INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230 – 8407

Review Article

RECENT TRENDS IN TREATMENT AND VALIDITY OF SCREENING MODELS USED IN TYPE 2 DIABETES MELLITUS: A REVIEW

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Article Received on: 01/12/20 Approved for publication: 29/01/21

DOI: 10.7897/2230-8407.1201110

ABSTRACT

Type II Diabetes mellitus (NIDDM) is a complex and metabolic disease that affects and presents a serious health problem for more than 100 million people around the world. Genetics and the environment are the variables which affect NIDDM. Reasonable screening models of animals will easily understand the pharmacological screening of different therapeutic agents. NIDDM animal models are acquired either naturally or caused by chemical reagents or by dietary, surgical or combination manipulation. A significant number of new genetically engineered animal models, including knock-out, transgenic, and tissue-specific knockout mice, have been designed for the Diabetes mellitus (D.M.) research in the past year. With regard to their characteristic characteristics and processes by which they arise, this analysis focuses on the animal models of NIDDM. In addition, this analysis explicitly discusses the optimal selection and use of various animal screening models for the treatment of NIDDM in preclinical research.

Key words: Animal screening models, preclinical trial, NIDDM, Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is commonly known as diabetes. It is a group of heterogeneous disorders of high blood sugar levels over a long period of time. Diabetes mellitus is also known as "sugar diabetes"[1-3]. The symptoms of NIDDM include:

- High frequency of urination
- Frequent Thirst
- Increase in frequency of Hunger

If it is left untreated, then it can cause many complications. Some of the major complications of NIDDM are:

- Acute complications which include diabetic keto-acidosis and non-ketotic hyperosmolar coma.
- Chronic complications which include cardiovascular disease, neuronal and cardiac stroke, kidney failure, foot ulcers, and retinopathy [3-5]

Diabetes is caused mainly due to:

- If pancreas fails to produce more insulin,
- If the body cells fail to response properly to the insulin produced by the pancreas [5]

TYPES OF DIABETES MELLITUS

Diabetes Mellitus is commonly of three types:

- Type 1 DM which results from the pancreas inability to produce enough insulin. Also called as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes" and its cause is still unknown.
- Type 2 DM is a condition in which body cells fails to response to insulin properly. As the disease progresses, lack of insulin development occurs. It is also known as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The main cause I excessive body weight.
- Gestational diabetes: It is the third main form of diabetes and occurs when pregnant women without a previous history of diabetes develop a high blood-sugar level. [4-8]

PATHOPHYSIOLOGY

The release of insulin is triggered by food, especially food rich in carbohydrates and lipids.
Insulin is the principal hormone that regulates the uptake of glucose from the blood into most of the body cells, especially liver, muscle, and adipose tissue. Therefore, its deficiency and its insensitivity of its receptors play a major role in all forms of diabetes mellitus.
The body obtains glucose from three main places:

- The intestinal absorption of food,
- The breakdown of glycogen,
- Gluconeogenesis (the generation of glucose from non-carbohydrate substrates in the body).

Insulin is released from beta cells (β-cells) of the pancreas. Lower the glucose levels lower will be insulin release and lower will be breakdown of glycogen to glucose. This process is controlled by glucagon, which acts via opposite mechanism to insulin. [9-12]

Table 1: Causes of diabetes mellitus [13]

FEATURE	TYPE 2 DIABETES
Onset	Gradual
Age at onset	Mostly in adults
Body size	Often obese
Keto-acidosis	Rare
Auto-antibodies	Absent
Endogenous insulin	Normal, decrease or increased
Concordance in identical twins	90%
Prevalence	~90%

SIGN AND SYMPTOMS

Figure 1: Sign and Symptoms of Diabetes Mellitus [13,14]

TYPE 2 DIABETES MELLITUS [13,14,15]

In obese and overweight children, NIDDM is normal. It is characterized by resistance to insulin and also by decreased secretion of insulin. Due to desensitization of insulin receptors, the defective response of body tissues to insulin is thought to be involved. Important decreases in insulin sensitivity occur in the early stages. High blood sugar may be reversed by drugs at a later level. The medications include drugs which: [15]

- Improves insulin sensitivity or
- Reduces the liver's glucose production.

