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Mini Review

Recent Advances in the Management of Diabetes Mellitus

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance or insulin deficiency. There are so many challenges in the management of diabetes. This paper aims to review the available current evidences regarding the recent advances in the management of diabetes. Continuous glucose monitoring system (CGMS) and Ambulatory glucose profile (AGP) are now used for monitoring of blood glucose. New Oral antidiabetic drugs like gliptins, sodium glucose transporter2 inhibitors (SGLT 2 I) and injectables like Glucagon like peptide 1 receptor agonist (GLP 1RA), newer insulin analogues, now plays an important role in the present day management of diabetes. Along with this, many other exciting drugs are in the pipeline.

Keywords: *Diabetes Mellitus; Antidiabetic Drugs; Insulin Analogues*

Introduction

Diabetes is a chronic metabolic disorder characterised by hyperglycemia due to defect in insulin sensitivity or insulin secretion or both. Diabetes is further related to long term complications which includes both micro and macrovascular complications. Recent IDF estimates show that globally there are 425 million with diabetes and by 2045, this number will reach an estimated 693 million [1]. Exciting developments have occurred in all aspects of diabetic care over the past decade. Inspite of the remarkable advances, management of diabetes still remains as a great challenge to the treating physician.

Current challenges in the management

Diabetes is no more a single disease. At one end of the spectrum there is type 1 diabetes which is autoimmune predominant and other end type 2 diabetes dominated by metabolic dysfunction. In between there occurs various types like MODY, LADA, early onset type 2 diabetes. Land mark trials like UKPDS and DCCT showed that management of diabetes aggressively in the initial years leads to clinical benefits in later years [2]. This is known as legacy effect or memory effect. There are so many unmet needs in the management of diabetes which includes (1) Halting the progressive deterioration of beta cell function. (2) Addressing multiple pathophysiological defects. (3) Avoiding hypoglycaemia and weight gain. (4) Reducing cardiovascular risk. (5) Long term safety of drugs.

Monitoring of blood glucose

Triad of glycemic control includes FBS, PPBS, HbA1c. Now it is a glycemic pentad which consists of above triad with hypoglycemia and Glycemic variability. Patients with similar mean glucose or HbA1c can have markedly different daily glucose profiles, with differences both

in number and duration of glucose excursions. Now it is clearly known that glycemic variability is an important cause for cardiovascular disease [3]. CGMS and AGP are the two recently developed monitoring systems in diabetes which helps to reveal glycemic variability and hypoglycaemia more effectively.

Continuous glucose monitoring system

A continuous glucose monitoring system (CGMS) is a device that records glucose levels throughout day and night. It can provide upto 288 glucose readings every 24 hours. The system is used to measure average glucose for upto 6 days while the person with diabetes continues daily activities at home and at work. A tiny flexible electrode inserted just underneath skin. It measures glucose in the interstitial fluid. The use of CGMS in clinical practice would provide the required monitoring tool to minimise glycemic variability and superoxide overproduction and may potentially reduce diabetic complications [4].

Ambulatory glucose profile

Ambulatory glucose profile (AGP) is a visual report that collapses all glucose readings from several days or weeks as if they occurred in a single 24 hour period [5]. AGP provides more data than SMBG, making it easier to build comprehensive graphs that provide information about glucose variability, hypoglycemia and hyperglycemia. Advantages of AGP over CGMS are (1) sensor is less intrusive and insertion is painless. (2) Measures glycemic profile over 14 days. (3) Calibration with finger stick not required. (4) one reader can be used for multiple patients. (5) Less cost.

Clinical indications for CGMS and AGP includes (1) Patient with type 1 and 2 diabetes not at their HbA1c target, with frequent hypoglycaemia. (2) During pregnancy. (3) Brittle diabetes. (4) Patients having discrepancies between their HbA1C and SMBG.

Recent advances in the management

Management of diabetes is now mainly by an individualised approach. Tailor treatment individually for every patient. There are many guidelines including ADA, EASD, AACE, IDF and ADA-EASD Position statement [6]. Metformin is the first drug of choice for type 2 diabetes. After that the options are sulphonyl ureas, thiazolidinediones, gliptins, GLP-1 RA, SGLT2 inhibitors, insulins. Major advances happened in the last four group of mentioned drugs.

