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Review Article

Metabolic reasons of diabetes mellitus: An update

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ABSTRACT

Diabetes Mellitus (DM) goes beyond just a lack of insulin. Type 2 Diabetes Mellitus (T2DM) is heavily influenced by insulin resistance. Cells become less responsive to insulin's signal to absorb glucose, leading to high blood sugar levels. Excess body fat, particularly around the abdomen, and a sedentary lifestyle are ley culprits for this resistance. The pancreas struggles to keep up with the demand for insulin in T2DM. Initially, it compensates by producing more, but over time, this ability declines due to factors like genetics and high blood sugar levels. Glucagon, normally working opposite insulin becomes imbalanced in T2DM. Its levels rise, further promoting glucose production and worsening hyperglycemia. The contributing factors include fasting, high protein diet, and pancreatic issues. The liver's ability to regulate glucose production is impaired in T2DM. This dysregulation leads to the excessive release of glucose into the bloodstream, contributing to chronic hyperglycemia. Certain genetic disorders affecting carbohydrate metabolism can increase the risk of diabetes. These disorders can lead to changes that mimic pre-diabetes, further contributing to insulin resistance. In T2DM, increased lipolysis releases excessive free fatty acids (FFAs) into the blood stream. These FFAs worsen insulin resistance and damage insulin-producing cells, further exacerbating hyperglycemia. Obesity, with its high fat stores and increased lipolysis, is a major risk factor. The kidneys play a crucial role in reabsorbing filtered glucose from the urine. In T2DM, this reabsorption might be heightened contributing to hyperglycemia. Additionally, chronic kidney disease can impair glucose metabolism, potentially impacting diabetes management. While insulin deficiency plays a role, diabetes is a complex interplay of factors. Unravelling the intricate dance between insulin, glucagon, the liver and cellular responses is crucial for effective management and prevention of diabetes-related complications. This review delves into the intricate metabolic reasons behind this condition, focusing in Type 2 Diabetes Mellitus (T2DM).

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1. Introduction

Diabetes mellitus (DM) is often perceived as a simple deficiency of insulin, the hormone regulating blood sugar levels. However, this understanding falls short of capturing the intricate metabolic dance that unfolds in the body during this condition. This text delves deeper, exploring the key metabolic reasons behind the development and progression of diabetes, particularly type 2 diabetes mellitus (T2DM), the most common form.

The review deep dives into the body's intricate metabolic pathways, dissecting the roles of insulin resistance, impaired insulin secretion, and the interplay between insulin and glucagon. The text investigates the liver's glucose production and how it goes awry in diabetes. Additionally, it explores the connections between inborn errors of metabolism, altered carbohydrate metabolism, and the risk of diabetes development. Furthermore, the text sheds light on the crucial role of fat metabolism in diabetes. It examines how lipolysis, the breakdown of fat stores, and the resulting

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free fatty acids can exacerbate insulin resistance and beta-cell dysfunction. We'll also delve into the kidneys' role in glucose regulation and how impaired renal function can further complicate the diabetic picture.

By the end of this exploration, a deeper appreciation for the complex tapestry of metabolic factors woven together in diabetes mellitus is gained. This comprehensive understanding is crucial for developing effective management strategies and preventing the complications associated with this chronic condition.

2. Insulin Resistance

Insulin resistance is a metabolic condition characterized by the diminished effectiveness of the insulin in lowering blood sugar levels. This condition is a central feature of type 2 diabetes mellitus (T2DM) and is closely associated with obesity and physical inactivity.[1] At the cellular level, insulin resistance arises when cells in muscles, fat and liver respond inadequately to insulin. This impaired response means that glucose is less effectively taken up by these cells, leading to elevated blood glucose levels. Overtime, the pancreas compensates for this resistance by producing more insulin, a state known as hyperinsulinemia. However, if the pancreas cannot keep up with the demand for more insulin, blood glucose rise, leading to prediabetes and eventually T2DM.[2] The reasons for insulin resistance are multifactorial. Excess body fat, particularly around the abdomen, and a sedentary lifestyle are significant contributors. Ectopic lipid accumulation in the liver and skeletal muscle impairs glucose uptake and glycogen synthesis, further exacerbating insulin resistance.[3]

