IJPSR (2013), Vol. 4, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 August, 2012; received in revised form, 13 December, 2012; accepted, 29 December, 2012

NEED FOR NEW HYPOGLYCEMIC AGENTS: AN OVERVIEW

Muhammad Shoaib Akhtar [1], Nadeem Irshad*[1], Abdul Malik [1] and Yousaf Kamal [2]

Department of Pharmacology, Faculty of Pharmacy, University of Sargodha [1], Sargodha, Pakistan
Hamdard Institute of Pharmaceutical Sciences, Hamdard University [2], Islamabad campus, Pakistan

Keywords:
Diabetes mellitus, DPP-IV inhibitors, Insulin, Micro vascular complications

Correspondence to Author:

Nadeem Irshad

Department of Pharmacology, Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan

E-mail: ndmirshad@gmail.com

QUICK RESPONSE CODE

IJPSR:
ICV: 5.07

Website:
www.ijpsr.com

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases. Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, meglitinide, DPP-IV inhibitors, α- glucosidase inhibitors, thiazolidenediones, bile acid sequestrant, D2 dopamine receptor agonist, GLP-1 receptor agonist, amylin analogues. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycemic agents or insulin (pharmacological). The main side effects are weight gain and hypoglycemia with sulphonylureas, gastrointestinal (GI) disturbances with metformin, weight gain, GI disturbances and liver injury with thiazolidinediones, GI disturbances, weight gain and hypersensitivity reactions with meglitinides and flatulence, diarrhoea and abdominal bloating with alpha-glucosidase inhibitors. In this article, different types of diabetes, current treatment and their adverse effects which lead to development of new hypoglycemic agents have been studied.

INTRODUCTION: Diabetes mellitus is a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins [1]. DM encompasses a family of disorders of carbohydrate metabolism that are characterized by hyperglycemia and the development of long term macro vascular, micro vascular and neuropathic complications [2]. It has been reported that diabetes is mostly due to the environmental and hereditary causes which lead to high level of glucose in the blood called hyperglycemia [3]. As the disease progresses tissue or vascular damage ensues which lead to severe diabetic complications such as retinopathy [4] neuropathy [5] nephropathy [6] cardiovascular complications [7] and ulceration [8]. Thus, diabetes covers a wide range of heterogeneous diseases.

Types of Diabetes mellitus: American Diabetes Association (2009 a, 2009 b) has divided the diabetes into four clinical classes. Majority of the cases of diabetes fall into two major etiopathogenetic categories that is type 1 and type 2 diabetes.

1. **Type 1 Diabetes Mellitus:** Type 1 diabetes mellitus formely known as insulin dependent diabetes mellitus (IDDM) which occurs as a result of cellular-mediated autoimmune destruction of the pancreatic β- cells. Generally this demolition of the beta cells leads to absolute insulin deficiency [9, 10]. As the beta cells destruction is quite rapid in infants and children therefore prevalence of type 1 diabetes is greater in children and young as compared to others [11]. It also developed in many type 2 diabetic patients with severe insulin resistance [12]. This form accounts for only 5 - 10% of the diabetic patients [13].

2. **Type 2 Diabetes mellitus:** It is also known as the non-insulin dependent diabetes mellitus (NIDDM) and occurs as a result of progressive insulin secretory defect along with insulin resistance [14, 15, 10]. Its different forms are characterized by a variable degree of insulin resistance and β cells dysfunction [16]. It is the most common form of diabetes. About 90 to 95% of people with diabetes are suffering from type 2 DM [17, 13]. It is related with family history, age, ethnicity, previous history of gestational diabetes and physical inactivity [18, 19].

3. **Gestational Diabetes mellitus:** This type develops by glucose intolerance with onset or first recognition during pregnancy [13]. In certain cases, unrecognized glucose intolerance may have started along with the pregnancy [20]. Women suffering from gestational diabetes may have a chance of developing type 1 or type 2 diabetes [21, 22].

Diabetes due to other causes (e.g., genetic defects or medication induced):

A. Genetic defect of β-cell function characterized by mutation in hepatocyte nuclear transcriptional factor (HNF) 4α [Maturity-onset diabetes of the young (MODY 1)], Glucokinase (MODY 2), HNF-1α (MODY 3), insulin promoter factor IPF 1 (MODY 4), HNF-1β (MODY 5), NeuroD1 (MODY 6) and mitochondrial DNA.

