Int J Pharma Res Health Sci. 2020; 8 (3): 3161-66
DOI:10.21276/ijprhs.2020.03.02
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Review Article

A Review Study on the World Wide Estimation Apropos of Pharmacotherapeutic Management in Diabetes Mellitus Population

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ARTICLE INFO

Received: 17 May 2020
Accepted: 12 Jun 2020

ABSTRACT

The clinical condition namely Diabetes mellitus (DM) is an incessant disorder affecting the blood glucose metabolism, which progressively has become ubiquitous in global phenomenon. In the view of this denouement, it has been swiftly turning into an epidemic, for considerable extent in few nations with the vulnerable population foreseen to be over the twice in the subsequent ten year period attributable to the rise of geriatric population, emanating burden to the hitherto conditions implied on healthcare personnel, peculiarly in less developed countries. This structured review draws its basis through compendium of veritable sources namely the Medline, the Cochrane Database of Systemic Reviews, and citation lists of relevant publications. Subject captions and key words utilized include diabetes mellitus, incessant, ubiquitous. Evaluation and diagnosis is nevertheless hinged upon the World Health Organization (WHO) and American Diabetes Association (ADA) criteria which comprises of both clinical and laboratory investigation parameters. No contemporary panacea has been introduced for this disorder. Although, therapeutic modalities include lifestyle alterations, administration of oral hypoglycemic agents and insulin sensitizers like metformin, a biguanides that reduces insulin resistance, is still the recommended first line medication and also other medications include sulfonylurea, thiazolidinediones and the direct component as insulin.

Keywords: Diabetes Mellitus, Diagnosis, Management, Metformin, sulfonylurea, and insulin

1. INTRODUCTION

The two terms “Diabetes” and “Mellitus” are derived from Greek and Latin languages correspondingly. “Diabetes” denotes “a passer through, a siphon” whereas “Mellitus” denotes the word “sweet”. It is understood that the word illustrates exaggerated urine production, which is

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characteristic feature in the diabetic patients [1, 2]. Initial discovery that described clinical features similar to that of Diabetes Mellitus were recognized 3000 years ago, by the ancient Egyptians. Araetus of Cappadocia (81-133AD) exposed a feature "Increased frequency of urination", later Britisher Thomas Willis rediscovered that the urine and blood in patients is sweeter [3, 4]. Since then, vast development and progress has been registered in the knowledge of Diabetes Mellitus.

Diabetes Mellitus is a serious, chronic and complex illness, which is characterized by hyperglycemia that is produced from the pancreatic β-cells [5], which generates deficient insulin (a hormone that adjusts blood glucose). The table 1 summarizes a rough estimate of diabetic patients in the years 2015 and 2040. From the table, it can be observed that in the developed countries, approximately 87% to 91% are estimated to have type II diabetes, 7% to 12% are estimated to have type 1 diabetes and 1% to 3% to have other types of diabetes. World health organization has categorized Diabetes Mellitus as the 7th leading cause of Mortality in USA and it was estimated that 422 million adults had diabetes in 2014, which is 4 times higher than the recorded cases in (1980) [6]. Clinicians also believe that Diabetes Mellitus may occur due to the carbohydrates and fat those are present in the daily diet, given that starch digestion in mammals is accomplished by a-amylase and a-glucosidase. Inhibition of starch digestive enzymes or glucose transporters can thus reduce glucose release and absorption of it in the small intestine. This decrement could help to manage Diabetes Mellitus [7, 8].

In 21st Century Diabetes Mellitus is recorded as the highest reported health crisis and the public health authorities are more aware of the prevalence of disease and its complications. Although there is no detailed study of type I and type II diabetes in developed and developing countries, the complications due to them are widely acknowledged. The type I is less prevalent than type II as per reports identified every year. It is also identified that the incidence increased by 3% every year. The children and adolescents were identified to be associated with type I, while type II is most prevalent condition according to the studies of most developed countries. Also, type II Diabetes was known to be accelerated due to sociocultural alterations such as ageing population, increasing people living in urban areas, low physical activity, increased sugar consumption as well as low fruit and vegetable intake [9].

