

Mitochondrial Dysfunction and Diabetes

Mehmet ÖZSAN^{1*} ve Canan CEYLAN²

¹Basic Medical Sciences/ Faculty of Medicine, Niğde Ömer Halisdemir University, Türkiye

²Basic Medical Sciences/ Institute of Health Sciences, Selçuk University, Türkiye

*(mehmet_ozsan@hotmail.com)

Abstract – Diabetes is a condition characterized by high blood sugar levels in the body and can lead to various long-term complications. Mitochondria are organelles responsible for energy production in our cells. Recent research indicates that diabetes can both cause and result from mitochondrial dysfunction. Diabetes can trigger mitochondrial DNA damage, oxidative stress, and inflammation due to mitochondrial dysfunction. Dysfunction in mitochondria can increase the production of free radicals, leading to increased oxidative stress. Oxidative stress can cause cellular damage and inflammation, thereby supporting the development of diabetes. Additionally, it is believed that diabetes can also affect mitochondrial processes such as mitochondrial biogenesis, mitochondrial mobility, and mitophagy.

Keywords – Diabetes, Mitochondria, Insulin Resistance, Type 2 Diabetes, Dysfunction

I. INTRODUCTION

The development of insulin resistance and mitochondrial dysfunction can contribute to the onset of acute or chronic illnesses, leading to a decrease in overall quality of life. Mitochondrial dysfunction can both be a cause and a consequence of insulin resistance [1].

Insulin, recognized as one of the key hormones involved in regulating energy metabolism [2], experiences diminished response in insulin-targeted cells in the presence of insulin resistance, which plays a crucial role in the development of type 2 diabetes [3]. Mitochondria, the primary functional components responsible for energy oxidation and ATP production within cells [4], have been observed to have a connection between their oxidative capacity and insulin activity [5]. Research suggests that mitochondrial dysfunction can initiate the development of insulin resistance [5], and the assessment of insulin sensitivity can be influenced by the oxidative capacity of mitochondria [6].

II. INSULIN RESISTANCE

Insulin resistance refers to a condition where the body's cells exhibit reduced responsiveness to the insulin hormone. Under normal circumstances, insulin facilitates the absorption of glucose from the bloodstream into cells for energy utilization. However, individuals with insulin resistance experience decreased sensitivity of their cells to insulin, leading to inefficient glucose uptake and elevated blood glucose levels. The crucial role of skeletal muscles in regulating approximately 80% of glucose utilization is emphasized [7]. Diabetes manifests when the body encounters challenges in maintaining proper blood sugar levels. Mitochondrial dysfunction can impact the cells' ability to respond to insulin signals, contributing to insulin resistance and potentially fostering the development of type 2 diabetes.

III. CLASSIFICATION OF DIABETES

Diabetes is a medical condition resulting from either inadequate production of insulin or ineffective utilization of insulin within the body. The American Diabetes Association (ADA) categorizes diabetes into type 1, type 2, and other specific types based on their causes, with gestational diabetes mellitus (GDM) being widely recognized [8]. It's essential to acknowledge that diabetes (DM) encompasses a range of diseases leading to persistent hyperglycemia. The classification of various diabetes types is determined by the distinct mechanisms underlying their development [9].

A. Type 1 Diabetes (Type 1 DM)

Type 1 Diabetes (Type 1 DM) is a condition characterized by an autoimmune attack on the beta cells in the pancreas responsible for producing insulin. This attack impairs the pancreas' ability to produce sufficient insulin, resulting in reduced insulin levels in the bloodstream. Individuals diagnosed with type 1 diabetes must undergo daily insulin injections for their entire lives. Level-2 and level-3 headings can be used to detail main headings [10].

B. Type 2 Diabetes (Type 2 DM)

Type 2 Diabetes (Type 2 DM) is a form of diabetes characterized by high blood sugar levels, insufficient insulin production, and resistance to insulin's effects. Elevated blood sugar levels contribute to the impairment of pancreatic beta cells and the development of insulin resistance. The exact causes of insulin deficiency and resistance can be complex, involving a combination of genetic and environmental factors. Insulin resistance, which is commonly observed in individuals with type 2 diabetes, is assessed using the HOMA IR test. Type 2 diabetes is frequently linked to factors such as obesity, lifestyle choices, and genetic predisposition. Treatment for type 2 diabetes typically involves lifestyle adjustments, dietary changes, physical activity, weight management, and occasionally medication. In more advanced cases, insulin injections may be required [11].

C. Type 2 Diabetes (Type 2 DM)

Gestational Diabetes (GDM) is a form of diabetes that originates or is first identified during pregnancy. The likelihood of developing GDM is

higher in cases where there is a family history of diabetes among close relatives, if the mother is obese, of advanced maternal age, experiences glucosuria, or has previously had macrosomia, polyhydramnios, or a history of stillbirth in a prior pregnancy [12].

D. The category of Other Specific Types of DM

The category of Other Specific Types of DM includes all forms of diabetes that are distinct from Type 1, Type 2, and gestational diabetes. This group comprises conditions such as monogenic disorders affecting beta cell functions, genetic disorders impacting insulin activity, diseases affecting the exocrine pancreas, endocrinopathies, drug-related effects, and infections, all of which can contribute to the development of these specific types of diabetes [13].