NIDDM occurs primarily due to lifestyle factors like: [15]

- Genetical factors include obesity, lack of physical activity, poor diet and stress.
- Dietary factors also influence the risk of developing NIDDM.
- It is less severe than IDDM.
- It also increases the risk of heart disease and stroke

ETIOLOGY

With NIDDM, insulin is released by the pancreas, but the amount it produces is not enough for the human body's normal needs, or

the cells are immune to it. Obese individuals have resistance to insulin. With insulin resistance, in order to produce more insulin, the pancreas also has to work hard. There is no remedy for diabetes, but weight management, diet, and exercise can regulate NIDDM. The body obtains glucose from three main sites: [15]

- The intestinal absorption of food,
- The breakdown of glycogen (the storage form of glucose found in the liver) and
- Gluconeogenesis (the generation of glucose from non-carbohydrate substrates in the body)

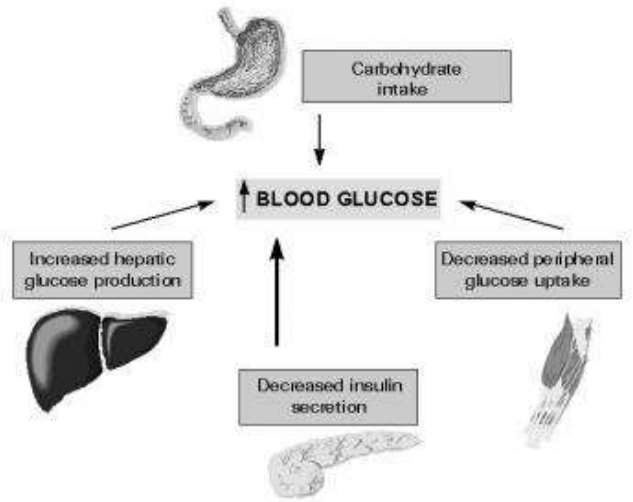


Figure 2: Role of glucose in type 2 diabetes mellitus [13,14]

DIAGNOSIS

Table 2: Different Diagnosis Conditions [14,15]

Condition	2 Hour Glucose	Fasting Glucose	HbA_{1c}
Unit	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol
Normal	<7.8 (<140)	<6.1 (<110)	<42
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46
Diabetes Mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48

PREVENTION [15]

A change in diet is often known to be effective measure in preventing diabetes. It includes

- A diet rich in whole grains and fiber, and by taking fats such as polyunsaturated fats which are more in nuts, vegetable oils, and fishes.
- By limiting the sugary beverages and by consuming less red meat and other sources of saturated fat.
- Smoking cessation.

TREATMENT AND MEDICATIONS [14,15]

Treatment of NIDDM includes:

- Eating healthy diet
- Regular exercise
- Possible diabetes drugs
- Insulin therapy
- Blood sugar level monitoring

Eating Healthy Diet

Contradiction with the popular thinking, there is no adequate diet for diabetic patients. However, it is important to center the diet on the high-fiber, low-fat foods:

- Fruits
- Vegetables
- Whole grains

Patients also need to consume animal products, refined carbohydrates and sweets.

Physical Activity: Everyone needs an aerobic exercise regularly.

Monitoring of Blood Sugar Level: Depending upon the treatment, patients need to check and records their blood sugar level every now and if the patient is on insulin, it should multiple times a day.

Diabetes Medications and Insulin Therapy

People who have NIDDM can achieve their target blood sugar levels with diet and exercise but many also need diabetes medications and insulin therapy. Examples for possible treatments for NIDDM include [15]

Metformin: Metformin was the first medication prescribed for NIDDM. It works via improving the sensitivity of the body tissues to insulin so that the body uses insulin more effectively. It also lowers glucose production.

