Recent Advances In The Management Of Diabetes Mellitus

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ABSTRACT
Diabetes mellitus is a group of common metabolic disorders in which a person has high blood glucose either because the body does not produce enough insulin or because cells do not respond to the insulin. 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 the main cause of the diabetic epidemic is type2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. Life style modification, oral hypoglycaemic agents, insulin therapy and islet cell transplantation are some of the approaches in the management of diabetes mellitus. Several classes of oral hypoglycemic agents like sulfonylureas, biguanides and alpha-glucosidase inhibitors are available for the treatment of type II diabetes and newer drugs such as GLP-1 mimetic ,DPP-4 inhibitors, SGLT-2 inhibitors, dual peroxisome proliferation activated receptor(PPAR) agonist and G-protein receptor agonist are now available or are being introduced. The goals of this article are to review the current treatments and innovations in the management of diabetes mellitus, highlight the basic pharmacology for new drugs used in diabetes mellitus and discuss the indications and treatment strategies with regards to the newer therapies.

INTRODUCTION
Diabetes Mellitus (DM) comprises of a group of common metabolic disorders with inappropriate hyperglycaemia due to either an absolute deficiency of insulin secretion or reduction in the biological effectiveness of insulin or both. The prevalence of DM has risen dramatically over the last two decadesl. Its prevalence is expected continue to rise in the future because of increasing obesity, reduced activity levels and increasing agel. According to the World Health Organization (WHO, 2014), 347 million people worldwide have diabetes and 80% of people with diabetes live in low and middle income countries. WHO also projects that diabetes deaths will double between 2005 and 2030 and diabetes will be the seventh leading cause of death by 2030 [2]. From these figures, one can infer that diabetes mellitus constitute a worldwide public health challenge.
Despite the availability of many antidiabetic agents and pharmacotherapies targeting cardiovascular risk factors, the morbidity, mortality and economic consequences of type 2 DM are still a great burden to patients, society, health care systems and the economy [3].

MANAGEMENT
The goal of management of diabetes mellitus is to correct the metabolic imbalance and keep blood glucose level as close to normal as safely as possible. This will help to eliminate symptoms and prevent or at least slow the development of complications. Management requires a multidisciplinary team of health professionals with expertise in diabetes, working in collaboration with the patient and family. This is achieved by:
1) Lifestyle modification (Diet and Exercise)
2) Medications
3) Appropriate self – monitoring of blood glucose
4) Laboratory assessment

1) LIFESTYLE MODIFICATION
Diet
Diabetic patients should eat a healthy diet low in fat and sugar. Complex carbohydrates such as bread, pasta and rice are good as they release slow energy. However, saturated fats such as pastries and fast food, are bad [4]. The mix of carbohydrate, protein and fat are adjusted to meet the metabolic goals and individual preferences of the person with diabetes mellitus. Carbohydrate (more of complex CHO) should be 50 -65% of the diet, protein 10 -20%, fat <30% (more of unsaturated fat) and salt <3g/day[1]

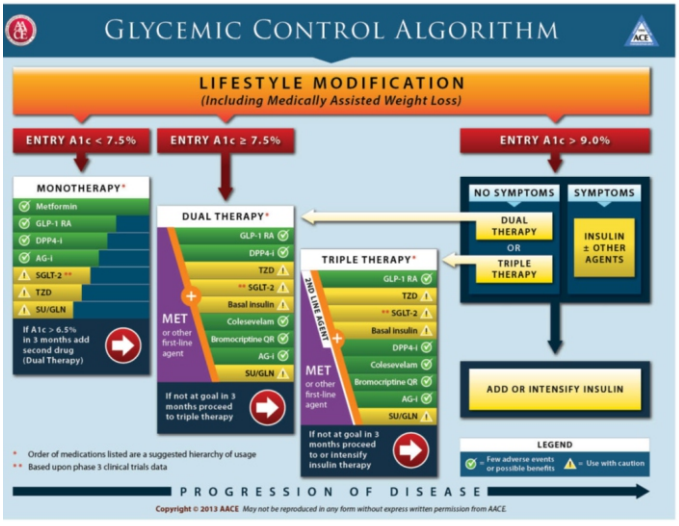
Exercise
Regular aerobic physical activity is recommended such as brisk walking for at least 30 minutes on most days. Several trials have shown that regular exercise reduces the risk of progression to type 2 diabetes by 30-60%. Both aerobic and resistance training improve insulin sensitivity and metabolic control in type 1 and type 2 diabetes [5].