3. Impaired Insulin Secretion

Impaired insulin secretion is a hallmark of T2DM where the pancreatic beta cells fail to produce adequate amounts of insulin in response to blood glucose levels. This deficiency in insulin secretion is due to both a decrease in the functional mass of beta cells and a dysfunction in the cells' insulin producing machinery. In the early stages of T2DM, insulin resistance prompts an increased demand for insulin, which initially leads to a compensatory rise in insulin production.[4] However, over time, the beta cells become unable to maintain the heightened level of insulin secretion due to progressive beta cell dysfunction. The pathophysiology behind impaired insulin secretion involves genetic predispositions, environmental factors, and the toxic effects of high glucose and fatty acid levels on beta cells, a phenomenon known as glucolipotoxicity.[5]

Additionally, the deposition of amyloid in the islets of Langerhans and low grade inflammation further exacerbates beta cell damage.[6] The decline in beta cell mass is also attributed to increased beta cell apoptosis, which is not sufficiently compensated by neogenesis or replication of new beta cells.[7]

4. Increased Glucagon Levels

Increased glucagon levels play a significant role in the pathogenesis of diabetes, particularly T2DM. Glucagon, a hormone produced by the alpha cells of the pancreas, works in opposition to insulin, promoting hepatic glucose production and raising plasma glucose levels. In healthy individuals, a delicate balance exists between insulin and glucagon to maintain optimal blood glucose levels. However, in T2DM, this balance is disrupted, leading to hyperglycemia- an excess of glucagon in the blood.[8]

Increased glucagon levels can be attributed to several factors, including fasting, high protein diet, low insulin levels, liver diseases and scarring, Pancreatitis and tumors of pancreas. Hyperglycemia contributes to the hyperglycemia characteristic of diabetes by stimulating gluconeogenesis and glycogenolysis in the liver, processes that increase glucose output. Moreover, glucagon's role extends beyond glucose metabolism; it also influences lipid and bile acid metabolism, which are crucial in the overall metabolic dysregulation seen in diabetes.[9]

This interplay between increased glucagon levels and diabetes is complex. Insulin deficiency, commonly seen in diabetes, leads to unopposed glucagon action, exacerbating hyperglycemia and ketone production. This state of glucagon excess is more critical to the development of diabetes than insulin deficiency alone.[10]

5. Abnormal Glucose Production By The Liver

Abnormal glucose production by the liver, known as hepatic gluconeogenesis, is a critical factor in the development of diabetes mellitus, particularly T2DM.[11] it is a complex physiological phenomenon where the live produces and releases glucose into the bloodstream at inappropriate times or in excessive amounts. This dysregulation can be attributed to several factors, including hormonal imbalances. Genetic predispositions and lifestyle influences such as diet and physical activity levels. In the context of diabetes, particularly T2DM, the liver's ability to respond to insulin is impaired, leading to an overproduction of glucose. Normally insulin suppresses glucose production to maintain blood sugar levels but in T2DM, this suppression is impaired, leading to excessive glucose release into the blood stream.[12] This contributes to the chronic hyperglycemia characteristic of diabetes. Additionally, a key protein called FOX06 has been identified as a regulator of this process. High levels of FOX06 in diabetic mice correlate with increased glucose production by the liver, suggesting that this protein plays a significant role in abnormal glucose output observed in diabetes.[13] Furthermore, conditions such as visceral obesity also contribute to the liver's aberrant glucose production by promoting insulin resistance.[14] So

this can be concluded that abnormal glucose production by the liver and diabetes mellitus have a complex interrelationship with each other.

6. Altered Carbohydrate Metabolism

Patients with inborn errors of metabolism (IEMs) can have an increased risk of developing diabetes, particularly if the metabolic disorder affects pathways shared with diabetes pathogenesis. For example, disorders that impact fatty acid and amino acid metabolism can exhibit biochemical changes similar to those observed in the prediabetic state, such as ectopic lipid storage and increased levels of acylcarnitine and branched-chain amino acids.[15] These metabolic intermediates can contribute to insulin resistance, a key feature of T2DM.[15]

However, the relationship is complex and not all IEMs may confer the same level of risk. The specific gene defect and the metabolic intermediates that accumulate as a result can vary widely among different IEMs. Some metabolic gene defects might lead to insulin resistance, while others may not have any effect or could even improve insulin sensitivity.[16]

It's important to note that while there is a potential link between certain inborn errors of metabolism and an increased risk of diabetes, this does not mean that all patients with Items will develop diabetes. This risk is influenced by a combination of genetic, environmental and lifestyle factors.[17] Ongoing research continues to explore these connections to better understand the risks and develop targeted treatments for those affected.