IV. MITOCHONDRIAL DYSFUNCTION

Over the last two decades, there has been significant progress in understanding the structure, functions, and mechanisms involved in mitochondria biogenesis [14]. Mitochondria play a crucial role in regulating the body's metabolism, ensuring energy homeostasis by metabolizing nutrients to produce ATP and heat [15]. Additionally, mitochondria have been found to participate in cell signaling during apoptosis and can have adverse effects on the heart, skeletal muscles, and nervous system when their functions are impaired [14]. Mitochondrial dysfunction can be identified by reduced mitochondrial content [14] or decreased mitochondrial activity and oxidative phosphorylation [17]. Such dysfunction can lead to diminished mitochondrial oxidation of carbohydrates and lipids, resulting in decreased oxidative phosphorylation [18].

Mitochondrial dysfunction can disrupt normal cellular processes, leading to an overproduction of harmful free radicals and an increase in oxidative stress. This oxidative stress can cause cellular damage and inflammation, which in turn can contribute to the development of diabetes. Impaired mitochondrial functions have been linked to various conditions that can diminish the quality of life, including cardiovascular diseases [19], sarcopenia (loss of muscle mass and strength) [20], insulin resistance, type 2 diabetes [21], aging-related issues [22], and a decline in aerobic

capacity. These conditions can have detrimental effects on overall health and well-being [23].

V. THE RELATIONSHIP BETWEEN INSULIN RESISTANCE AND MITOCHONDRIAL FUNCTION

Insulin resistance is a characteristic trait found in chronic diseases that impact the body's energy metabolism [17]. The utilization of glucose and lipids for energy in cells relies heavily on the functioning of mitochondria. Insufficient nutrient oxidation leads to a decrease in the ratio of ATP production to oxygen consumption, resulting in an elevated presence of superoxide anions in the surroundings [24]. This can give rise to various issues, including the generation of reactive oxygen species (ROS), increased DNA mutations, and the activation of proinflammatory processes. Alongside ROS production, factors like genetics, aging, and reduced mitochondrial biogenesis also contribute to the impairment of mitochondrial function [17].

Considering the link between mitochondrial dysfunction and oxidative phosphorylation-related gene expression, it is hypothesized that mutations arising in mitochondrial genes due to cellular stress or aging could potentially contribute to insulin resistance, as it is associated with insulin resistance [16].

Mitochondrial dysfunction-induced insulin resistance can initiate metabolic and cardiovascular disorders, ultimately leading to cardiovascular diseases. Insulin plays a vital role in regulating blood glucose levels by aiding the entry of glucose into cells. In individuals with diabetes, inadequate or ineffective insulin results in sustained high blood sugar levels. Prolonged elevation of blood sugar levels can contribute to diabetes complications and harm organs. Considering these findings, it is hypothesized that mitochondrial dysfunction may be a key factor in the emergence of complications associated with insulin resistance [16].

While insulin resistance is frequently connected to type 2 diabetes, it can also be associated with various other conditions like obesity, lack of physical activity, metabolic syndrome, and polycystic ovary syndrome. In response to insulin resistance, the body increases insulin production as the pancreas attempts to compensate. However, if the pancreas fails to meet this increased demand

over time, it can lead to elevated blood glucose levels and the onset of type 2 diabetes [7].

Research has demonstrated that individuals with obesity, insulin resistance, prediabetes, or type 2 diabetes mellitus often experience mitochondrial dysfunction. This impaired mitochondrial function raises the likelihood of developing type 2 diabetes mellitus and gestational diabetes later in life. Placental tissue in pregnant women with gestational diabetes shows a decrease in mitochondrial content. As insulin secretion relies on mitochondrial ATP, these individuals struggle to produce an adequate amount of insulin.

Patients with type 2 diabetes mellitus exhibit mitochondrial respiratory dysfunction, compromised ATP synthesis, excessive fission and fusion processes, and alterations in mitophagy within the beta cells' mitochondria in the pancreas, responsible for insulin secretion.

The decline in mitochondrial function leads to a reduced oxidation of fatty acids within the mitochondria, resulting in fat accumulation in the body and elevated levels of diacylglycerol (DAG) and ceramide (CER). Increased DAG and CER levels hinder insulin secretion and activity, thereby amplifying insulin resistance. In obesity, mitochondria within adipocytes undergo fragmentation and heightened production of reactive oxygen species (ROS), while liver cell mitochondria experience fragmentation, a decline in components of the electron transport chain, impaired membrane potential, and decreased ATP synthesis [25], [26].

Mitochondrial dysfunction can occur due to various factors such as mutations in mitochondrial DNA, a decrease in mitochondrial content or biogenesis, disrupted dynamics (fission/fusion), impaired mitophagy, deficiencies in bioenergetics caused by nutrient and vitamin deficiencies, reduced enzyme activity, increased oxidative stress, or disrupted calcium balance. As a result, the oxidation of glucose and lipids is impaired. This impaired lipid oxidation leads to an accumulation of lipid intermediates like diacylglycerol and ceramide, which interfere with the effectiveness of insulin. The decrease in glucose and lipid oxidation leads to a reduction in oxidative phosphorylation within the mitochondria, causing electron leakage, the formation of superoxide, and damage to the mitochondria. Mitophagy plays a role in removing these damaged

mitochondria to maintain a balance. However, if mitophagy is impaired, the elimination of damaged mitochondria becomes ineffective, further worsening the problem [25], [26].

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