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DIABETES MELLITUS WITH THEIR EXPERIMENTAL ANIMAL MODEL

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ABSTRACT

Diabetes Mellitus (DM) encompasses a spectrum of metabolic disorders characterized by hyperglycemia, stemming from impaired insulin secretion, action, or both, impacting carbohydrate, lipid, and protein metabolism. Insulin, pivotal as an anabolic hormone, modulates metabolic pathways predominantly in skeletal muscle, adipose tissue, and the liver. Insufficiency in insulin levels, responses, or signalling cascades leads to metabolic dysregulation. Severity varies with diabetes type and duration, with uncontrolled cases risking coma and fatality. Experimental diabetes research, crucial for understanding pathophysiology and therapeutic developments, relies on animal models, primarily mice, due to their practicality and translational relevance. This review consolidates diverse in vivo animal models for diabetes research, crucial for drug evaluation and therapy assessment. The classification delineates three primary diabetes types: Type I, stemming from beta-cell destruction, necessitating insulin administration; Type II, characterized by insulin resistance and deficiency, often linked with lifestyle factors; and Gestational Diabetes, emerging during pregnancy, elevating long-term type II diabetes risk. Specific monogenetic types also exist, each with distinct etiologist and clinical manifestations. Diabetes pathogenesis involves diverse mechanisms including insulin resistance, abnormal glucose metabolism, and specific receptor dysfunctions. Common signs and symptoms encompass cellular glucose deprivation, leading to multi-organ complications including retinopathy, nephropathy, and neuropathy. Treatment modalities range from stem cell therapy to dietary management, aiming at glycemic control and complications prevention. Animal models, including chemically-induced, genetic, and spontaneous types, play pivotal roles in understanding diabetes pathophysiology and therapeutic interventions. These models mimic human disease conditions and aid in developing novel therapies and preventive strategies.

KEYWORDS: Diabetes mellitus, causes, Animal model, Insulin Resistance, Therapeutic Interventions.

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases caused by hyperglycemia resulting from a violation of insulin secretion, insulin action, or both. The difference in carbohydrate, lipid and protein metabolism is due to the importance of insulin as an anabolic hormone. Low levels of insulin to achieve an adequate response in target tissues (mostly skeletal muscle, adipose tissue and to a lesser extent liver) and/or at the level of insulin, signaling and/or enzymes or genes. It is responsible for metabolic abnormalities. The severity of symptoms depends on the type and duration of diabetes. Uncontrolled diabetes can lead to coma, coma, and death if left untreated.[1,3]

Experimental research on diabetes in animal models is important for better understanding andunderstanding of disease pathology and finding new treatments. Therefore, animal models ofdiabetes are useful in biomedical research as they are expected to provide new insights into human diabetes. Models are mostly based on mice due to their small size, short duration and financial concerns. Experimental diabetes is studied with many methods, including chemical, surgical and genetic control.[4] It is also important to select appropriate animal models for evaluating new drugs (NCEs) and other therapies for the treatment of diabetes. The main aim of this review was to bring together all in vivo animal models.[5]

CLASSIFICATION

The three main types of diabetes are type I, which is known to be associated with total insulindeficiency, type II progressive insulin deficiency and gestational diabetes, which is digram based in the second or third trimester of pregnancy. While type I cannot be prevented, type II can be prevented through good health, exercise and a healthy diet. Early diagnosis is important for diabetes

management. However, type II affects many people and causes problems in many organs (heart, blood vessels, eyes, kidneys, etc.) Diabetes is divided into the following three groups

1. Type I Diabetes: The result of beta cell destruction, often resulting in insulin deficiency. Formerly known as insulin-dependent childhood or childhood-onset diabetes, this diabetes is caused by an autoimmune response in which the body's immune system attacks the insulin-producing beta cells of the pancreas. Type I diabetes is caused by insufficient insulin production in the body. In this type of diabetspatients need to inject insulin every day to normalize blood sugar. Without insulin, their lives are at risk and can even lead to death. The cause of this type of IDM has not been determined but it can no longer be prevented. Although the cause of type I diabetes is unknown, changes in environmental risk factors and/or infectious diseases may play a role in the development ofDM. Frequent urination and thirst, constant hunger, weight loss, blurred vision and fatigue arethe main symptoms of this type of diabetes. Overall, the number of people diagnosed with type I diabetes continues to increase.