B. Genetic defect in insulin action.

C. Endocrinopathies such as acromegaly, Cushing's syndrome and hyperthyroidism.

D. Drug or chemical induced such as beta blockers, nicotinic acid, protease inhibitor, thiazides and glucocorticoids.

E. Infections such as congenital rubella and cytomegalovirus [23].

Prevalence of Diabetes mellitus: Diabetes mellitus is a global epidemic affecting approximately 285 million people worldwide, that will increase to 439 million by 2030 [24]. South Asians, including Bangladeshis, Indians, Pakistanis, and Sri Lankans, are particularly vulnerable to diabetes but their occurrence rates differ across South Asian ethnicities, and show higher prevalence than Caucasians [25].

South Asian children have increased plasma insulin in normal plasma glucose levels, which is an early sign of insulin insensitivity [26, 27]. Diabetes is the fourth leading cause of death in most developed countries (International Diabetic Federation, 2010) with Pakistan currently ranking at 7th position in the list of countries with major burden of DM and it is expected to move to 4th position if present situation continues [28].

Incidence of type 1 diabetes was estimated to be 1.02/100000 per year in Karachi, Pakistan [29] and rate of gestational diabetes in Pakistan range from 3.2% to 3.5%, comparable to Western populations but the rates of complications both to mother and fetus were found to be higher which may be due to poor glycemic control [30, 31]. Incidence rate of diabetes, especially Type-2 diabetes in Pakistan is posing threats to the economy and quality of life of people [32].

Pharmacotherapy: The primary aim of the treatment is to save life and alleviate symptoms. Secondary aims are to prevent long term diabetic complications and, by eliminating various risk factors, to increase longevity. The first aim is not difficult to attain and in some elderly patients or those who lack motivation it is the only aim [33]. The care of diabetes on self management is based on the patient's clinical status and his/her ability to participate in self-care. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM.

Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, meglitinide, DPP-IV inhibitors, alpha glucosidase inhibitors, thiazolidenediones, bile acid sequestrant, D2 dopamine receptor agonist, GLP-1 receptor agonist, amylin analogues and insulin [34] .

The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes.

Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes (NIH, 1995).

Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycemic agents or insulin (pharmacological).

Non-pharmacological management of Diabetes: In Pakistan, combine survey on the prevalence of diabetes mellitus conducted by Diabetic Association of Pakistan in collaboration with WHO shows that prevalence of diabetes is over 10% in both sexes in the people aged 25 years or above. Impaired Glucose Tolerance (IGT) was found to be over 13% in women and over 7% in men. Thus overall Abnormal Glucose Tolerance (AGT) was present in 20% of the subjects examined. Prevalence of glucose intolerance increased with age in both sexes. Age specific prevalence of IGT was higher for women than men at almost all ages.

Diabetes self-management: Diabetes self-management training is the process of educating the individuals that they enable to manage their diabetes which is considered an important part of clinical management since the 1930 [35]. The goals of diabetes education are to optimize metabolic control, prevent acute and chronic complications, and optimize quality of life with minimum and acceptable costs.

Exercise: Exercise plays an important role in improving health, particularly in persons with obesity and its related health complications. Regular activity may reduce lipid levels, blood pressure, and the risk of osteoporosis and improve insulin sensitivity, abdominal adiposity, and glycemic control in patients with Type-2 diabetes [36, 37].

Life style activity: The obese diabetic patients increase their energy expenditure with their lifestyle activity [38, 39]. Lifestyle activity involves increase energy expenditure throughout the course of the day, without concern for the intensity or duration of the activity. Patients can increase their lifestyle activity by parking further away from store entrances, taking stairs rather than escalators, or getting off the bus 3 stops early and walking the remainder of the way. The energy expenditure associated with such events may sum to 300 kcal per day, the equivalent of walking 3 miles [36].

