvovaginitis as well as in those who have delivered large infants (4.1 kg) or have had polyhydramnios, pre-eclampsia, or unexplained fetal losses.

MONITORING OF BLOOD GLUCOSE

Blood glucose testing: The glucose concentration is 10-15 % higher in plasma or serum than in whole blood because structural components of blood cells are absent.

Venous blood sample: The laboratory methods commonly used for determining plasma glucose utilize enzymatic methods, colorimetric methods or automated methods.

Capillary blood samples: Several strip based portable, battery operated meters utilize glucose oxidase method. Latest generation devices represent a noninvasive method relying on infrared absorption spectra.

TESTING FOR KETONURIA / KETONEMIA

Most strips utilize a nitroprusside re-action that measures only acetone and acetoacetate. Although these tests do not detect β -hydroxybutyric acid, the semi quantitative estimation of the other ketone bodies is nonetheless usually adequate for clinical assessment of ketonuria.

GLYCOSYLATED HEMOGLOBIN

The major form of glycohemoglobin (HbA_{1c}) is abnormally elevated in

Correspondence: Dr. Mohd Ashraf Ganie, Deptt. of Endocrinology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Post Box 930 GPO Srinagar, J&K, India e-mail: ashrafendo@rediffmail.com / ashraf.endo@gmail.com

diabetics. Glyco-hemoglobin generally reflects the state of glycemia over the preceding 8-12 weeks, thereby providing a method of assessing chronic diabetic control⁷.

DIAGNOSTIC CRITERIA

The diagnosis of diabetes mellitus is based on measuring venous plasma glucose in the fasting state and 2 hours after a 75 gram glucose load (recommended by the WHO). The details of the diagnostic criteria are given in Table 1^{8,9}.

- All values are venous plasma glucose
- To convert mg/dl to mmol/L, divide by 18.
- In case of an abnormal test result, the test should be repeated on a different day.

Oral glucose tolerance test (OGTT) is recommended by WHO and not by ADA for epidemiological purposes.

Table 1: Diagnostic criteria for Diagnosis of Diabetes mellitus

Category	WHO	ADA
Impaired fasting glucose (IFG)	BGF=100 to < 126 mg/dl	BGF=100 to < 126 mg/dl
Impaired glucose tolerance (IGT)	2 hr post glucose > 140 mg/dl and < 200 mg/dl	-
Diabetes mellitus (DM)	BGF ≥126 mg /dl or 2 hr Post glucose ≥ 200 mg/dl (OGTT)	BGF ≥126 mg /dl or Casual = 200 mg/dl + Osmotic Symptoms
Normal	FPG=100 mg/dl and PP ≤ 140 mg/dl	FPG=100 mg/dl and PP ≤ 140 mg/dl

MANAGEMENT OF DIABETES MELLITUS

Diabetes mellitus is condition associated with number of complications including coronary heart disease, retinopathy, neuropathy etc. It is now clear that tight control of blood glucose significantly reduces the risk of complications of diabetes. Therefore, multidisciplinary approach, involving dieticians, endocrinologists /diabetologists, cardiologists, nephrologists, ophthalmologists, chiropractors etc. is needed for management of diabetes mellitus.

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Non-pharmacological Therapy : Non-pharmacological measures including diet, exercise and stress alleviation are as important interventions for the management of diabetes.

Medical Nutrition Therapy (MNT): A proper diet is important component of therapy in all patients with diabetes. In patients with T2 DM recommendations for caloric distribution is as follows: 55-60% energy from carbohydrate, 10-15% from protein and 20-25% from fats. This dietary distribution is also indicated in patients with type 1 diabetes on intensive insulin regimens in whom near-normoglycemic control is less achievable on diets higher in carbohydrate content.

Dietary Fiber: Fibers such as cellulose or hemicelluloses, as found in bran, termed as insoluble fibers increases intestinal transit time and may have beneficial effects on colonic function. Soluble fibers such as gums and pectin's, as found in beans, oatmeal, or apple skin, tend to decrease gastric and intestinal transit slowing glucose absorption thus decreasing hyperglycemia.