Weight
Weight loss is advised especially for overweight and obese patients as studies have demonstrated that moderate weight loss (5% of body weight) is associated with decreased insulin resistance, improved measures of glycaemia and lipidaemia and reduction in blood pressure.[6]

Smoking and Alcohol
Adults with diabetes who drink alcohol should limit intake to a moderate amount (one drink per day or less for women and two drinks per day or less for adult men). Smoking should be reduced or stopped.

2) MEDICATIONS
The factors to consider when initiating pharmacologic therapy is whether the patient is insulin deficient, insulin resistant or both. Treatment options include insulin, insulin sensitizers, insulin secretagogues, alpha glucosidase inhibitors, incretins, pramalintide, bromocriptines as well as newer drugs. American Association of Clinical Endocrinologist (AACE), 2013 recommendation for glycaemic control is shown in the table below.

AACE GUIDELINE FOR GLYCAEMIC CONTROL



INSULIN THERAPY

Insulin is indicated for all type 1 DM and in type 2 DM with primary or secondary drug failure, diabetic foot, diabetic emergencies, diabetics undergoing surgery, diabetics with septicaemia and gestational diabetes.. The table below summarizes the insulin therapies available.

Type	Examples	Onset	Peak	Duration
Rapid acting	Lispro, Aspart, Glulisine	5 – 15 minutes	30 – 90 minutes	3 – 4 hours
Short acting	Regular insulin	30 -90 minutes	2 -3 hours	5 -8 hours
Intermediate	Neutral Protamine Hagedorn (NPH)	2 -5 hours	6 – 10 hours	10 -18 hours
Long acting	Glargine, Detemir, Ultralente	4- 8 hours	10 -16 hours	18 -24 hours

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 pens[7].

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 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 sub-stance 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.

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'[8].

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. 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'[9]. However, despite advances, this technology is in its infancy and its current role in the management of type Idiabetes is unclear.

B)INSULIN SENSITIZERS

Biguanides (e.g metformin), Thiazolidinediones (e.g rosiglitazone, pioglitazone)

Table 1.2 summarizes the various insulin sensitizers.

Subgroup	Generic name	Advantages	Complications
Biguanides	Metformin	Weight loss, improved lipid profile	Lactic acidosis, diarrhoea, metallic taste
Thiazolidinediones	Rosiglitazones (Avandie), Pioglitazones (Actos)	Reduces insulin requirement, reduces triglycerides	Fluid overload, hepatocellular injury.

C) INSULIN SECRETAGOGUES

These are drugs that increase insulin secretion. Examples include Sulphonylurea and meglitinides.

Insulin secretagogues	Examples	Advantages	Complications
Sulfonylureas; 1st Generation	Tolazamide Tolbutamide Chlorpropamide	Tolbutamide has a short half-life, preferable in elderly. Chlorpropamide has a very long half-life.	Hypoglycaemia, weight gain, hyperinsulinaemia
2nd Generation	Gliclazide Glipizide Glyburide	Lowers fasting blood glucose	Hypoglycaemia, weight gain, hyperinsulinaemia, contraindicated in renal or liver disease
3rd Generation	Glimepiride	Lowers fasting blood glucose	Hypoglycaemia, weight gain, hyperinsulinaemia, contraindicated in renal or liver disease
Meglitinides	Nateglinide Repaglinide	Short onset of action, lowers post prandial glucose, safe in sulphur allergy.	Severe hypoglycaemia if meal is skipped.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS

Agonists of the nuclear transcription factor family of PPARs are established drugs for the treatment of metabolic disease. Fibrates activate the primarily hepatic expressed PPAR $\propto$ leading to a reduction in serum triglycerides, whereas thiazolidinediones activate the primarily adipose tissue expressed PPARγ leading to improved insulin sensitivity[10]. The clinical relevance of both drug classes has however been challenged recently. Although fibrates effectively reduced cardiovascular events in the prestatin area[11], they more recently failed to prove beneficial as an add-on therapy to a preexisting statin medication[12]. In addition, heterogeneity for cardiovascular risk reduction has been reported for PPARγ agonists with pioglitazone proving beneficial effects in the proactive trial, whereas rosiglitazone was associated with increased myocardial infarction [13, 14].

