International Journal of Pharmaceutical Archive-2(9), 2013, 216-223 **CIJPA** Available online through www.ijpaonline.info ISSN 2319-7226

REVIEW ARTICLE

NOVEL THERAUPETICS IN THE TREATMENT OF TYPE-II DIABETES

Ramani Gade*, Sravan Kumar.T, M. Sai Sowjanya and V. Manasa Rosamble

Department of pharmaceutics, Priyadarshini Institute of pharmaceutical Education and Research, Pulladigunta, Guntur (DT), Andhrapradesh, 522017-India.

(Received on: 21-08-13; Revised & Accepted on: 11-09-13)

ABSTRACT

T ype II diabetes is characterised by insulin resistance accompanied by progressive deficiency in insulin secretion. Type II diabetes is increasingly a common disease that is closely associated with obesity. Observational studies and clinical trials show that improved glycimic control reduces micro (eye, kidney and nerve) and macro (heart) vascular complications. However the effect of specific oral diabetes medications on these outcomes is less certain.

As new classes of medications have become available for the treatment of diabetes, clinicians and patients have faced a bewildering array of oral medications with different mechanism of action. This review will be helpful as new classes of oral diabetic medication. Furthermore, it may help policy makers and insurers to have better insight when deciding on policies, relating to medication coverage.

Key words: type II diabetes, insulin secretion, obesity, glycemic control, oral diabetic medication.

INTRODUTION

Definition: Diabetes mellitus is a group of metabolic disorders characterized by hyperglycaemia associated with abnormalities in carbohydrate, fat and protein metabolism; and resulting in chronic complications including micro vascular and neuropathic.

What is diabetes?

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels, which result from defects in insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes (and in this article will be referred to as "diabetes"), was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic medical condition, meaning although it can be controlled, it lasts a lifetime.¹

Classification of Diabetes: 2,3

Diabetes is of mainly two types

- 1. Type 1 (also called Insulin-Dependent Diabetes Mellitus or IDDM)
- Diabetes arises when the beta cells in the pancreas fail to produce enough of the hormone insulin
- 2. Type 2 (also called Non-Insulin-Dependent Diabetes Mellitus or NIDDM) Diabetes arises when the body cannot effectively use the insulin produced. *90% of people with diabetes have type 2 diabetes*

Corresponding author: Ramani Gade*

Department of pharmaceutics, Priyadarshini Institute of pharmaceutical Education and Research, Pulladigunta, Guntur (DT), Andhrapradesh, 522017-India. E-mail: ramanigade169@gmail.com

Other specific types of Diabetes:

- Genetic defects of β-cell function (eg. MODY)
- Genetic defects in insulin action
- Diseases of the endocrine pancreas
- Endocrinopathies
- Drug or chemical induced
- Infections
- Gestational Diabetes Mellitus (GDM)

Causes for type-I Diabetes:

• Insufficient production of insulin (either absolutely or relative to the body's needs), production of defective insulin (which is uncommon),

Causes for type-II Diabetes:

• The inability of cells to use insulin properly and efficiently leads to hyperglycaemia and diabetes. This latter condition affects mostly the cells of muscle and fat tissues, and results in a condition known as "insulin resistance." This is the primary problem in type 2 diabetes. In type 2 diabetes, there also is a steady decline of beta cells that adds to the process of elevated blood sugars.



Fig.1: schematic representation of reasons for type-II Diabetes.

Symptoms of type-II Diabetes:

Type 2 diabetes is often without symptoms in its early stages. That's the reason there are 40% of people with Type 2 diabetes are unaware of their disease. When there are symptoms, they may occur gradually. If present, they usually are:

- O feeling tired and weak
- O passing large volumes of urine, especially during the night
- O having frequent infections
- O having blurred eyesight
- O Weight-loss
- O Excessive hunger and thirst

Risk factors:

If left untreated this, Diabetes can cause many life threatening complications:

- Blindness
- Chronic Renal Failure= kidney failure
- Atherosclerosis= heart attacks and stroke
- Diabetic Neuropathy= numbness and pain to hands and feet
- Foot Ulcers
- Autonomic Neuropathy= diarrhea, rapid heartbeat, and low blood pressure
- Coma or death may occur as a result in Diabetic Ketoacidosis (caused by infection)
- People who smoke are a much higher risk at heart attacks, stroke, infections, and problems with poor circulation

© 2013, IJPA Online, All Rights Reserved



Fig.2: schematic representation of symptoms of type-II Diabetes

Diagnostic criteria for diabetes and its risk states:⁴

Table1.Fasting plasma glucose test (FPG) results

	Diabetes	126mg/dl or greater		
	Pre-diabetes	125mg/dl to 100mg/dl		
	Normal	Less than 100mg/dl		
;	*mg/dl=milligram/decilitre			