Artificial Sweeteners: The nonnutritive sweetener saccharin is widely used as a sugar substitute. Aspartame may prove to be the safest sweetener for use in diabetics which is 180 times as sweet as sucrose. A major limitation is its heat lability, which precludes its use in baking or cooking. These should be used in moderation.

Fruits: Fruits (whole) should be taken in moderation. However, very sweet fruits and fruit juices can be avoided.

Alcohol: Alcohol intake is best avoided and if used must be in moderation as it may worsen the dyslipidemia, neuropathy and glycemic control.

Common Salt: Up to 6 gms /day of are permitted. Restrict pickles, papad, chatni and salty processed foods.

Tobacco: Smoking and the use of tobacco in any form should be prohibited.

Physical activity: In T2DM exercise programme to achieve weight reduction and calorie counting is central to the management. The best form of exercise is a stepwise increase in aerobic exercises. All diabetics need to be evaluated to rule out any contraindication like CAD, proliferative diabetic retinopathy, autonomic neuropathy etc. before any exercise programme. Brisk walking for 30-60 minutes or equivalent should be enforced regularly. Yoga, a traditional Indian system, has been demonstrated to have beneficial effect in diabetes. Some aspects of Yoga like, Asanas (involving postures), Pranayama (involving breath), Dhayana (meditation) and Bhavana (visualization) are beneficial but need to be learnt under expert guidance⁽¹⁰⁾.

PHARMACOLOGICAL THERAPY

Oral agents for the treatment of hyperglycemia (Table 2).

The drugs for treating T2 DM can be divided into three categories⁽¹¹⁾.

1. Drugs that primarily stimulate insulin secretion, known as insulin secretagogues.
2. Drugs that sensitize tissues (primarily liver and adipose tissue) to the action of insulin named as insulin sensitizers.
3. There are drugs that principally affect absorption of glucose by retarding the

Table 2: Characteristics of oral antidiabetic drugs

Sulfonylureas			Commonly used, lower cost, effective in severe hyperglycemia. Can be used in combinations. S/E: Hypoglycemia, wt gain. Contraindicated if S Cr. >2 mg/dl.
Glibenclamide	1.25- 20 mg OD / BID	Up to 24 hours	
Gliclazide	80-320 mg / BID	Up to 24 hours	
Glipizide	2.5-40 mg / ODBID	6-12 hours	
Glimeperide	1-8 mg / OD	Up to 24 hours	
Meglitinide analogues			For mild hyperglycemia, variable meal schedule, postprandial hyperglycemia and renal insufficiency. High cost
Repaglinide	0.5 - 4 mg / before major meals	3 hours	
Nateglinide	60-240 mg / before major meals		
Biguanides			No hypoglycemia. Weight neutral, post meal hyperglycemia; can be combined. S/E: GI, CI if S Cr>1.5 mg/dl; age > 70 yrs; systemic diseases.
Metformin	1-2.5 g with meals / 2 or 3 times daily	7-12 hours	
Thiazolidinediones			
Rosiglitazone	4-8 mg / ODBID	24-30 hours	
Pioglitazone	15-45 mg / OD	30 hours	
Alpha-glucosidase inhibitors			S/E=GI, Hypoglycemia in combination with other agents, less potent and costly. Better for post meal, erratic meal schedule and combinations.
Acarbose	75-300 mg / in 3 divided doses with first bite of food	4 hours	
Miglitol	75-300 mg in divided doses with first bite of food	4 hours	

* Tolbutamide, chlorpropamide, acetohexamide and tolazamide are no longer in routine clinical use.

INSULIN SECRETOGOGUES

Sulfonylureas: The proposed mechanisms of action of the sulfonylureas include: (a) augmentation of insulin release from pancreatic b cells and (b) potentiating of insulin action on its target cells.

Pancreatic b cells have specific receptors, consisting of two proteins, one that binds the sulfonylurea (SUR) and the other which is an ATP-sensitive potassium channel (Kir6.2). It has been shown that activation of these receptors closes potassium channels, resulting in de-polarization of the b cell. This depolarization allows calcium to enter the cell and actively promote insulin release. Table 2, enlists various sulfonylureas along with their characteristics.