Table 1: IDF Diabetes Atlas global estimates, 2015 and 2040

	2015	**2040**
Total word population	7.3 billion	9.0 billion
Adult population (20-79 years old)	4.72 billion	6.16 billion
Child population (0-14 years old)	1.92 billion	-
Diabetes (20-79 years)	2015	2040
Global prevalence	8.8% (7.2-11.4%)	10.4% (8.5-13.5%)
Number of people who are diagnosed with diabetes	Average of 415 million.	Average of 642 million
Mortality due to Diabetes	5.1 million	-
Expenditure incurred due to diabetes (20-79 years)	2016	2041
Total expenditure in USD	673 Billion USD	802 Billion in USD
Hyperglycemia in pregnancy (20-49 years)	2015	2040
Proportion of live births affected	16.20%	-
Number of live births affected	20.9 million	-
Impaired glucose tolerance (20-79) years	2015	2040
Global prevalence	6.7% (4.5-12.1%)	7.8%(5.2-13.9%)
Number of people who are presented with impaired glucose tolerance	212.2-571.6 million with average of 318	317.1-855.7 million with average of 481 million
Type I diabetes (0-14 years)	2015	2040
Number of children diagnosed of Type 1 DM	5,42,000	-
New cased diagnosed each year	85,000	-

The exact etiology for Diabetes Mellitus is still uncertain. Nevertheless, the scientists believe that the major risk factors for Diabetes Mellitus are genes, environmental factors and pathological conditions such as autoimmune eradication of the pancreatic β-cells, which gives rise to insulin deficiency and other anomalies.

The main symptoms of Diabetes Mellitus are Polyphagia, Polydipsia and Polyuria which are called as the 3 P's signs. The presence of 3 P's indicates high blood sugar levels. 3P's develop quickly in Type I DM whereas in Type II DM, the 3P's are either absent or develop gradually. Some of the rare symptoms that are reported are weight loss, blurred vision and increased susceptibility to infections. The most life-threatening complication of DM is hyper-glycemia with ketoacidosis. Diabetic patients may also have high blood pressure and abnormality of lipoprotein metabolism. Other long-term symptoms include retinopathy with possible vision loss, nephropathy including kidney failure and peripheral neuropathy [10].

1.1. Classification

Diabetes can be classified into the following types: -

1. Type 1 diabetes (Caused due to the destruction of β-cells which usually leads to deficiency of insulin).
2. Type 2 diabetes (Caused due to the loss of β-cell insulin secretion progressively).
3. Gestational Diabetes Mellitus (which is usually diagnosed in the second or third trimester of pregnancy).
4. Other specific types of diabetes diagnosed due to other causes which include Monogenic Diabetes syndromes (like neonatal diabetes), Diseases of the exocrine pancreas (like cystic fibrosis and pancreatitis) Drug or Chemical-Induced Diabetes (Like glucocorticoid use in the treatment of HIV/AIDS, or after organ transplantation).

The Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentations and disease

progression may vary significantly. Classification of Diabetes Mellitus is important in determining the therapy, but some adults cannot be classified as type I or type II at the time of diagnosis. This disease can occur both in the children and adults. Hallmark symptoms in children are polyuria, polydipsia and diabetic ketoacidosis (in one third of the children) [11].

Hyperglycemia is a condition where there is a progressive loss of beta cells takes place in both Type 1 and Type 2 diabetes. Once hyperglycemia occur patients with both type1 and type 2 diabetes patients are at risk for developing the same chronic complications although rate of progression may differ. The identification of beta cell dysfunction path is required for better characterization and individual therapy. Characterization of underlying pathophysiology is more developed in type 1 diabetes than in type 2 diabetes. The studies state that having first degree relatives of diabetes and having two or more auto antibodies is a predictor of clinical hyperglycemia [12].

The rate of progression is dependent on the age at detection of antibody and number of antibodies, antibody specificity and antibody titer, glucose and A1c levels rise well before the clinical onset of diabetes making diagnosis feasible well before the onset of diabetes ketoacidosis. The paths of beta cell dysfunction are less well defined in type 2 diabetes compared to deficient beta cell insulin secretion frequently in insulin resistance appear to be the common denominator [13].