Sulfonylurea's: These drugs help the pancreas to secrete more insulin. Drugs include glyburide, glipizide and glimepiride. Side effect includes low blood sugar and weight gain.

Meglitinides: These drugs work like sulfonylurea's and act by stimulating the pancreas to secrete more insulin. They are faster acting and have short duration of action. They have a risk of

causing low blood sugar, but this can be is lower by taking sulfonylureas. There is a possibility of increase in the body weight. Drugs include repaglinide and Nate-glinide.

Thiazolidinedione: Like metformin, these also make the body tissues more sensitive to insulin. They cause weight gain and other serious side effects like an increased risk of heart failure and fractures. It includes drugs like Rosiglitazone and pioglitazone.

DPP-4 Inhibitors: They help in reducing blood sugar levels. They do not lead to weight gain. It includes drugs like sitagliptin, sax-gliptin and linagliptin.

GLP-1 Receptor Agonists: These drugs slow digestion and also lower blood sugar levels, less effective than sulfonylureas, cause weight loss. Exenatide and liraglutide are potent examples of this category. ADRs include nausea and pancreatitis.

SGLT2 Inhibitors: These are newest drugs in the market. They prevent re-absorbing sugar into the blood. Drugs include canagliflozin and dapagliflozin. Side effects may include yeast infections, UTIs and frequent urination and hypotension.

Insulin Therapy: Those who have NIDDM need insulin therapy. In past, insulin therapy was used as a last weapon, but today it is quite often prescribed sooner because of its benefits. Insulin must be injected as its oral administration affects digestion. An insulin injection involves use of a fine needle and syringe or simply an insulin pen injector, -which look similar to ink pen only exception is the cartridge filled with insulin.

SURGERY: Surgery includes pancreas is occasionally done in IDDM and weight loss surgery in those with obesity and NIDDM.

DIAGNOSTIC TEST: [14,15]

GLYCATED HEMOGLOBIN (A1C) TEST

The blood test shows the average level of blood sugar for the past two to three months. It measures how much hemoglobin, which is the oxygen-carrying protein in RBCs, is attached to blood sugar (red blood cells).[15] Higher the blood sugar level, more hemoglobin will have the sugar attachment.

LEVELS	STAGES
6.5%	Diabetes
Between 5.7% and 6.4%	Pre-diabetes
5.7 %	Normal individual

RANDOM BLOOD SUGAR TEST

At any random time, a blood sample is taken. Blood sugar values are expressed in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L). the signs and symptoms of D.M, are frequent urination and extreme thirst. [15]

Blood sugar LEVEL	Condition
200 mg/dl (11.1mmol/L)	Diabetes

FASTING BLOOD SUGAR TEST

After an overnight fast, a blood sample is taken.

Blood Sugar LEVEL	Condition
<100 mg/dl (5.6 mmol/L)	Normal
100 to 125 mg/dL	Pre-diabetes
126 mg/dL (7 mmol/L	Diabetes

ORAL GLUCOSE TOLERANCE TEST

For this, overnight fasting, and the fasting blood sugar level is measured or determined. After that drink a sugary liquid, and again blood sugar levels are tested periodically for next two hours.

Blood sugar LEVEL	Condition
<140 mg/dl (7.8 mmol/L)	Normal
140 to 199 mg/dL	Pre-diabetes
200 mg/dL (7 mmol/L	Diabetes

ADVERSE DRUG REACTIONS

The various adverse effects associated with type-II is listed below:

- High blood sugar (hyperglycemia).
- Hyperglycemic hyperosmolar nonketotic syndrome (HHNS).
- Increased ketones in your urine (diabetic ketoacidosis
- Low blood sugar (hypoglycemia) which also causes**:**
    1. Sweating
    2. Shakiness
    3. Weakness
    4. Hunger
    5. Dizziness
    6. Headache
    7. Blurred Vision
    8. Heart Palpitations
    9. Slurred Speech
    10. Drowsiness
    11. Confusion
    12. Seizures