The earlier generation sulfonylurea's, like glibenclamide and chlorpropamide, have a long duration of action and high probability of inducing hypoglycemia. Glipizide and gliclazide have short duration of action and thus need more frequent dosing. Glimeperide, is the newer generation sulfonylurea, it is given as monotherapy or in combination with other oral agents or insulin in a single daily dose. (Max.dose is 4 mg)¹¹ for each sulfonylurea the decline in blood glucose for each unit increment in the dose is best seen till the half-maximal dose of the drug is reached. After half maximal dose is achieved, further increase in the dose results in a smaller decline in blood glucose.

There has been concern of possible cardiovascular effects of sulfonylureas, because the ATP sensitive K⁺ channel, which is responsive to sulfonylurea

action, is ubiquitous in its distribution. Some animal experiments and short term human studies have suggested that earlier sulfonylurea's like glibenclamide and tolbutamide may have adverse cardiovascular effects but many large trials using sulfonylureas have not provided any evidence for cardiovascular risk. Since most sulfonylureas are metabolized in the liver and excreted through the kidney their use is prohibited in case of liver dysfunction and renal failure.

MEGLITINIDES

This is another class of secretagogues. They are similar to sulfonylureas in their mechanism of action but lack the sulfonic acid-urea moiety products. Repaglinide is given three times a day 15 minutes before each meal (max. dose of 16 mg/day); nateglinide is given 60 mg three times a day. The drug may be useful for postprandial hyperglycemia, elderly and in patients with renal impairment. There are less chances of hypoglycemia and useful in patients who have an inconsistent daily schedule with long gaps between meals⁽¹²⁾. Several novel insulin secretagogues have been reported to act by closing the K-ATP channels. The meglitinide derivative mitiglinide (KAD-1229) appears to bind at the benzamide site on SUR1¹³.

INSULIN SENSITIZERS

Biguanides

Phenformin has been discontinued because of its association with the development of lactic acidosis in patients with coexisting liver or kidney disease. Metformin (1, 1-dimethylbiguanide hydrochloride) was introduced in France in 1957 as an oral agent for therapy of T2 DM, either alone or in combination with sulfonylureas. In 1995 FDA approved its use in the United States but has been used in most of the countries, including India, for over 4 decades. The exact mechanism of action of metformin is not clear but it may reduce hepatic gluconeogenesis, slow down gastrointestinal absorption of glucose and increase up-take by skeletal muscle. It can be used as monotherapy, an adjunct to diet, sulfonylurea's, thiazolidinediones or insulin. Metformin is relatively contraindicated in patients with cardiorespiratory insufficiency, impaired renal function, any state likely to be associated with tissue hypoxia, general anesthesia, use of radiographic contrast media, and age of 70 years. Maximum dose of metformin is 2550 mg daily. Common side effects of metformin are gastrointestinal symptoms (anorexia nausea vomiting, abdominal discomfort, diarrhea. Lactic acidosis, though uncommon with metformin in contrast to phenformin, is reported in cases with associated risk factors such as renal, hepatic, or cardiorespiratory insufficiency, alcoholism and advanced age¹⁴.

Thiazolidinediones

These agents sensitize peripheral tissues to insulin by binding to a nuclear receptor called peroxisome proliferators-activated receptor-gamma (PPAR- γ). Other effects including, increased glucose transporter expression (GLUT 1 and GLUT 4), decreased free fatty acid levels, decreased hepatic glucose output, and increased differentiation of preadipocytes into adipocytes have also been observed. Troglitazone, was withdrawn because it caused acute liver failure. Rosiglitazone and pioglitazone are used as monotherapy, or in combination with sulfonylurea's, metformin, and insulin. Common side effect is weight gain, especially when the drug is combined with a sulfonylurea or with insulin. The dosage of rosiglitazone is 4-8 mg daily and of pioglitazone 15-45 mg daily. The Thiazolidinediones should not be given to patients if ALT is 2.5 times greater than the upper limit of normal, and liver function tests should be performed once every 2 months for the first year and periodically thereafter¹⁵. Recently Rosiglitazone is withdrawn from India and most other countries due to cardiac safety.