Characterization of sub type of this heterogenous disorder has been developed and validated in Scandinavian and northern Europe population but have not been confirmed in other ethnic and racial groups Type 2 diabetes is primarily associated with insulin secretion defects related to inflammation and metabolic stress among other contributors including genetic factors [14]. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlaying beta cells dysfunction and the stage of disease as indicated by glucose status.

2. DIAGNOSTIC TESTS FOR DIABETES MELLITUS

Diabetes Mellitus could be diagnosed mainly on the basis of A1C criteria, plasma glucose criteria, the fasting plasma glucose (FPG) or the 2-h plasma glucose value after a 75-g oral glucose tolerance test (OGTT). The same diagnostics are utilized to screen for and diagnose DM as well as to detect individuals with prediabetes.

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinologists (AACE) suggest an HbA1c level of 7.0% and ≤6.5%, respectively, for decreasing the risk of diabetic compromises in most patients [15,16]. The Table 2 shows the main criteria that are set in order to diagnose prediabetes and diabetes.

Table 2: The set criteria for the diagnosing prediabetes and diabetes

	Normal	Prediabetic	Diabetic
HbA1c	<5.6%	5.7-6.4%	>6.5%
FPG	<99mg/dl	100-125mg/dl (5.6-6.9 mmol/lt)	>126mg/dl (7.0mmol/lt)
OGTT	<139mg/dl	100-140-199mg/dl (7.8-11mmol/lt)	>200mg/dl (11.1mmol/lt)*
RPG	RPG>200mg/dL (11.1mmol/lt) **		

***Results are needed to be confirmed after repeat testing. Readings in nonappearance of unequivocal hyperglycemia. ** Feature is a diagnostic criterion in patients showing classic symptoms of Hyperglycemia or its crisis. RPG denotes random plasma glucose.**

3. UPDATED GUIDELINES ON TREATMENT OF DIABETES MELLITUS

The 2016 Guidelines for Diabetes treatment, according to the American Diabetes Association are very certain and not controversial. The guidelines of European Association for the Study of .Diabetes are quite like these. These presented guidelines are in most common use and most clinicians obey on them. Firstly, for DM type I the main course of treatment includes only insulin in various forms, which are fast acting, long acting and finally the intermediate acting insulin [17].

3.1. Current status on medications for type I and II diabetes mellitus

There are a variety of pharmacological agents for the type II diabetic patients to choose, however, for type I patients the list is too short. The most significant limitation on Antidiabetics treatment is the type of drug administration. In general, pharmacological agents differs for TYPE I and TYPE II Diabetes mellitus. The limitations of Antidiabetics treatment depend on the type of drug administration. Usually, the oral formulation of insulin leads to a better quality of life. In most cases, insulin is the only drug used to reduce the glucose levels. Recently, many researchers are focusing on the usage of novel drugs to improve the quality of life. Every patient diagnosed with Type I requires lifelong insulin therapy of which the three main categories are the rapid-acting insulin, long-acting insulin and intermediate options to be chosen.

The FDA approved Pramlintide, an injectable medication for the people who had Type 1 Diabetes Mellitus and Insulin for those who had Type II Diabetes Mellitus. Pramlintide mechanism was based on the fact of how Amylin, a natural hormone from the pancreatic beta cells works. The main mechanism of how it acts was that it promotes excess weight loss, thereby keeping the blood glucose levels lower and suppresses the production of glucagon. However, some researchers believe that Metformin and Sodium Glucose Co-Transporter 2 Inhibitors are also approved for type II Diabetes Mellitus and could also be involved for Type I Diabetes Mellitus [18]. Medications of type II Diabetes Mellitus includes several active ingredients along with insulin. As it was already referred, Diabetes type II is known

to complicate the health of the patients and affect a huge adult population.