2. Type II diabetes: The disease, originally called non-insulin-dependent diabetes or adult diabetes, is considered to be the result of constant insulin use. causes secretion disorders. Type II diabetes is the most common form of DM. In this type, the body can produce insulin but becomes insulin resistant. From that moment on, insulin may become insufficient. "Journal of Pharmaceutical Sciences"study. Hyperglycemia is both insulin resistance and insulin deficiency. Given that these symptoms (like symptoms of type I diabetes) are often mild or absent, the disease may go undetected or undiagnosed for years until complications arise. For years, type IIDM was seen only in adults, and now it has started to be seen in children as well. Although the exact cause of the development of type II diabetes is not known to date, some important risks have been pointed out. The most important problems include being overweight, being underweight and not eating enough. Other risk factors include race, family history of diabetes, previous history of gestational diabetes, and increasing age.[6,9]

3. Gestational diabetes (GDM): is a type of diabetes that is not obvious but is identified in the second or third trimester of pregnancy. GDM is a temporary condition that occurs during pregnancy and increases the risk of developing type IIdiabetes in the long term. Women with slightly high blood sugar levels are diagnosed with gestational diabetes, while women with high blood sugar levels are diagnosed with gestational diabetes. GDM usually begins around the 24th week of pregnancy. For this reason, screening with oral cavity height measurement is recommended and needed.[6,8,9]

4. Other specific types (monogenotypes): The monogenic type of diabetes is usually caused by a mutation on chromosome 12 in the liver transcription factor called hepatocyte nuclear factor (HNF)-1a. These are also called beta deficient cells. This type of diabetes is usually caused by the onset of high blood sugar at a young age, usually before age 25. These are also called adult-onset diabetes of the young (MODY)[11] or adult-onset diabetes with insulin resistance; people with exocrine pancreas disease such as pancreatitis or cystic fibrosis; persons with other endocrine diseases persons with disease-related dysfunctions (e.g. acromegaly); patients with pancreatic dysfunction caused by medications, medications, or diseases.[12] Some medications are also used along with HIV/AIDS treatment or after organ transplantation. Genetic abnormalities that cause the inability to convert proinsulin to insulin have been found in some families, and these traits are inherited in a somatic chromosomal dominant pattern. They constitute less than 10% of diabetic patients.[10]

CAUSES OF DIABETES MELLITUS

Problem or abnormality in glucose receptors that enables the cell to respond to more glucose or relative cellular defects.However, insulin release is affected; Battery failure may occur.[14] The principle of neuronal hypoxia arises from microvascular disease and the direct effect of hyperglycemia on neuronal metabolism.[15]

1. Peripheral tissues are less sensitive to insulin: the number of insulin decreases and insulin control decreases. Many allergies and hyperinsulinemia but normoglycemia; It is associated with dyslipidemia, hyperuricemia and obesity. For this reason, insulin resistance occurs especially in the liver, muscles and fat. Hyperinsulinemia is associated with vasculopathy.[13]

2. Too much blood sugar (glucagon) and other/fats; causes relative insulin deficiency – cells are left behind. Both theories suggest that abnormalities in nitric oxide metabolism lead to changes in perineural blood flow and nerve damage.[14]

3. Other rare causes of diabetes are those resulting from specific diseases (type 3) such as developmental diabetes (MODY), other endocrine diseases, pancreatectomy and gestational diabetes (GDM).[13]

4. Diabetes may occur due to lack of specific receptors. Some specific receptors are glucagon-like peptide-1 (GLP-1) receptor, peroxisome proliferator-activated (γ) receptor (PPARγ), beta 3 (γ3) thermoreceptor, alpha glycosidase, dipeptidyl peptidase IV enzyme, etc.[13]