Gliptins

Gliptins or DPP4 inhibitors have several advantages like moderate efficacy, low risk of hypoglycemia, weight neutral. Now these group of drugs has become one of the mainstay treatment of type 2 diabetes. They take care two unmet needs like alpha cell dysfunction and chronic beta cell decline. Gliptins which are available are sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin. Teneligliptin is a low cost gliptin which came recently. Many new Gliptins are expected in the coming years. Cardiovascular safety trials of Gliptins like TECOS [7] (Sitagliptin) and SAVOR TIMI trial (Saxagliptin) showed that gliptins are safe. Linagliptin can be used in renal failure patients without dose modification.

GLP 1 RA

The development of GLP- 1 RA (Glucagon like peptide 1 Receptor agonist) have revealed a new avenue in managing diabetes [8]. They are given as subcutaneous injection, and have better glycemic lowering effect, less hypoglycemia and also produces weight loss. Short acting GLP RA are exenatide and lixisenatide, while long acting ones are albiglutide, dulaglutide, liraglutide. Dulaglutide is a once weekly used GLP 1RA. The main side effects include nausea and vomiting. Cost is the major problem. Cardiovascular superiority of liraglutide has been well proved in the leader trial.

SGLT 2 inhibitors

SGLT 2 inhibitors (Sodium glucose co transporter 2 inhibitors) are a new class of drug that acts by inhibiting enzyme SGLT 2 in the proximal convoluted tubules of the kidney, thereby inhibiting 90% of glucose reabsorption and excreting it through urine [9]. Most important aspect is it has got an insulin independent mechanism of action. Advantages of this class of drugs include good glycemic control, weight loss, blood pressure reduction. With their unique mechanism of action and good safety and tolerability profiles, the SGLT2 inhibitors are an important addition to existing treatments for type 2 diabetes. Drugs which are available are dapagliflozin, canagliflozin and empagliflozin. Main side effects include urogenital infections. Cardiovascular outcome event trial of empagliflozin (EMPA-REG outcome) [10,11] showed that it offered cardiovascular benefits beyond mere glucose lowering especially reduction in CV mortality and heart failure. Thus SGLT 2 Inhibitors have now emerged as a mainstay of treatment for diabetes after metformin in patients with Atherosclerotic cardiovascular disease (ASCVD).

A combination of empagliflozin (SGLT 2I) and DPP4I (Linagliptin) (Glyxambi) which address many core pathophysiological defects in T2DM came to market recently.

Insulin analogues

Insulin analogues are produced by genetic engineering wherein amino acid sequence in human insulin is changed to alter its pharmacokinetics. However, they bind to insulin receptors in the same way as human insulin and produce similar effects. The various insulin analogues which are available are (1) Rapid acting analogues- lispro, aspart, glulisine. (2) Long acting analogues- glargine and detemir. (3) Premix formulations. Recently, an Ultra long acting insulin degludec was introduced. Various other insulin analogues are in pipeline. Merits of Insulin analogues include (1) They mimic physiologic insulin secretion. (2) Better control of postprandial hyperglycemia. (3) Low risk of hypoglycaemia. (4) Greater flexibility in dosing as rapid acting ones can be given just before meals.

Insulin degludec (Tresiba) is an ultra long acting insulin analogue for once daily dosing and allows adults to even change their long acting insulin day to day dose timing. The coformulation ryzodeg 30/70, (IDegAsp) comprises of long acting insulin degludec (70%) and rapid acting insulin as part (30%). This novel coformulation offer patients with progressive T2DM a simpler, injectable insulin regimen with fewer injections as compared to basal bolus/basal plus therapy. Unlike Premix insulins ryzodeg shows better reductions in fasting glucose levels and nocturnal hypoglycaemic episodes.

Xultophy is a novel combination of degludec and GLP 1RA Liraglutide. It is indicated in patients withT2DM inadequately controlled on basal insulin or GLP1 RA. It is administered as once daily injection.

Alternate routes of Insulin delivery under research are (1) Inhaled Insulin (Affreza-approved by FDA in June 2014) [12]. (2) Buccal spray. (3) Transdermal delivery. (4) Oral insulin.