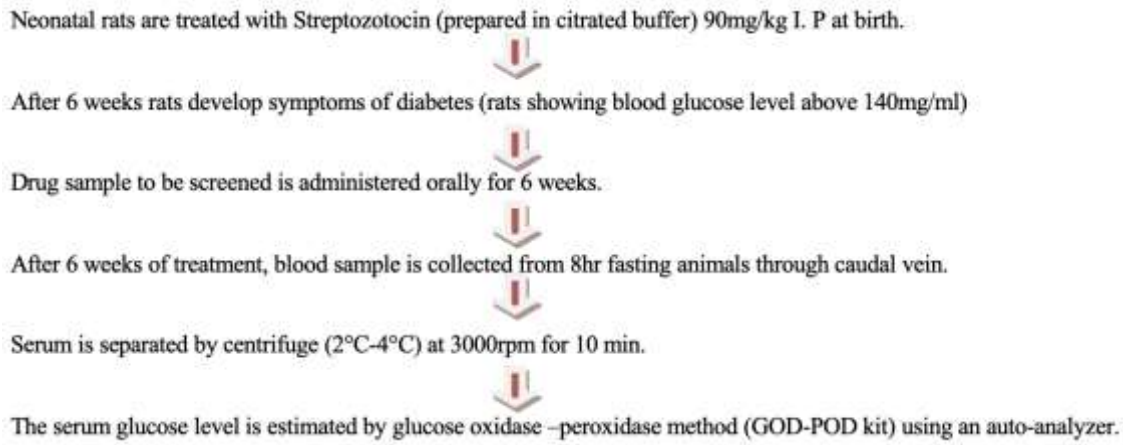
ANTI-DIABETIC SCREENING MODELS OF ANIMALS FOR TYPE-2 DIABETIC MELLITUS: [16]

Neonatal Streptozotocin Induced Diabetes Rat Model (N-STZ): Different stages of type 2 diabetes mellitus, such as impaired glucose tolerance, and mild, moderate and severe glycemia, are shown in the n-STZ model (with change of dose and day of STZ injection).

Chemical Properties

Streptozotocin is a mono-functional nitrosourea derivative. First it was isolated from Streptomyces achromogenes. Streptozotocin has a broad-spectrum antibiotic activity.

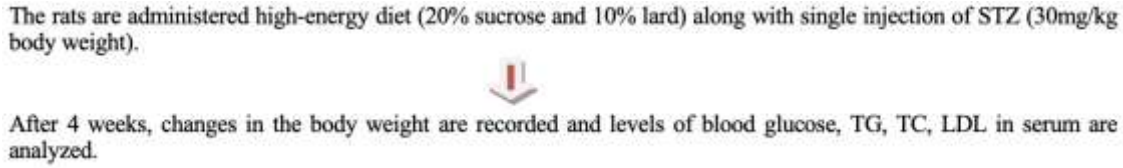
Procedure



Low Dose STZ with High Fat Diet-Fed Rat Model:

Validity: This model replicates the natural history and metabolic characteristics of type-2 diabetes.

Procedure:



Inference: The results suggested that a combination of low dose STZ and high-energy diet intake can effectively induce type-2 diabetes by altering the related gene expressions in major metabolic tissues.

Gold-thioglucose (GTG) Obese Diabetic Mouse Model:
Type-2 obesity diabetes is induced by I.P gold-thioglucose injection (200 mg/kg) in mice. Obesity, hyper-insulinaemia, hyperglycemia and insulin resistance develop gradually over a period of 16-20 weeks after GTG injection. It also increases lipid, hepatic lipogenesis and triglyceride secretion in the body, increases lipogenesis of adipose tissue and decreases muscle glucose metabolism.

Chemical Properties
It is a sugar-glucose derivative. With methanol, gold-thioglucose is precipitated and recrystallized with water and methanol.

Mechanism of Action
Obesity produced by gold thioglucose induces diabetes in genetically normal mouse strains. Dilute Brown Non- Agouti (DBA/2), C57BLKs, and BDF1 mice treated with gold thioglucose gained weight quickly and significantly increased the level of non-fasting plasma glucose within 8-12 weeks. These mice showed impaired secretion of insulin, mainly in the early stages following loading of glucose and reduced insulin content in the pancreatic islets.