5. Current research on diabetic neuropathy focuses on oxidative stress, advanced glycation end products, protein kinase C, and the polyol pathway. Diabetes Mellitus Diagnosis of diabetes in asymptomatic individualsshould not be based on normal blood sugar levels. If a diagnosis of diabetes is made, the doctor must

ensure that the diagnosis is made accurately, as its impact on the patient is significant and lifelong.[15]

SOME COMMON SIGNS AND SYMPTOMS

In Diabetes Mellitus, cells cannot metabolize glucose normally and die of starvation.[16] Longterm effects of diabetes include the development of retinopathy, which can lead to blindness, nephropathy, which can lead to kidney failure, andneuropathy, which can lead to foot pain, Charcot syndrome bones, and autonomic and sexual dysfunction.[13] diabetes has more problems. Many symptoms occur due to i. Glycogenesis of amino acids and proteins in the body causes muscle atrophy, tissue breakdown, and causes blood sugar to rise. ii. two. Body fat is catabolized, some energy is released, and excess ketone bodies are formed.[16]

TREATMENT OF DIABETES MELLITUS

A. Types of therapies involved in diabetes mellitus

1. Stem Cell Therapy

Researchers have shown that monocytes/macrophages can have a significant impact on chronic inflammation and insulin resistance in patients with T2DM.[17] Stem cell training therapy is a new technology developed to control or reverse the immune system. Methods include: collection of the patient's bloodstream by closed loop, purification of lymphocytes from whole blood, in vitro coculture with blood from pluripotent cell stem cells (CB-SC), and control of learning lymphocytes.[18]

2. Antioxidant therapy

Many antioxidants, such as vitamins, supplements, herbal products and drugs with antioxidant effects, are used in the treatment of oxidative stress. It is high in T2DM patients. . Vitamin C, vitamin E and beta carotene are the best medications to prevent oxidative stress and its complications.[19] Antioxidants play an important role in reducing the risk and complications of diabetes.

3. Treatment to prevent the disease

These changes show that inflammation plays an important role in the pathogenesis of T2DM and its complications.[20,21] In T2DM, these include changes in cytokine and chemokine levels, especially in adipose tissue, pancreatic islets, liver, vascular system and circulating leukocytes, the number and activation power of leukocyte differentiation, increased apoptosis and tissue fibrosis.[22,23] Administer immunomodulatory medications.

B. Health management

Adequate calories Both diabetics and non-diabetics should receive proper nutritional management such as:

1. Equal protein, carbohydrate, and fat in all cases. should limit carbohydrate intake.

2. It should be as close as possible

3. Food should be divided into regular meals that are like each other.

4. Reduce total calorie intake by reducing fat and carbohydrates

5. Patients should be instructed to maintain the same diet every day.

C. New insulin delivery products

Various innovations have been developed to improve the ease and accuracy of insulin administration and provide tight glycemic control. These are insulin syringes, pens, insulin inhalers, insulin pumps, pumps, other methods of insulin delivery.

D. Oral hypoglycemic or antidiabetic drug

The main clinical biguanide, phenformin, was created at the same time as the sulfonylureas in 1957. People are constantly looking for new ways, and recently there are thiazolidinediones, meglitinide analogs, α-glucosidase inhibitors, and of course dipeptidyl peptidase-4 (DPP-4) inhibitors.[13]