INHIBITORS OF INTESTINAL CARBOHYDRATE ABSORPTION

Alpha-Glucosidase Inhibitors

Acarbose and miglitol are competitive inhibitors of intestinal brush border

alpha-glucosidases, thus delaying the absorption of carbohydrates and reduce postprandial glycemic excursion. Both of these agents are potent inhibitors of glucoamylase, α -amylase, and sucrase. They are less effective on isomaltase and are ineffective on trehalase and lactase. The common adverse effect is flatulence. Troublesome diarrhea seen in 3% of cases. The starting dose of acarbose is 25 mg twice daily and can be gradually increased to 100 mg three times daily. A slight rise in hepatic aminotransferases has been noted in clinical trials (5% versus 2% in placebo controls, and particularly with doses greater than 300 mg/d). Miglitol is structurally similar to glucose, is absorbable and is similar to acarbose in terms of its clinical effects. Miglitol should not be used in renal failure since its clearance is impaired in this setting¹⁶.

INCRETIN MIMETICS: Insulin has been shown to be released more effectively through an oral glucose load than intravenously and this is known as the incretin effect. This incretin effect is mediated by number of peptides released from intestine. Insulin stimulating benefits of peptides such as GLP-1 are rapidly diminished as GLP-1 is rapidly metabolised by the glycoprotein dipeptidyl peptidase (DPP-IV). It is possible to enhance incretin effect either by increasing the effect of GLP-1 or by slowing its breakdown.

Glucagon-like polypeptide 1 analogues: Exenatide is the first synthetic agent belonging to the class of GLP-1 agonists. It augments insulin release in response to ingested glucose. In addition, GLP-1 suppresses inappropriately high glucagon values which in turn suppress hepatic glucose output. It also reduces the rate of gastric emptying, thus promoting satiety, resulting in reduced caloric intake and weight reduction^{15pmj}. It has also been shown that GLP-1 analogues may preserve β cell reserves. The recently published data on subjects completing over 2 years of treatment with exenatide showed a sustained reduction in HbA1c and weight after 104 weeks of treatment.

Dipeptidyl peptidase inhibitors: This class of drugs act slowing breakdown of GLP-1 analogues. These agents work by enhancing the sensitivity of β cells to glucose, which causes enhanced glucose dependent insulin secretion. Many studies using sitagliptin and vildagliptin alone or in combination have shown a positive effect on values of HbA1c¹⁷.

Phosphodiesterase inhibitors and other and approaches: The β - cell expresses several phosphodiesterases (PDEs) that degrade cAMP and so reduce insulin release. Transient inhibition of these enzymes in β - cells, especially isoform PDE - 3B, which exerts most influence on glucose induced insulin secretion, could be a possible intervention¹³.

Peroxisome proliferator activated receptor agonists: current, thiazolidinediones (pioglitazone and rosiglitazone) exert their "insulin sensitizing" effects largely by stimulating the peroxisome proliferator activated receptor γ . Stimulation of these receptor increase adipogenesis, enhance insulin sensitivity. Additional thiazolidinediones that stimulate PPAR γ are being developed (e.g. rivoglitazone), and non thiazolidinedione PPAR γ agonists have been reported¹³.

Other peroxisome proliferator activated receptor agonists: To take advantage of the blood lipid lowering and anti-inflammatory effects of low affinity binding to PPAR α various thiazolidinediones and non - thiazolidinedione molecules have been described with binding affinities for both PPAR α and PPAR α so called dual PPAR α/γ agonists (glitazars). The two glitazars (muraglitazar, tesaglitazar) were discontinued because of side effects. Pan PPAR agonist or SPPARM selective PPAR modulator could offer therapeutic advantages¹³.

Vitamins and Minerals: Whether supplementation of the antioxidant vitamins C (ascorbic acid), E (α -tocopherol) and β -carotene can measurably benefit insulin sensitivity and reduce cardiovascular risk is not clear. Vitamin D3, appears to be necessary for normal insulin production and secretion, and may be required for normal insulin action. Diabetic patients are often deficient in circulating vitamin D3 and preliminary data suggest that vitamin D supplementation in deficient individuals might benefit glycemic control. Insulin like antidiabetic effects has been reported for zinc, lithium, selenium, molybdenum, tungsten, mercury and cadmium¹³.