7. Lipolysis and Free Fatty Acids(FFAs)

Lipolysis is a process of breaking down triglycerides into free fatty acids(FFAs) and glycerol within the body's fat cells. This process is essential for providing energy when glucose when glucose levels are low. However, in the context of diabetes, particularly T2DM, lipolysis can have detrimental effects.

In individuals with T2DM, insulin resistance impairs the ability of insulin to suppress lipolysis, leading to an increased release of FFAs into the bloodstream. High levels of circulating FFAs can exacerbate insulin resistance by interfering with glucose uptake in muscle cells and promoting glucose production in the liver.[18] Additionally, the accumulation of FFAs can lead to beta cell lipotoxicity, which impairs the pancreas's ability to produce insulin, further contributing to hyperglycemia. Short term elevation of FFAs has been shown to rapidly induce insulin resistance and beta cell lipotoxicity in youth, highlighting the significant relationship between lipid metabolism, insulin sensitivity and insulin secretion.[18] This relationship underscores the importance of managing FFA levels to maintain glucose homeostasis and prevent the progression of diabetes. Moreover, obesity, characterized by excess fat stores and increased adipose tissue lipolysis, a major risk factor for T2DM. The hydrolysis of triglycerides and the release of FFAs in obese individuals contribute to the development of insulin resistance and diabetes.[19]

8. Renal Glucose Handling

The kidneys are not only responsible for filtering waste products but also play a crucial role in glucose regulation. Glucose is filtered from the blood into the renal tubules. Normally, most of this filtered glucose is reabsorbed back into the bloodstream. Sodium-glucose cotransporter 2 (SGLT2), located in the proximal tubules of the kidneys, is responsible for reabsorbing about 90% of filtered glucose.[20]

Impaired renal glucose handling itself is not typically a direct cause of diabetes. However, it is closely associated with the progression and management of diabetes, especially T2DM. In T2DM, the kidneys' ability to reabsorb glucose from the urine is often heightened due to increased expression of the sodium-glucose cotransporter 2, which can contribute to hyperglycemia.[21] In the context of chronic kidney disease (CKD), impaired glucose metabolism is common. Some patients with advanced CKD exhibit hyperglycemia in response to glucose loads, while others maintain normal blood sugar levels by increasing plasma insulin levels.[22] Renal impairment can affect the physiology of glucose homeostasis by reducing tissue sensitivity to insulin and decreasing insulin clearance.[23]

Recent researches have suggested that when the kidneys are damaged and cannot filter waste products from the blood effectively, it can lead to high blood levels of the waste product urea. This condition can prevent the pancreas from producing insulin properly, which may cause diabetes.[24] Additionally, a study published in the journal of clinical investigation concluded that urea buildup in the blood due to kidney failure could cause diabetes.[25]

This finding indicates a bidirectional relationship between diabetes and kidney disease. While diabetes is a well-known cause of kidney disease, it appears that kidney disease can also lead to changes in glucose metabolism that may result in diabetes.

Therefore, while impaired renal glucose handling is more of a consequence of diabetes and CKD, it can exacerbate the hyperglycemic state in patients with patients with diabetes and potentially influence the disease's management and progression.[26] It's important to note that the relationship between renal function and diabetes is complex and multifaceted, often involving a combination of genetic, environmental and lifestyle factors.

9. Conclusion

Most of the times, in general population Diabetes mellitus is considered to a disease caused by diminished, defective

or absolute lack insulin production by the pancreas. But the intricate interplay of insulin, glucagon, liver function, and cellular responsiveness contributes to the pathogenesis of diabetes mellitus. Understanding these metabolic factors is essential for effective management and prevention of complications associated with diabetes.

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11. Conflict of Interest

None.

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