INVIVO ANIMAL MODELS USED IN DIABETES MELLITUS

Alloxan induced diabetes

Alloxan is widely used in diabetes research. Alloxan maycause selective necrosis of pancreatic beta cells. Alloxan can be used in various ways, including intravenous, intraperitoneal and subcutaneous. Alloxan is used to induce diabetes in laboratory animals such as mice, rats, rabbits, and dogs. The need and dose of alloxan application may vary depending on the species.[24] The first short hypoglycemic phase lasts 30 minutes from the first minute of alloxan application. The hypoglycemic episode may be due to stimulation of insulin secretion and increased plasma insulin levels. The mechanism behind hyperinsulinemia is due to short-term ATP availability and glucokinase inhibition. The second phase is an increase in blood sugar and a decrease in plasma insulin concentration one hour after alloxan administration. Symptoms of hyperglycemia lasting 2-4 hours are due to decreased insulin levels in plasma. This is due to inhibition of insulin secretion and beta cell toxicity. The third phase is the hypoglycemic phase that lasts 4-8 hours after alloxan application.[25,26] Alloxan treatment causes an increase in insulin secretion with or without glucose. Insulin release occurs until inhibitionof the islet response to glucose is complete. Alloxan reacts with two sulfhydryl groups in glucokinase to form a disulfide bond and inactivate the enzyme. Alloxan is reduced by GSH. Superoxide radicals release ferric ions from ferritin and reduce them to iron ions. Fe3+ can also be reduced by alloxan radicals.[27] Another proposed mechanism is DNA fragmentation in beta cells exposed to alloxan. Disturbance of intracellular calcium levels also contributes to the diabetic effect of alloxan.[28]

Streptozotocin-induced diabetes

Streptozotocin (STZ) is a naturally occurring drug specific to the beta cells of the pancreas. It is used as an animal model of hyperglycemia in clinical research.[29]

STZ changes blood insulin and glucose concentration. Two hours after the injection, hyperglycemia occurs due to the decrease in insulin concentration in the blood. After six hours, hypoglycemia occurs due to high insulin levels in the blood. Eventually hyperglycemia occurs and blood insulin levels drop. STZ impairs glucose oxidation[30] and reduces insulin synthesis and release. STZ was initially found to suppress the B cell response to glucose. STZ inhibits GLUT2 activity. STZ alters DNA in pancreatic B cells. B cell death results from alkylation of DNA by STZ. STZ induced DNA damage activates polyADPribosylation. Activation of polyADP-ribosylation is more important for STZ induced diabetes than free radical formation and DNA damage. Calcium can also cause necrosis.[32,33]

Insulin antibodies induced diabetes

Insulin antibodies have the affinity and ability to bind to insulin. Insulin deficiency may cause more postprandial hyperglycemia due to the inability of tissues to absorb insulin resistance, but the period of postprandial hyperinsulinemia may lead to hyperglycemia.[34]

Virus-Induced Diabetes

Viruses can cause diabetes by destroying and infecting the beta cells of the pancreas. Various human viruses used to induce diabetes include RNA picornaviruses, coxsackie B4, encephalomyocarditis (EMC-D and M variants), Mengo-2T, retrovirus, and lymphocytic choriomeningitis.[35] Hormone-induced diabetes. Growth hormone-induced diabetes. Restoration of growth hormone in experimental animals can cause diabetes with ketonuria and ketonemia. Long-term use of hormones can lead to chronic diabetes; loss of pancreatic islet tissue and beta cells.[36]

Corticosteroid-induced diabetes

Corticosteroid induced diabetes is called steroid diabetes. Prednisolone and dexamethasone can cause steroid diabetes. Glucocorticoids stimulate gluconeogenesis in the liver, leading to an increase in liver glucose and induction of insulin resistance and hyperglycemia.[37]

Spontaneous Diabetic Obese Rodent Models

Ob/ob mice: The ob/ob mouse strain develops leptin deficiency due to mutations in the leptin gene, resulting in severe insulin resistance. ob/ob mice rapidly gain weight and develop insulin resistance and hyperinsulinemia.[38] In the ob/ob model, hyperinsulinemia occurs at 3 to 4 weeks of age and is accompanied by hyperphagia and insulin resistance. Type 2 DM symptoms in ob/ob mice resulted in younger age, continued decrease in plasma insulin levels in the second year, impaired glucose tolerance, and insulin resistance.[39]

Db/db mice: The db gene mutation occurs in leptin receptor-deficient C57BL/KsJ mice and is originally derived from a mutation on chromosome 4. db/db mice become bulimic, hyperinsulinemic, and insulin resistant within 2. week and obese from 3 to 4 weeks. Hyperglycemia occurs between 4 and 8 weeks of age. At this age, mice show ketosis and lose weight. db/db mice are used to study renal and microvascular diseases in diabetes.[40,41]