Pharmacological management of Diabetes mellitus:

1. **Insulin treatment in Diabetes mellitus:** The introduction of insulin to treat diabetes has saved an estimated 5 million years of life for patients with type 1 diabetes during the year 2000 [40]. Considerable progress has been made, in recent

years, in the production, formulation and delivery of insulin preparations, as well as the development of insulin treatment regimens which maintains long-term-normoglycaemia, with a low risk of hypoglycemia [41, 42]. The importance of the aim of preventing or slowing the progression of chronic micro vascular complications has been conclusively proven during the last decade, in both type 1 and type 2 diabetes (UKPDS, 1998). Unfortunately, patients treated with insulin have uniformly poorer glycemic control compared to those treated with other therapies.

2. **Oral hypoglycemic agents:** Oral hypoglycemic agents are summarized in **table 1** along with their adverse effects.

TABLE 1: PHARMACOLOGIC AGENTS FOR GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES

Class	Agent (Brand Name)	Expected reduction in HbA1c level %	Advantages	Disadvantages	Cost
Oral					
Biguanides	Metformin (Glucophage)	1.0–2.0	Extensive clinical experience; hypoglycemia rare; improved lipid profile; decreased cardiovascular disease events; some weight loss in most patients	Gastrointestinal intolerance; lactic acidosis rare (avoid in patients at increased risk, such as men with a serum creatinine level of ≥1.5 mg/dl and women with a serum creatinine level of ≥1.4 mg/dl); vitamin B12 deficiency	Low (generic)
Sulfonylurea	Glyburide (Diabeta), glipizide (Glucotrol), Gliclazide(Diamicron), glimepiride (Amaryl)	1.0–1.5	Extensive clinical experience	Hypoglycemia; less durability; weight gain	Low (generic)
Meglitinide	Nateglinide (Starlix), repaglinide (Prandin)	0.5–1.0	Short duration of action, hepatic clearance, glucose-dependent postprandial action	Low efficacy, hypoglycemia in some patients, weight gain	High
Thiazolidine-dione	Rosiglitazone (Avandia), pioglitazone (Actos)	0.5–1.4	Hypoglycemia rare, more durable effect than that of metformin or sulfonylurea, improved lipid profile, some evidence of beneficial effect on coronary atherosclerosis (with pioglitazone)	Edema, heart failure, weight gain, increased risk of long-bone fractures and potential risk of bladder cancer and cardiovascular events (with rosiglitazone); use of rosiglitazone highly restricted	High
DPP-IV inhibitor	Saxagliptin (Onglyza), linagliptin (Tradjenta), vildagliptin (Galvus), sitagliptin (Januvia)	0.5–0.8	Hypoglycemia rare, infrequent side effects	Less efficacy than GLP-1–receptor agonists, angioedema, unknown long term safety, risk of pancreatitis	High
α-glucosidase inhibitor	Miglitol (Glycet), voglibose (Volix),§ acarbose (Precose)	0.5–0.9	Decreased level of postprandial glucose, hypoglycemia rare, possible decrease in risk of cardiovascular disease events	Flatulence, diarrhea	Moderate
Bile acid sequestrant	Colesevelam (Welchol)	0.5	Lowering of LDL cholesterol level; hypoglycemia rare	Gastrointestinal side effects, including constipation; low efficacy; only approved agent in class	High
D2 dopamine–receptor Agonist	Bromocriptine, rapid release (Cycloset)	0.5	Hypoglycemia rare	Low efficacy; gastrointestinal side effects, including nausea; fatigue; dizziness; rhinitis; only rapid-release agent approved	High

Injectable					
GLP-1–receptor agonist	Exenatide (Byetta), exenatide once weekly (Bydureon), liraglutide (Victoza)	0.5–1.5	Hypoglycemia rare, weight loss in most patients; possible protective cardiovascular effects	Nausea and vomiting; risks of pancreatitis, thyroid C-cell hyperplasia, and tumors (with liraglutide and weekly exenatide); unknown long-term safety	High
Amylin analogue	Pramlintide (Symlin)	0.5–1.0	Weight loss in most patients, control of postprandial glycemia	Nausea and vomiting, modest effect, hypoglycemia with insulin use, unknown long-term safety	High
Insulin	Short-acting: human insulin (Novolin R or Humulin R), aspart (Novolog), glulisine (Apidra), lispro (Humalog); long-acting: neutral protamine Hagedorn (Novolin N or Humulin N), detemir (Levemir), glargine (Lantus); mixed insulin preparations	1.0–2.5	Large effect in all patients	Hypoglycemia, weight gain	Moderate to high

DPP-IV denotes dipeptidyl peptidase IV, GLP-1 glucagon-like-peptide-1, and LDL lowdensity Lipoprotein [34]

CONCLUSON: The review has summarized that there is potential need of new hypoglycemic agents which are free from noxious effect, favorably like herbal treatment.