2. Blood Glucose Targets for Adults

- Pre-meal or fasting: 80-120mg/dl
- 2 hours post-meal: 80-140mg/dl
- Bedtime: 80-140 or 100-140mg/dl

3. HbA1c: the blood test for diagnosis of diabetes

When hemoglobin picks up glucose from bloodstream, the hemoglobin becomes glycosylated. Glycosylated hemoglobin is HbA1c. The HbA1c test measures the percentage of HbA1c in blood—a number that corresponds to your average blood glucose for the previous 3 months.

Table2. Diagnosis of type-II diabetis based on HbA1C Level

Diagnosis*	HbA1C Level
Normal	below 5.7 percent
Diabetes	6.5 percent or above
Prediabetes	5.7 to 6.4 percent

*Any test for diagnosis of diabetes requires confirmation with a second measurement unless there are clear symptoms of diabetes.

4. Other diagnostic methods

Blood pressure< 130/80 mmHg for non-pregnant adults. High density lipids HDL (good) cholesterol – >40 mg/dl (men); >50 mg/dl (women) Low density lipidsLDL (bad) cholesterol – <100 mg/dl Triglycerides – <150 mg/dl

Treatment for type- I Diabetes: ⁵

Insulin therapy:

Insulin is the mainstay of treatment for patients with type1 diabetes, insulin is also important in type 2 diabetes when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications.

Commonly used insulin types

- 1. Humlog and novolog / very short acting
- 2. Regular / short acting

© 2013, IJPA Online, All Rights Reserved

- 3. NPH / Inter mediate acting
- 4. Lente / Inter mediate acting.
- 5. Ultrot Lente / Long acting
- 6. Lanctus.

Treatment methodology for type-II Diabetes: ⁶

1. Dietary therapy:

Diet and exercise are the first treatment of choice for patients with type 2 diabetes. 'Diabetic foods' are not recommended as they are often expensive and their nutritional content is not always compatable with healthy eating advice.

Two basic types of diet are used in the treatment of diabetes: low-energy, weight-reducing diets and weight maintenance diets.

(a) Low-energy, weight-reducing diets:

Dietary prescriptions, which cause a daily deficit of 500kcal, provide a realistic diet and induce a weekly weight loss of around 0.5kg. Rapid weight reduction may provoke loss of lean body tissue, and care must be taken in the elderly to avoid the omission of essential nutrients, vitamins and minerals. Caloric restriction is essential for the obese diabetic patient treated with insulin and most oral agents, to try to minimize the weight gain, which these can promote. In such individuals, the omission of snacks between meals is often necessary.

(b)Weight maintenance diets:

These are necessary for individuals with a normal Body Mass Index (BMI) and should be high in carbohydrate and low in fat, with particular attention being paid to the type of fat ingested.

Meal Planning:

With type 2 Diabetes you have to eat healthy in order to keep your sugar levels well maintained. That means:

- o Fruits and vegetables (apples, bananas, broccoli, spinach, etc.)
- o Whole grain, cereals, and bread. (Wheat, barley, rice and bran.)
- o Dairy products (yogurt, skim milk, cream)
- o Meat: fish, poultry, eggs, dried beans

Weight-loss:

- > Obesity increases insulin resistance and can lead to many other cardiovascular health problems.
- However the diabetic that carries the disease and loses weight, will see a decrease in blood glucose levels and a decrease in taking oral medication

When the diet and exercise do not achieve adequate blood glucose control, initiation with oral anti- diabetic is advocated.

(3)Oral Hypoglycemic Agents:⁷

- I. Sulfonyl ureas:
- (a) I Generation

Tolbutamide Chlorpropamide

- (b) II Generation
- Glibenclamide Glipizide Gliquidone Gliclazide Glimepiride

II Biguanides:

Metformin

III Non Sulfonyl urea insulinotropic: repaglinide (Prandin) and nateglinide (Starlix)

IV Thiazolidine diones:

Rosiglitazone Pioglitazone

Based on what is known, medications for type 2 diabetes are designed to:

- 1. Increase the insulin output by the pancreatic β cells. Ex: sufonylureas and maglitindes.
- 2. Insulin released by closing ATP dependent potassium channels in pancreatic β cells. Ex: Non sufonylureas & maglitindes.
- 3. Decrease the amount of glucose released from the liver. Ex: Biguanides.
- 4. Increase the sensitivity (response) of cells to insulin. Ex: thiazolidines diones.
- 5. Decrease the absorption of carbohydrates from the intestine. Ex: precose

New medication for type-II Diabetes: 8-10

New medications that effect glycemiccontrol – Symlin (pramlintide):

Symlin is the first in a new class of injected antihyperglycemic medications for use in patients with type 2 or type 1 diabetes treated with insulin.