Zucker Diabetic Fat (ZDF) mice: Zucker Diabetic Fat (ZDF) mice are low in fat, have more insulin, and rapidly develop diabetes due to insufficient insulin production. Male ZDF rats become diabetic at 12 weeks. In male ZDF rats, insulin levels peak around 7 to 10 weeks of age but do not respond to glucose stimulation and insulin levels decline.[42]

New Zealand Obese (NZO) Rats: New Zealand obese mice gain weight at 10 weeks of life due to hyperphagia, hyperglycemia, and hyperinsulinemia. NZO mice show insulin resistance at an early age. Hyperglycemia and glucose tolerance increase as NZO mice grow, with blood glucose reaching 300 to 400 mg/dLby 20 to 24 weeks of age. It is a good model for examining obesity and diabetes.[43]

Otsuka Long-Evans Tokushima Fatty (OLETF) rats: OLETF rats develop hyperglycemia at approximately 18 to 25 weeks of age. OLETF mice showed obesity, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, and early-onset diabetes similar to human type 2 diabetes. Various genes on multiple chromosomes, including the X chromosome, have been shown to play a role in the development of diabetes in OLETF mice.[44]

Nagoya Shibata Yasuda (NSY) rat: NSY rat, which causes type 2 diabetes in humans, has the characteristics of mild obesity, insulin deficiency and insulin resistance against the development of diabetes with age. Among NSY mice, all males had diabetes, whereas only 30% of females had diabetes. NSY mice are especially useful in investigating age-related damage and phenotypes in type 2 DM.[45]

Tsumura Suzuki Obesity Diabetic (TSOD) Mice: At 2 months of age, TSOD mice showed obesity and insulin resistance resulting in hyperinsulinemia and hyperglycemia. Pancreatic islets are hypertrophic in TSOD mice. Disruption of GLUT4 mutations in skeletal muscle and adipocytes of TSOD mice resulted in decreased insulin sensitivity and insulin resistance.[46]

M16 mice: M16 mice showed hyperphagia-induced obesity in all age groups. At 8 weeks of age, all M16 mice exhibited hyperglycemia, hyperinsulinemia, and hypercholesterolemia.[46]

Spontaneous Diabetic Non-obese rodent model

Cohen diabetic mouse: Cohen diabetic mouse is a genetic dietary model to control type 2 diabetes. Model of type 2 diabetes from mice to synthetic 72% sucrose deprivation. People detected type 2 diabetes in copper

foods for 2 months. Symptoms include obesity, hyperinsulinemia, and insulin resistance. Cohen's diabetic mice showed a genetic sensitivity to carbohydrate-rich foods, a feature of type 2 diabetes in humans.[48]

Spontaneous Diabetic Torii (SDT) Rat: The SDT rat is a new non-obese species. It is characterized by glucose intolerance, hyperglycemia, hyperinsulinemia and hypertriglyceridemia. Due to severe hyperglycemia, SDT rats developed diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. This model is suitable for studying complications of human T2DM.[49]

Diabetes Surgery Model: Surgical procedures used to induce diabetes in order to completely remove the pancreas. Limitations of this process include a high level of expertise and insufficient workspace. A pancreatectomy was performed; Major surgery is required to achieve mild to moderate hyperglycema.[50]

CONCLUSION

Diabetes Mellitus remains a significant global health challenge, with its complex pathophysiology necessitating comprehensive research efforts for effective management and treatment. Animal models, serving as invaluable tools in elucidating disease mechanisms and evaluating therapeutic strategies, play a crucial role in advancing our understanding of diabetes. From chemically-induced models to genetically-modified organisms, these models offer insights into the diverse facets of diabetes, including insulin resistance, beta-cell dysfunction, and metabolic abnormalities. Such preclinical research endeavors pave the way for the development of novel therapeutic interventions and preventive measures aimed at alleviating the burden of diabetes and its associated complications. By leveraging the translational relevance of animal models, future endeavors can strive towards improved management strategies and ultimately, better outcomes for individuals affected by diabetes.

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