REFERENCES:

1. Mushtaq A, Shoaib MA, Tahira M, Anwar HG. Hypoglycemic action of the flavonoid fraction of *Cuminum nigrum* seeds. . *Pharm. Med*. 2000. 16: 103-106.
2. Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus. *Diabetes Care* 2002, 25**,** 5–20.
3. Tierney LM, McPhee SJ, Papadakis MA. Current medical Diagnosis & Treatment. International edition. New York: Lange Medical Books/McGraw-Hill. 2002, 1203–1215.
4. Hove MN, Kristensen JK, Lauritzen T, Bek T. T he prevalence of retinopathy in an unselected population of type 2 diabetes patients from Arhus County, Denmark. *Acta Ophthalmol Scand;* 2004, 82: 443-448.
5. Moran A, Palmas W, Field L. Cardiovascular autonomic neuropathy is associated with Microalbuminuria in older patients with type 2 diabetes. *Diabetes care*; 2004, 27: 972-977.
6. Huang C, Kim Y, Caramori ML. Cellular basis of diabetic nephropathy: II. The transforming growth factor-beta system and diabetic nephropathy lesions in type 1 diabetes. *Diabetes*, 2002, 51: 3577-3581.
7. Saely CH, Aczel S, Marte T. Cardiovascular complications in type 2 diabetes mellitus depends on the coronary angiographic state rather than on the diabetes state. *Diabetologia*; 2004, 47: 145-146.
8. Wallace C, Reiber GE, LeMaster J. Incidence of falls, risk factors for falls, and fall-related factures in individuals with diabetes and a prior foot ulcer. *Diabetes Care*; 2002, 25: 1983-1986
9. Atkinson, M.A. and N.K. Maclaren .The pathogenesis of insulin dependent diabetes. *N. Engl. J. Med;* 1994, 331:1428-1436
10. American Diabetes Association (ADA). Standards of medical care in diabetes. *Diabetes Care.* 2009 a, 32(1):S13-S61.
11. Zimmet, P.Z., T. Tuomi, R. Mackay, M.J. Rowley, W. Knowles, M. Cohen and D.A. Lang. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet. Med*.; 1994, 11:299-303.
12. Suehiro, T., F. Osaki, Y. Ikeda, K. Arii, F. Nakayama, K. Ota and K. Hashimoto. Type 1 diabetes developed in a type 2 diabetic patient with severe insulin resistance. *Diabetes Research and Clinical Practice,* 2005, 70:298-302
13. American Diabetes Association (ADA). Diagnosis and classification of diabetes mellitus. *Diabetes care*, 2009 b, 32(1):S62-S67.
14. Turner, R.C, R.R. Holman, D. Matthews, T.D.R. Hockaday and J. Peto. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism*, 1979, 28:1086-1096.
15. Olefsky, J.M., O.G. Kolterman and J.A. Scarlett. Insulin action and resistance in Obesity and noninsulin-dependent type 2 diabetes mellitus. *Am. J. Physiol*.; 1982, 243:15-30.
16. American Diabetes Association (ADA) .Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, 2001, 24(1):S5-S20.
17. DeFronzo, R.A. Pathogenesis of type 2 diabetes: Metabolic and molecular Implication for identifying diabetes genes. *Diabetes Rev*., 1997, 5:177-267.
18. Bogardus, C., S. Lillioja, D.M. Mott, C. Hollenbeck and G. Reaven. Relationship between degree of obesity and *in-vivo* insulin action in man. *Am. J. Physiol*., 1985; 248:286-291.
19. Zimmet, P.Z .Kelly West Lecture. Challenges in diabetes epidemiology: from west to the rest. Diabetes Care, 1992, 15(2):232-252.