Other potentiators of insulin action: Bromocriptine: The dopamine D2 receptor agonist bromocriptine, used in the treatment of Parkinson disease, galactorrhea and prolactinomas, has long been known to improve insulin sensitivity and glycemic control in T2DM. Bromocriptine as monotherapy or an adjunct to other antidiabetic agents for up to 1 year has reduced HbA1c

by 0.5 – 1.2% ,reduced triglyceride, reduced some cardiovascular events, has not caused serious hypoglycaemia¹⁸.

Lipoic acid, isoferulic acid and angiotensin-converting enzyme inhibitors: The antioxidant α - lipoic acid, used in some countries to treat diabetic neuropathy, increases insulin sensitivity and improves glycemic control. Isoferulic acid increases expression of GLUT -4 and decreases gluconeogenesis. Modest improvements of insulin sensitivity have been seen during treatment with angiotensin converting enzyme (ACE) inhibitors, possibly because of improved hemodynamics resulting from increased bradykinin¹⁹.

Anti-obesity agents: Several centrally acting appetite suppressing and satiety inducing anti - obesity agents also exert peripheral effects that improve some actions of insulin and assist glycemic control in overweight patients.

Sibutramine and Rimonabant: has already been withdrawn because of side effects²⁰.

β -3 Adrenoceptor agonists: Various β -3 adrenoceptor agonists have been shown to stimulate insulin release, improve insulin mediated glucose disposal and improve glycemic control in obese diabetic rodents, but adequate efficacy have yet to be demonstrated in humans¹³.

Sodium glucose cotransporter 2 inhibitors: Glucose is filtered through the renal glomeruli and all that has been filtered is reabsorbed in the proximal tubules. Reabsorption is mediated mostly via the sodium glucose co-transporter 2 (SGLT2) systems. Thus, specific inhibition of these transporters reduces hyperglycemia by elimination of excess glucose in the urine. Selective inhibitors of SGLT2 (termed "inozins") have been developed recently²¹. Possible adverse effects of osmotic diuresis during SGLT2 inhibition include risk of dehydration and electrolyte imbalance, as well as infection in the urinary tract and urogenital region.

Sirtuins: Sirtuins comprise a group of seven enzymes that are nicotina mide-adenine-dinucleotide(NAD)-dependent-histone deacetylases and/orADP ribosyltransferases. Sirtuin SIRT1 is widely expressed in mammalian tissues including liver, muscle and fat, and appears to promote mitochondrial biogenesis and activity in some tissues, increasing thermogenesis and reducing susceptibility to weight gain, diabetes and cardiovascular disease. SIRT1 in pancreatic β - cells may also facilitate insulin secretion. Several small molecule activators of SIRT1 have been studied in animal models²².

COUNTER REGULATORY HORMONES

These hormones increases blood glucose by stimulating hepatic glycogenolysis and gluconeogenesis. Agents that interfere with the secretion or action of counter regulatory hormones could potentially be therapeutically useful¹³.

Glucocorticoid antagonists: Increased glucocorticoid concentrations can result in truncal obesity, insulin resistance and hyperglycemia, any approach to reduce the glucocorticoid action will reduce these adverse effects. Selective inhibitors of 11 β - HSD1 have been shown to improve insulin sensitivity, glycemic control and plasma lipids in obese diabetic rodents²³.

Insulin: Insulin is required in patients with T2 DM who have developed sulfonylurea failure or those who are undergoing an acute infective or operative event.

CONCLUSIONS

Previously available treatments for T2DM have improved glycaemic control but have been accompanied by weight gain and increased risk of hypoglycaemia. T2DM is a progressive disease and more conventional agents do not address the decline of β cell function. Newer agents thus add to the choice of treatment options already available for T2DM and are welcome, especially in light of the recent safety concerns with some of the more modern agents.

Management of type 1 diabetes mellitus

Insulin is the only therapy available for patients with type 1 diabetes. Insulin replacement in patients with type 1 diabetes has been less than optimal because it is not possible to completely reproduce the normal physio-logic pattern of insulin secretion into the portal vein. The problem of achieving optimal insulin delivery remains unsolved with the present state of technology.