3.2. Biguanides

Biguanides are regarded as a class of drugs that are commonly used for their anti-diabetic properties. A very commonly used drug, Metformin is an example of a drug from this class. They are organic compounds with this basic chemical formula:

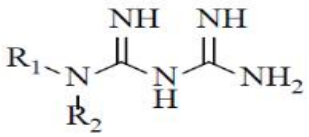

Fig 1: Chemical Formula of Biguanides

Metformin is the most significant analogue of Biguanides and was known since 1959, but it was only commercially available from the late 90's.Itworks by reducing the hepatic production of glucose, it increases the insulin sensitivity and the peripheral utilization of glucose in the body, thereby decreasing the blood glucose levels. It is mainly used to treat Type II Diabetes Mellitus. It is either used individually or alongside in combination with other anti-diabetic agents. It lowers the Hba1c levels in the body by 1-2% [18]. Metformin use in DM2 may contribute to reduced mortality rates in Cancers. Gold nanoparticles (AuNPs) were conjugated with Hyaluronic Acid (HA) and loaded with metformin on HA capped AuNPs (H-AuNPs). These nanoparticles have an affinity to easily bind to the surface of the liver cancer cells, exhibiting promising results.

Metformin is formulated in different delivery systems. Metformin is an aqueously soluble molecule which makes it difficult to turn it into a sustained release formulation matrix. Sustained release is necessary for oral routes as it decreases the frequency of the drug which in turn, increases the adherence of the drug from the patient's side. Therefore, current researches on Metformin avoid burst release and focus on a way to deliver a longer duration of action of the drug in the body [19].

Sustained release dosage forms prepared by wet granulation method included a variety of hydrophilic macromolecules such as Hydroxyl-propyl methylcellulose (HPMC) K15M, HPMC K100M, HPMC K200M), Polyacrylate polymers, Eudragit RL100 and Eudragit RS100. These were investigated as drug delivery systems of metformin-controlled administration. The in vitro release studies of the above systems indicated that the different combinations of these materials may modify the dissolution rates of the drug in the body. An extended release tablet containing Metformin was successfully prepared using melt granulation combining the hydrophobic stearic acid and hydrophilic polyethylene oxide. The matrix tablet formulation showed a controlled drug release profile [20].

The carriers were designed by a process called as Solvent Evaporation and co-grinding technique. It is identified that the ratio of the polymer effects the release rate of the drug. Similar solid dispersions were also formulated by solvent evaporation and closed melt method, using Compritol 888 ATO as the polymer. Solvent evaporation helped to design the sustained release forms. Gastro retentive floating tablets containing metformin were produced using wet solid dispersion methodology with cellulose derivatives such as HPMC K4M, HPMC K15M in different ratios, sodium bicarbonate and citric acid gas generating agents and other excipients. Floating tablets were prepared by wet solid dispersion method. Adjustment of different parameters ensured that the releases were controlled, and formulations were stable [21].

3.3. Sulfonylureas

These compounds were discovered in the year 1937, when their hypoglycemic properties were noticed by the doctors. Figure 3 below shows the chemical formula of these compounds. Their mechanism of action is to trigger insulin release from pancreatic b-cells45. In addition can decrease the hepatic glucose production and the uptake of hepatic insulin while can increase the glucagon secretion by pancreatic α-cells [22].

The main disadvantage of using these compounds is that, they produce insulin excessively upon release and thereby induce hypoglycemia. Some of the first-generation drugs include Tolbutamide, Acetohexamide, Tolazamide, Carbutamide, Metahexamide and Chlorpropamide. The second-generation drugs are Glicazide, Glibenclamide and Glyclopyramide. Glimepiride is considered as third generation drug [23].

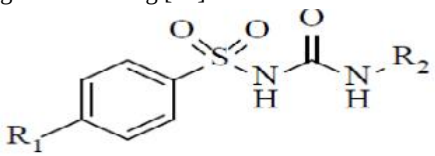

Fig 2: Chemical Formula of Sulfonylureas

Pharmaceutical formulations for the delivery of sulfonylureas are varied. In most case sulfonylurea agents are lipophilic molecules which their low solubility decreases their bioavailability and therapeutic efficacy. Pharmaceutical technology purposed to improve their water solubility by the preparation of solid dispersions and other pharmaceutical formulations. More specifically, solid dispersions of the Glibenclamide were developed by solvent evaporation utilizing hydrophilic polymers as PEG 6000, PVP K30, Sorbitol, Mannitol, Mannitol, citric acid and urea in various concentrations. The results depicted that the amorphous formulation present high dissolution rates [24].