Pramlintide, the active ingredient in Symlin, is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized from pancreatic beta cells that contributes to glucose control during the postprandial period. Amylin, similar to insulin, is absent or deficient in patients with diabetes. When used with insulin, this compound can help patients achieve improved glycemic control with additional benefits that cannot be realized with insulin alone.

Symlin reduces post meal blood sugar peaks, reduces glucose fluctuations throughout the day, enhances satiety (the sensation of fullness) leading to potential weight loss, and lowers mealtime insulin requirements.

Side effects:

The major side effect of Symlin is nausea, and this can be abated with a slow steady increase in dosing. The other major concern is the risk of hypoglycaemia. To avoid this, the dose of mealtime insulin should be cut in half when starting Symlin. Of note is the degree of weight loss seen with Symlin therapy. Studies out to 6 months show weight loss of greater than 6 pounds more than placebo (inactive pills for comparison).

A nonpeptidic agonist of glucagon-like peptide I receptor-Byetta (exenatide):

Byetta (exenatide) is a new medication on the market that has it's origins in an interesting place the Gila monster's saliva. This substance was similar in nature to a gut hormone found in humans known as GLP-1. Ultimately, after modifying this hormone.

In addition to enhancing the normal physiology of the beta cell, Byetta suppresses glucose release from the liver, slows stomach emptying and the absorption of nutrients including carbohydrate, and reduces the food intake. Just like Symlin, Byetta is given by an injection, but it is given twice a day (usually before breakfast and dinner meals). This medication is temperature sensitive and most be stored at $36-46^{\circ}$ F.

Side effects:

Nausea, most likely due to its effects on stomach emptying. Weight reduction is seen with Byetta in the majority of patients. This makes it particularly suitable for the typical patient with Type 2 diabetes who is also overweight.

New medications that effect DPP 4 Inhibition- Vildagliptin Galvus® (Novartis), Sidagliptin Januvia TM (Merck) They act by Reducing fasting and postprandial glucose, reduce HbA1c and decreasing glucagon response to ingested meal.

Alpha-Glucosidase Inhibitors for Type 2 Diabetes-Acarbose (Precose), Miglitol (Glyset)

Acarbose and miglitol help keep blood sugar levels within a target range by slowing the digestion of complex carbohydrates, also called starches. Alpha-glycosidase inhibitors lower haemoglobin A1C by 0.5% to 0.8%.

Side effects:

Common side effects of this medicine includes Passing of gas, Feeling bloated, Belly pain, Diarrhea.

Cannabinoid 1 Receptor Blockade Improves Incretin-Mediated Insulin Secretion in Pancreatic Beta Cells

CB1R signalling in pancreatic islets may improve β -cell glucose responsiveness and preserve β -cell function in type 2 diabetes. CB1R antagonists contribute to the physiological regulation of glucose homeostasis through inhibiting CB1Rs expressed in peripheral tissues.

Combination Medications:

Glyburide/metformin (Glucovance), rosiglitazone/metformin (Avandamet), and glipizide/metformin (Metaglip) are 3 relatively new combination pills that are on the market to treat diabetes. The benefit to these agents is fewer pills to take, hopefully leading to better compliance.

Introduction to TAK-875:¹¹⁻¹³

TAK-875, which is an oral drug and is glucose-dependent, works by boosting insulin secretion. This makes it possible for the drug to help control blood sugar levels, without affecting insulin secretion if the levels of glucose are normal. Therefore, there is no risk of hypoglycaemia (low blood sugar).



Fig.3: Structure of TAK-875

Mechanism of action of various classes of drugs against type-II Diabetes:



Fig.4: schematic representation of mechanism of action of various classes of drugs against type-II Diabetes.

Agonists and compound 2 is an allosteric agonist, of the GLP-1 receptor (GLP-1R), although the exact mechanism by which it works is unknown. Dipeptidyl peptidase-4 (DPP4) inhibitors potentiate the effects of GLP-1.