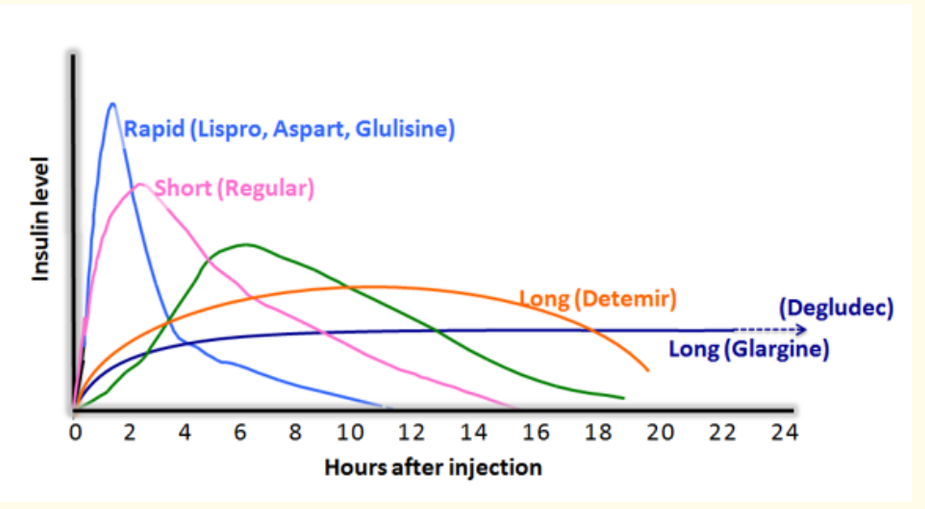

Figure 1: *Therapeutic options of insulins.*

Insulin pumps

A major milestone in the history of insulin delivery systems was the discovery of insulin pumps by Dr. Arnold Kadish in 1963. Insulin pump therapy is the most scientific mode of insulin delivery available today and provides higher level of reproducibility in insulin delivery, better quality of life, improved psychosocial functioning and more flexibility with lifestyle [13]. Continuous glucose monitoring (CGM) devices, rapid acting insulin analogues and development of control algorithms have led to rapid advancements in this technology. Research is being made to develop a fully closed loop (CL) system i.e. an Artificial Pancreas system with help of sophisticated control algorithms, would be able to monitor blood glucose levels as well as automatically adjust the delivery of insulin (and/or glucagon) to reduce glycemic variations with little or no input from the patient [13]. The first hybrid CL system Minimed 670G system got FDA approval in September 2016. Bionic pancreas, a dual hormone configuration of artificial pancreas, comprises of two pumps, one each for insulin and glucagon, a CGM and a control algorithm [13].

Bariatric surgery

Obesity plays a key role in the development of type 2 diabetes. Recently bariatric surgery has proved its efficacy in obtaining marked weight loss, good glycemic control and even diabetes remission. It was accepted that these procedures have antidiabetics hormonal actions beyond weight loss [14].

Transplantation of pancreas, islet cell, stem cell

Transplantation of whole pancreas, islet cells and stem cells offers hope for cure of diabetes pancreas transplantation is a new treatment option in type 1 diabetes and involves surgical replacement of diseased pancreas with a healthy donor. Though proved effective it is associated with a high risk of surgical complication and technical failure [15]. Clinical studies have shown that transplantation of pancreas or purified pancreatic islet cells can support glucose homeostasis in type 1 diabetic patients [16].

Drugs under evaluation

Several new class of drugs are being evaluated for the management of type 2 diabetes. Some of these include Protein tyrosine phosphatase 1B inhibitors, diacylglycerol acyltransferase 1 (DGAT-1) inhibitor, AGE antagonists, glucokinase activators, glucagon receptor antagonists, glucose-6 phosphatase inhibitors [17,18]. A new once weekly DPP4 inhibitor (Omarigliptin) and an Oral GLP 1 analogue is in pipeline. A combined SGLT2 and SGLT1 inhibitor (Sotagliflozin) is also under evaluation.

Non-insulin based therapies for type 1 diabetes which are under evaluation include-GAD 65 therapy, DiaPep277 (immunomodulatory peptide that arrests beta cell function), Anti CD3 monoclonal antibodies that increase the regulatory T cells, Anti CD20 monoclonal antibodies that downregulate B lymphocyte signaling of T cells and many more [19,20].

Conclusion

Management of diabetes has undergone tremendous progress over the past decade. However, the disease remains a challenge because of its high prevalence and associated comorbidities. Recent advances in pharmacologic options offer promise of improving glycemic control for longer periods without much side effects. CGMS and AGP now plays an important role in management of diabetes. Several new drugs in the form of Gliptins, GLP-1 RA, SGLT 2 Inhibitors, Insulin analogues have emerged, and many more exciting drugs are in the pipeline.

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