20. Metzger, B.E .Summary and recommendations of the third international workshop conference on gestational diabetes mellitus. *Diabetes*; 1991, 40(2):197-201.
21. O'Sullivan, J.B. Diabetes after GDM .*Diabetes*, 1991, 40 (Suppl. 2):131-135.
22. Coustan, D.R., M.W. Carpenter, P.S. O'Sullivan and S.R. Carr. Gestational diabetes: Predictors of subsequent disordered glucose metabolism. *Am. J. Obstet. Gynecol*., 1993, 168:1139-1145
23. Dennis L. Kasper, Eugene Braunwald, Anthony S. Fauci, Stephen L. Hauser, Dan L. Longo. Diabetes mellitus. Harrison's Principles of internal medicines, 2005. 16: 2152-2180
24. Shaw JE, Sicree RA and Zimmet PZ .Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2009; 87(1):4-14.
25. Bhopal R, Unwin N, White M, Yallop J, Walker L and Alberti KG. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: Cross sectional study. *BMJ.* 1999; 319 (7204):215-20
26. Whincup PH, Gilg JA, Papacosta O, Seymour C, Miller GJ and Alberti KG .Early evidence of ethnic differences in cardiovascular risk: Cross sectional comparison of British South Asian and white children. *BMJ*, 2002,324 (7338):635
27. Ehtisham S, Crabtree N, Clark P, Shaw N and Barrett T. Ethnic differences in insulin resistance and body composition in United Kingdom adolescents. *J Clin Endocrinol Metab*; 2005, 90(7):3963-9.
28. Khuwaja AK, Fatmi Z, Soomro WB, Khuwaja NK. Risk factors for cardiovascular disease in school children--a pilot study. *J Pak Med Assoc*; 2003, 53:396-400
29. Staines A, Hanif S, Ahmed S, McKinney PA, Shera S and Bodansky HJ .Incidence of insulin dependent diabetes mellitus in Karachi, Pakistan. *Arch Dis Child*; 1997, 76:121-3.
30. Ahkter J, Qureshi R, Rahim F .Diabetes in pregnancy in Pakistani women: prevalence and complications in an indigenous south Asian community. *Diabet Med*; 1996, 13: 189-91
31. Rizvi JH, Rasul S, Malik S, Rehamatuallh A, Khan MA .Experience with screening for abnormal glucose tolerance in pregnancy: maternal and perinatal outcome. *Asia Oceania J Obstet Gynaecol;* 1992, 18:99-105.
32. Basit A, Hydrie M Z I, Ahmed K and Hakeem R. Prevalence of diabetes impaired fasting glucose and associated risk factors in a rural area of Baluchistan province according to new ADA criteria. *J Pak Med Assoc* 2002; 52: 357-60
33. Watkins PJ, Drury PL, Taylor KW .An Overview of management. In: diabetes and its Management. ED Blackwell Scientific Publication; fourth edition, 1990. pp 63-66.
34. Beigi FI. Glycemic Management of Type 2 Diabetes mellitus. *The New England journal of medicine;* 2012, 366:1319-27.
35. Bartlett E. Historical glimpses of patient education in the United States. Patient based therapy and beyond. *Circulation* 2008; 117(4): 574-584.
36. Blair SN and Leermakers EA.Exercise and weight management. In Wadden TA, Stunkard AJ (Eds), Handbook of obesity treatment. New York Guilford Press 2002; 283–300
37. Foreyt JP and Poston WSC. The challenge of diet, exercise, and lifestyle modification in the management of the obese diabetic patient. *Int J Obes Relat Metab Disord*. 1999; 23:5–11.
38. Epstein LH, Wing RR, Koeske R and Valoski A. A comparison of lifestyle exercise, Aerobic exercise calisthenics on weight loss in obese children. *Behav Ther* 1985; 16:345–356.
39. Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ and Franckowiak SC. Effects of lifestyle activity vs. structured aerobic exercise in obese women: a randomized trial. *JAMA* 1999; 281:335–340.
40. Owens DR, Zinman B, Bolli GB. Insulins today and beyond. *Lancet*; 2001, 358: 739-746.
41. Bolli GB. Hypoglycemia unawareness. *Diabetes Metab*; 1997, 23 (suppl 3): 29-35.
42. Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as non-intensive treatment of type 1 diabetes mellitus. *Diabetes Care;* 1999, 22 (suppl 2): 43-52.

How to cite this article:
Akhtar MS, Irshad N, Malik A and Kamal Y: Need for New Hypoglycemic Agents: An Overview. *Int J Pharm Sci Res*.,2013 4(1); 77-82.