Immunogenicity has been markedly reduced with the use of highly purified human insulin preparations, thereby reducing complications associated with impure insulins.

Human insulin is now been produced by recombinant DNA technology. "Purified" insulin is defined as containing less than 10 ppm of proinsulin, whether extracted from animal pancreas or produced from biosynthetic proinsulin. All human and pork insulins currently available contain less than 10 ppm of pro insulin and are labeled as "purified." The more highly purified insulins currently in use preserve their potency quite well; therefore, refrigeration while in use is not necessary. At present, insulins in the USA are available only in a concentration of 100 units/ml (U 100) while in India both U 100 and U40 are available and dispensed in 10-mL vials. Four principal types of insulin are available: (a) Ultra short-acting insulin, with very rapid onset and short duration of action; (b) short-acting insulin, with rapid onset of action; (c) intermediate-acting insulin; and (d) long-acting insulin, with slow onset of action (Table 3)²⁴.

Table 3: Characteristics of currently used preparations of human insulin and insulin analogues

Type of insulin	Onset action (min)	of Peak effect (min)	Dosing interval	Time point to monitor effect
Mealtime				
Lispro (rapid acting)	5-15	30-90	At meal	2 hr
Aspart(rapid acting)	5-15	60-120	At meal	2-3 hr
Regular(short acting)	30-60	120-240	30-45 min premeal	4 hr
Background				
NPH(intermediate acting)	2-4	4-6	Twice daily	8-12 hr
Ultralente (long acting)	3-5	Limited peak	Twice daily	10-12 hr
Glargine (long acting)	2-4	Peakless	Once daily	Fasting glucose
Detemir	2-4	Peakless	Twice daily	Fasting glucose

Ultra-short-acting and short-acting insulins are dispensed as clear solutions at neutral pH. All other commercial insulins have been specifically modified to obtain more prolonged action.

Rapid and long-acting insulin analogs: Rapid-acting insulin analogs, such as insulin aspart, insulin glulisine and insulin lispro have a faster onset of action, sharper and earlier peak activity and more rapid return to baseline levels than regular human insulin. Given before the evening meal, large doses of regular insulin increase the risk of nocturnal hypoglycemia. These problems are reduced with rapid-acting insulin analogs²⁵.

Long-acting insulin analogs, detemir and glargine, the first soluble insulin analogs have a flat and prolonged time action profile. Bolus/basal therapy that combines premeal aspart or lispro with glargine or detemir insulin has emerged as the 'gold standard' for intensive injection therapy provided through multiple daily injections (MDI) in adults with T1DM²⁶.

METHODS OF INSULIN ADMINISTRATION

A. Insulin Syringes and Needles

Single unit syringes (those with a needle fixed to the syringe to minimize dead space) are available for injection of insulin. 27- or 28-gauge, and more recently even 30- gauge attached needles have greatly reduced the pain of injections. Disposable syringes may be reused until blunting of the needle occurs (usually after three to five injections).

B. Pen devices

Pen devices contain cartridges of U 100 regular human insulin and retractable needles. Cartridges containing insulin lispro; regular insulin, NPH insulin and pre-mixed insulin are available for use with these pens²⁷.

C. Sites for Injection

Any part of the body covered by loose skin can be used as an injection site, including the abdomen, thighs, upper arms, flanks, and upper outer quadrants of the buttocks. Exercise facilitates insulin absorption when the injection site is adjacent to the exercising muscle. Rotation of sites is advised to avoid delayed absorption when fibrosis or lipohypertrophy occurs owing to repeated use of

a single site. For most patients the abdomen is the recommended site for injection, since it provides a considerable area in which to rotate sites and there may be less variability of absorption with exercise than when the thigh or deltoid areas are used.

NEW AND IMPROVED INSULIN DELIVERY DEVICES

Advances in diabetes technology have helped to improve the outcomes of management of T1DM in last three decades.