The release studies illustrated that the two methods were able to enhance and extend the release rate while the formulations were bioequivalent with a marketed product [25]. Various co-excipients such as HPMC K100M, starch and CMC, were also studied. It was investigated that the release was enhanced. Glyburide was encapsulated in a hard gelatin capsule using Avicel and Magnesium Stearate in various ratios like Atenolol. Some formulations showed that

can improve patient compliance by improving the ease of two drugs administration together [26].

An enhancement on the solubility of Glipizide was aroused after being dispersed with the help of the hydrophilic Poloxamer, Cyclodextrin, and Povidone. The optimized candidate was further entrapped into non-effervescent floating tablets (NEFT) with the use of Crospovidone and release retarding agents like HPMC and PEO. In-vitro buoyancy and release studies demonstrated that non-effervescent floating drug carriers can be a promising method to extent the gastric retention time and enhance bioavailability of glipizide [27].

Several systems incorporated Glibenclamide based on spray congealing were formulated with the use of enough excipients, solid at room temperature, as Myverol and Gelucire. Researchers believe that the spray congealing is an auspicious novel manufacturing technique of solid self-emulsifying systems [28] Microcapsules of gliclazide-deoxycholicacid using sodium alginate were studied for their efficiency and size, release kinetics, stability and swelling studies at various and temperatures. The micro-carrier displayed colon-targeted delivery and the addition of Deoxycholic acid prolonged Gliclazide release suggesting its suitability for the sustained and targeted delivery of both molecules to the lower intestine [29]

3.4. Insulin

Insulin was invented in 1922 and had a great significance in medicine and therapy in diabetes. Long before it was said that pancreas secreted a substance that controlled carbohydrate metabolism [30]. John Macleod: professor of physiology and department head at the University of Toronto, for laboratory space. May 17, 1921, by September they showed that the Depancreatised dog developed DM and they gave IV inj. With pancreatic extract i.e., Isletin, lowered the blood glucose. By the end of 1921, the biochemist J.B collop helped the existing research team to purify the Islet in for human use. Eli lilly initiated production of insulin from animal pancreas but fell short of the demand, and the potency varied up to 25%per lot. Isoelectric precipitation is a method which led to purer and most potent animal insulin. In 1923, AugustKrogh from the university of Copenhagen met with other scientist and he determined to pursue more information regarding insulin. A non-profit body, Nordisk insulin laboratory, began insulin production [31].

In 1930, H. Chagedorn, a chemist in Denmark, prolonged the action of insulin by adding Protamine. To that zinc was added to increase further action. Protamine zinc insulin lasted 24-36 hours. The Pka and effects of amorphous Lente insulin depends on proportion of zinc. In 1978 the first rDNA human insulin was prepared by David Goeddel by combining insulin A and B chains expressed in E. coli. In 1982, the 1st insulin utilizing rDNA technology, Humulin R and N were marketed [32].

In 1993, the diabetes control and complication showed linear relationship between the degree of glycemic control and complication.to reduce the incidence of hypoglycemia, which is the major limiting factor for intensive glycemic control. Modification of the site if amino acid in insulin changed the Pka and lead to faster absorption, earlier peak of action and shorter duration of action. Lispro-first short acting insulin in 1996; followed by as part in 2000; Glulisine in 2004 [33].

Currently, Glargine approved in 2000 and Detemir, approved in 2005 it has Glycine instead of asparagine at position A21 and extra 2 Arginine molecules at position B-30 and a pH of 4. Insulin has a 14-carbon fatty acid chain attached to lysine at position B-29 which slows its absorption [34] Exubera is a form of alternative delivery method for Insulin in inhalational form and was developed by Sanofi-Aventis and Pfizer and marketed by Pzifer in 2006. The inhaler device was bulky to use. It did not add physiologic benefit over rapid-short acting insulin analogs. It was taken off the market after two years when it failed to gain acceptance from patients and providers [35]

4. CONCLUSION

Diabetes Mellitus is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. Education of the populace is still key to the control of this emerging epidemic. Novel drugs are being developed, yet no cure is available in sight for the disease, despite new insight into the pathophysiology of the disease. Management should be tailored to improve the quality of life of individuals with Diabetes Mellitus.

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Conflict of Interest: None
Source of Funding: Nil