Fig.5: schematic representation of mechanism of action of TAK-875against type-II Diabetes. © 2013, IJPA Online, All Rights Reserved

Activation of FFAR1 is a viable therapeutic target for the treatment of type 2 diabetes mellitus. Free fatty acid receptor 1 (FFA1), also known as G protein-coupled receptor 40 (GPR40), plays a vital role in stimulating and regulating the production of insulin. It works by boosting the release of insulin from pancreatic β -cells when glucose and fatty acids rise in the blood, such as after a meal. The release of insulin results in a fall in blood glucose levels. Drugs that activate the FFAR1 receptor have the potential to help diabetics release more insulin and improve control of blood glucose levels.

A phase-2 clinical trial was recently completed which assessed the potential of TAK-875 in achieving control of blood glucose levels without causing hypoglycaemia or low sugar levels TAK-875 brings about its action by the activation of FFAR1 receptors.

Advantages:

It would be completely orally administered and could potentially provide effective glycemic control, a low risk for hypoglycemia, weight neutrality, a low risk for gastrointestinal side effects, β -cell preservation, and cardio protection. Such a combination of features would be quite appealing to patients, physicians, and payers and could bring the diabetes field significantly closer to the ideal therapy.

Introduction to TAK-475(Lapaquistat acetate):¹³

Squalene synthase is the enzyme that converts farnesyl pyrophosphate to squalene in the cholesterol biosynthesis pathway. 1-[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid (TAK-475), a novel squalene synthase inhibitor ias the best therapeutic agent in type-II diabetes, especially in case of obese patients.



Fig.7: schematic representation of mechanism of action of TAK-475 against type-II Diabetes.

CONCLUSION

It may be concluded that TAK-875, a new treatment for type 2 diabetes, improves blood sugar control and is equally effective as glimepiride, but has a significantly lower risk of creating a dangerous drop in blood sugar, called hypoglycaemia, according to a new study. TAK-875 is a novel oral medication designed to enhance insulin secretion in a glucose-dependant manner, which means that it has no effect on insulin secretion when glucose levels are normal, and as such has the potential to improve the control of blood sugar levels without the risk of hypoglycaemia. The drug targets cells in the pancreas that stimulate the production of insulin, without the risk of hypoglycaemia.

REFERENCES

- 1. David G. Gardner, Dolores (2011): Greenspan's basic & clinical endocrinology: McGraw Hill Medical Publishers, New York, Edn 9, Chapter 17.
- 2. Wild S, Roglic G, Green A, Sicree R, King H (2004): "Global prevalence of diabetes: estimates for 2000 and projections for 2030", Diabetes Care, 27 (5),1047–1053.
- 3. Herder C, Roden M (2011): "Genetics of type 2 diabetes: pathophysiologic and clinical relevance", European journal of clinical investigation, 41 (6), 679–92.
- 4. Fasanmade OA, Odeniyi IA, Ogbera AO (2008): "Diabetic ketoacidosis: diagnosis and management", African journal of medicine and medical sciences, 37 (2), 99–105.
- Ripsin CM, Kang H, Urban RJ (2009): "Management of blood glucose in type 2 diabetes mellitus", Am Fam Physician, 79 (1), 29–36.
- 6. Risérus U, Willett WC, Hu FB (2009): "Dietary fats and prevention of type 2 diabetes", Progress in Lipid Research, 48 (1), 44–51.
- Qaseem A, Humphrey LL, Sweet DE, M Shekelle P, Clinical Guidelines Committee of the American College of Physicians (2012): "Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians, Annals of Internal Medicine, 156(3), 218-231.
- 8. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S (2010): "Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation", Health technology assessment (Winchester, England), 14 (36), 1–248.
- 9. medicalnewstoday.com/articles/242201.php
- 10. medindia.net/news/healthinfocus/tak-875-versus-placebo-or-glimepiride-in-type-2-diabetes-mellitus-99014-1.htm
- 11. Prof Charles F Burant, Prabhakar Viswanathan, John Marcinak, Charlie Cao, et al (2012): TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomized, double-blind, placebo-controlled trial, The Lancet, 379(9824), 1403-1411.
- 12. clinicaltrials.gov/ct2/show/NCT00949091.
- 13. Diabetes Drug Improves Glucose Control without increasing Risk of Hypoglycaemia (2012), Pharma Times, 44(8), 33.
- Amin D., Rutledge R.Z., NeedleS.N., Galczenski H.F., Neuenschwander K., S cotese A.C., Maguire M.P., Bush R.C., Heled.J., Bilder G.E., Perrone M.H. RPR 107393, a potent squalene synthase inhibitor and orally effective cholesterol-lowering agent:comparison with inhibitors of HMG-CoA reductase. J. Pharmacol. Exp. Ther. 1997; 281:746–752. [PubMed].

Source of support: Nil, Conflict of interest: None Declared