Intranasal: soluble insulin administered intranasally is rapidly absorbed when given along with a detergent substance to facilitate adsorption. Preliminary clinical trials have demonstrated its efficacy in reducing post-prandial hyperglycemia in subjects with type 1 diabetes. However, its absorption is limited to less than 10% of the administered nasal dose. This reduces its cost-effectiveness, and most manufacturers have discontinued clinical trials until more progress is made in improving its bioavailability. Inhalers that can provide more precise delivery of drugs have been developed, and inhaled insulin is currently in phase III trials.

Insulin pumps and continuous subcutaneous insulin infusion: insulin pump devices have become smaller and increasingly more sophisticated in their functionality. Insulin is delivered through a cannula placed subcutaneously and replaced with a 72 h frequency. A continuous basal rate is programmed into the pump and additional boluses of insulin can be administered 'at the push of a button. Smart pumps' have a more sophisticated computer incorporated into the insulin pump. The delivery of CSII through insulin pumps has been extensively investigated in the paediatric and young adult population²⁸.

Continuous glucose monitoring (CGM) systems: This system, through which a subcutaneous, glucose oxidase coated sensor measures interstitial fluid glucose concentrations and converts them to a plasma glucose estimate, provides a promising modality for future management of type 1 diabetes. A plot of plasma glucose concentrations over a 24-h period are produced and can enable insulin adjustment to identify episodes of hyper or hypoglycaemia that may not have been identified using conventional capillary glucose monitoring. More recently, real-time CGM and CSII technologies have been combined in a single device and this exciting technology may represent a step towards an 'artificial pancreas'²⁹. However, despite advances, this technology is in its infancy and its current role in the management of type 1 diabetes is unclear.

Other modes of therapy in T1DM: Amylin analogues: Pramlintide is a synthetic analogue of amylin, a polypeptide hormone, co-secreted with insulin from pancreatic β cells. It is injected pre-prandially in addition to insulin and has shown modest improvements in post-prandial hyperglycaemia with 20-30% decrease of insulin dose³⁰. Treatment of type 1 diabetes with pramlintide is associated with fewer hypoglycaemic episodes and significant weight loss. Its use is limited by nausea and additional prick required besides insulin.

Pancreatic and islet transplantation: Whole-organ pancreatic transplantation for the treatment of type 1 diabetes has largely been reserved for those undergoing renal transplantation for end-stage diabetic nephropathy. While normalization of glycaemic control is achieved following successful transplantation, but this therapy carries the risk of pancreatic graft rejection and side effects of immunosuppression³¹.

Islet cell transplantation provides a promising treatment option for type 1 diabetes. β -cells isolated from a donor pancreas are injected into the portal venous system where they then lodge within liver sinusoids. These β cells remain glucose sensitive and secrete insulin into the portal system, in the same way as occurs in the physiological situation³². Variable β -cell yield using this isolation technique requires harvest from more than one pancreas to provide sufficient tissue for successful transplantation. Nonetheless, with the future promise of engineered β cells using stem cell differentiation methods, this technique of cell delivery/transplantation may provide a successful long-term treatment of glycaemia in type 1 diabetes.

IMMUNOTHERAPY

Pancreatic β -cell preservation using immune suppression or immune tolerance has been disappointing. When used as secondary prevention of type 1

diabetes, ciclosporin and anti-CD3 antibodies reduce the required insulin dose and prolong β -cell survival, as assessed by fasting and stimulated serum C-peptide concentrations³³. However, both of these treatment modalities have unacceptable side-effect profiles, particularly given the age of the target population. GAD-alum immunization in an attempt to promote immune tolerance in subjects with diagnosed type 1 diabetes did not significantly reduce their requirement for insulin or improve fasting serum C-peptide concentrations³⁴. The use of these therapies requires more research before their introduction as mainstream approaches to prevention of type 1 diabetes mellitus.

CONCLUSION

Future drug therapy of T1DM will depend on the success of ongoing and planned intervention trials. Immunomodulation alone, or possibly combined with immunosuppressive therapy, seems to be promising in reducing the loss of C-peptides after diagnosis. Studies of the function of the human immune system lag behind that of the mouse and rat. Since 2001, Trial Net, an international network of clinical research groups supported by the National Institutes of Health, has established an infrastructure for trials for predicting and preventing T1DM.

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