3) SELF-MONITORING OF BLOOD GLUCOSE (SMBG)

Self-monitoring is an effective way to evaluate short glycaemic control. Self- monitoring of blood glucose and interval measurement of Haemoglobin A1c (Hb A1c) are ways of assessing the quality of glycaemic control. It helps the patient and physicians to assess the effect of food, medications, stress and activity on blood glucose level. Frequency of checking depends on the type of medical therapy, risk of hypoglycaemia and need for short-term adjustment of therapy.

NEWER DRUGS

Glucagon- Like Peptide

GLP-1 is a 30 amino acid incretin hormone which gets secreted from intestinal L cells in response to nutritional stimuli. Circulating GLP-1 binds to its receptor on the pancreatic beta cell leading to increased insulin secretion and the pancreatic alpha cell causing suppression of glucagon release. Importantly, both mechanisms require the presence of glucose, leaving hypoglycaemia-induced contraregulatory circuits intact. Furthermore, GLP-1 has a variety of extrapancreatic effects including delay of gastric emptying, central nervous appetite reduction, weight loss and direct cardiovascular effects[15]. GLP-1 analogues already in use are exenatide and liraglutide.

DPP-4 Inhibitor

Glucose metabolism can similarly be improved by the inhibition of the GLP-1 degradation enzyme DPP-4. DPP-4 inhibitors prolong the half-life and increase the bioavailability of endogenous GLP-1 and other peptides holding prolin or alanin at position 2 of their peptide chain. 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 HbA1c [16].

SGLT2 Inhibitor

SGLT2 inhibition is a new concept of blood glucose lowering reached by inhibition of the renal sodium/glucose cotransporter [2, 17]. Being expressed in the proximal renal tubule, SGLT2 has low glucose affinity but high transport capacity sufficient for reabsorption of approximately 90% of primarily filtered glucose[18]. The remaining urinary glucose is targeted by the high-affinity low-capacity transporter SGLT1 which is located in the loop of Henle and distal tubule. Both transporters allow full recovery of urinary glucose within the physiological range, whereas glucosuria occurs under diabetic conditions as a consequence of receptor saturation. The restricted expression of SGLT2 to the kidney and its up regulation in response to hyperglycaemia make it an attractive target for antidiabetic therapy[19]. Safety of this approach is suggested by rare inactivating SGLT2 mutation which causes pronounced glucosuria in the absence of other disease manifestations [20,21]. A wide variety of SGLT2 inhibitors are currently in use, with dapagliflozin, canagliflozin and empagliflozin being the most advanced substances. These agents are already in use. Most of these substances feature strong selectivity for SGLT2 over SGLT1; inhibition of the latter has been suggested to cause gastrointestinal disturbance. Excretion of approximately 40% of primarily filtered glucose translates to a loss of 50–100 g glucose every day. The consequential decline in fasting and postprandial glucose leads to an HbA1c reduction of approximately 0.8% [22]. Occurrence of hypoglycaemic events is extremely rare owing to incomplete SGLT2 inhibition and undisturbed counter regulatory circuits.

Amylin Analogue

Pramlintide is a synthetic analogue of amylin, a polypeptide hormone, co-secreted with insulin from pancreatic b 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 dose. 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.

ISLET CELL TRANSPLANTATION

Islet transplantation is the transplantation of isolated islets from a donor pancreas into the diabetic patients. Islet cell transplantation is a procedure which effectively controls blood glucose level for diabetic patients. Once transplanted, the islets begin to produce insulin, actively regulating the level of glucose in the blood. For an average-size person (70 kg), a typical transplant requires about one million islets, isolated from two donor pancreases. Improved results with single-donor islet transplantation have also been reported [23]. 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 b cells remain glucose sensitive and secrete insulin into the portal system, in the same way as occurs in the physiological situation[24]. 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 b 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.

CONCLUSION

This review has provided information on the latest drugs and technology available for use in the treatment of diabetes mellitus. The new drugs offer alternatives to existing therapies and important new drugs (pramlintide and exenatide) that may be added to current therapies to provide better glycaemic control. As with all new drugs, patients should be counseled and educated on the proper use of these drugs.

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