Monosodium Glutamate:
Monosodium glutamate induces Type -2 diabetes mellitus without polyphagia.

Chemical Properties
- It is most abundant naturally occurring non- essential amino acid.
- Freely soluble in water.

Mechanism of Action: After ingestion, monosodium glutamate causes a very large insulin response. Glycosuria is developed in both male and female mice, but polyphagia is not induced. Total cholesterol and triglyceride levels were higher within 29 weeks of blood glucose concentration.

CHEMICAL INDUCED NIDDM MODELS:

Adrenaline Induced Acute Hyperglycemia:

Procedure

Adult Albino Rats Are Injected A Dose Of 0.1mg/Kg Through S.C Route.

⇓

The Dose Produces A Peak Hyperglycemic Effect At 1hr And Lasts Up To 4hrs.

⇓

Drug to Be Analyzed Is Administered Through S.C Route.

⇓

Blood Glucose Is Determined.

Chelating Agents: **Dithizone Induced Diabetes:**

Procedure

Adult rabbits (1.8-2kg) are divided into 2 groups of 6 animals each.

⇓

Ammoniacal solution of dithizone is injected at the dose of 50-200mg/kg which will produce triphasic glycemic reaction.

⇓

Initial hyperglycemia will be observed after 2hr and normoglycemia after 8hr, which persist for up to 24hr.

⇓

Permanent hyperglycemia is observed after 24-72hr.

⇓

The drug sample to be analyzed is administered through a suitable route and the blood glucose level is determined.

Chemical Properties

- The Chemical name of dithizone is 8- (p- toluene-sulfonylamino)– quinoline (8- TSQ).
- It is an organo-Sulphur compound that acts as a chelating agent and forms complexes with lead, zinc and mercury.
- It is used to assess the purity of human pancreatic islet preparations.

Mechanism of Action: Zinc-chelating agents, such as dithizone, are responsible for diabetes in laboratory animals. Dithizone has the capability to penetrate membranes and complex zinc inside liposomes with the release of protons, which can increase diabetogenicity. When these compounding agents are added to lipid vesicles (at pH 6) containing trapped zinc ions, the vesicle contents are acidified. Such proton release takes place within the zinc-containing insulin storage granules of the pancreatic beta cells; insulin solubilization would be induced, leading to osmotic stress and ultimately inducing rupture of the granules and ultimately diabetes.

Hormone Induced Diabetes: Growth Hormone Induced Diabetes:

- GH has a long-distinguished history in diabetes, with possible participation in the development of renal complications.
- Repeated administration of GH in cats and adult dogs induces diabetes with all symptoms of diabetes including severe ketonuria and ketonemia.
- More prolonged administration of GH produced permanent diabetes, there was loss of pancreatic islets tissues and of beta cells and only traces of insulin could be extracted from pancreas.

Corticosteroid Induced Diabetes:

- Corticosteroid used to reduce inflammation can lead to diabetes, which is called steroid diabetes.
- The most common glucocorticoids which causes steroid diabetes are prednisolone and dexamethasone.
- Glucocorticoids oppose insulin action and stimulate gluconeogenesis, especially in the liver, resulting in a net increase in hepatic glucose output and induce insulin resistance, hyperglycemia, and hyperlipidemia.

CONCLUSION

Worldwide, about 3 percent of the total population suffers from diabetes. Many anti-diabetic agents or drugs are used to minimize this data, and research is still ongoing for more effective anti-diabetic drugs. At the research level, many diabetic models are used to study diabetes. And the most appropriate screening models that mimic the physiology of human diabetes are summarized in this review.

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Cite this article as:

Ankita Tripathi *et al*. Recent trends in treatment and validity of screening models used in type 2 diabetes mellitus: A review. Int. Res. J. Pharm. 2021;12(1):10-16.
http://dx.doi.org/10.7897/2230-8407.1201110

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