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Hypomagnesemia and Insulin Resistance: Gaining Better Understanding of the Pathophysiology of Type 2 Diabetes

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Abstract

Diabetes mellitus is a metabolic disorder with a central theme of chronic hyperglycaemia which is due to a deficiency in insulin secretion and/or action. There are various types but type 2 is the commonest type of diabetes mellitus. The main pathophysiologic mechanisms of type 2 diabetes are insulin resistance and pancreatic β cell dysfunction. The pathophysiology of type 2 is not fully known so; different hypotheses keep coming up in the literature to explain its pathophysiology. One of these newer mechanisms to explain the pathophysiology of insulin resistance is deficiency of minerals. Magnesium is an essential mineral needed for various metabolic processes in the cells. Hypomagnesemia is more frequent in patients with type 2 diabetes and it has been linked with the pathophysiology of type 2 diabetes. Hypomagnesemia is associated with intracellular magnesium deficiency. Magnesium deficiency inside β cell is associated with reduced enzymatic activities insufficient intracellular ATP concentration leading to reduced insulin secretion. Also, magnesium deficiency in the cells is associated with impaired activities of the enzymes in the protein kinase B pathway of insulin action thereby contributing to insulin resistance. Hypomagnesemia is associated with increased production of pro-inflammatory cytokines which are the factors responsible for the low grade chronic inflammation associated with obesity and diabetes. Antioxidant activities are diminished in hypomagnesemia. These mechanisms are the possible explanations linking hypomagnesemia to the pathophysiology of type 2 diabetes mellitus.

Keywords: Type 2 diabetes; Pathophysiology of type 2 diabetes; Hypomagnesemia and type 2 diabetes; Insulin resistance and magnesium

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Introduction

Diabetes mellitus is a heterogeneous group of chronic metabolic disorders characterized by chronic hyperglycaemia that arises due to deficiency of insulin secretion and/or its action [1]. In diabetes mellitus, there is a disorder of carbohydrate, lipids and protein metabolism. According to the 2019 World Health Organization (WHO) classification, diabetes mellitus is classified into type 1 diabetes, type 2 diabetes, hybrid type, gestational diabetes mellitus, and other specific types of diabetes and the unclassified type [2]. WHO has reported that there are over 400 million people worldwide living with diabetes mellitus [2]. Unfortunately, it is projected that the prevalence will keep rising due to the obesity pandemic and westernization in the low and middle income countries [2].

International Diabetes Federation (IDF) stated that type 2 diabetes mellitus is the commonest class of diabetes and it accounts for about 90% of all cases of diabetes [3]. There are two key features in the pathophysiology of type 2 diabetes mellitus namely, insulin resistance and β cell dysfunction. Insulin resistance is said to occur when the physiologic response produced by a certain amount of insulin is reduced [4]. β cell dysfunction is the inability of the β cells to produce sufficient amount of insulin to drive insulin-mediated transport of glucose into the cells [5]. β cell dysfunction usually occurs as a consequence of insulin resistance. Therefore, insulin resistance is considered as the core abnormality in type 2 diabetes [4].

Despite the advances in the diagnosis and management of type 2 diabetes, there are still many things about the pathophysiology

that is unknown [6]. Therefore researches are continually being conducted to elucidate the pathophysiological mechanisms of diabetes. Among the efforts being made to understand diabetes more are the researches being conducted to study the role of minerals in the pathophysiology of type 2 diabetes [7]. The minerals, whose deficiency has been linked with insulin resistance, include magnesium, Zinc, iron, selenium, copper and cobalt [8].

Literature Review

Magnesium is an essential mineral that has to be consumed with the diet in order to prevent its deficiency and the consequences [9]. Studies have reported a higher prevalence of hypomagnesemia among patients with type 2 diabetes [9]. A study reported hypomagnesemia prevalence of 14-48% among patients with type 2 diabetes compared with 2.5-15% among healthy controls without diabetes [10]. Another study confirmed that people who consume less magnesium in their diets have a higher risk of developing type 2 diabetes [11].

Insulin resistance

Central to the pathophysiology of type 2 diabetes mellitus is the concept of insulin resistance. Insulin resistance is defined as the requirement for larger insulin concentration to produce the same physiological response [9]. The basic physiological role of insulin is to enhance the transport of glucose into the cells of organs, especially liver, skeletal muscle and adipose tissue [9]. In normal cell physiology, insulin binds to a heterodimer receptor which autophosphorylates into a tyrosine kinase leading to the recruitment of some substrates and eventual activation of some downstream signaling pathways [9]. Ultimately, there is incorporation of glucose transporters (GLUT) into the cell membrane and facilitate cellular glucose entry.

Insulin resistance is a combination of receptor and post-receptor abnormalities [12]. In insulin resistant tissues, there is decreased expression of insulin receptors in the cell membrane. A study quoted a reduction of about 5-10% in the quantity of insulin receptors in the cell membrane [12]. This study also suggested that there must be some post-receptor mechanisms to explain the profound insulin resistance in most patients with type 2 diabetes. Later on, the reduction in post-receptor signaling was reported. Researches are still going on to elucidate the specific defects in insulin signal transduction in insulin resistance. Recent findings have demonstrated hyperphosphorylation of some insulin receptor substrates [13]. Mitochondrial dysfunction has also been documented to be partly contributing to the mechanisms of insulin resistance.

Magnesium physiology

Magnesium is the 4th most abundant cation in the body and is second only to potassium among the intracellular cations [14]. A 70kg physiological man has about 25g of magnesium in his body [15]. Most of this magnesium content is located in the bone and the skeletal muscles. 99% of the total body magnesium is intracellular while the rest is extracellular [16]. Plasma magnesium exists as free ions, protein bound or complexed to anions such as phosphate and bicarbonate [17].

The recommended daily allowance for men is 310-360 mg and for women, 400-420 mg, according to the Institute of Health [17]. Food sources rich in magnesium include legumes, nuts, fruits, meat and fish. However, consumption of highly processed food, which is also associated with type 2 diabetes, means that many people are consuming less than the recommended amount because food processing leads to the loss of magnesium from the food [17].

Most of the ingested magnesium is absorbed in the distal small intestine although a little quantity is also absorbed in the large intestine out of about 360 mg of magnesium ingested per day, only about 100 mg is absorbed in the gastrointestinal tract while the rest is lost in faeces [16,17]. Daily urinary excretion of magnesium is about 100 mg so as to maintain homeostasis. So during a period of excess ingestion of magnesium, the kidney excretes it more while during the period of reduced intake of magnesium, the renal excretion of magnesium is reduced [17]. Most of the ingested magnesium is absorbed in the enterocytes of the proximal small intestine, mainly in the distal jejunum and proximal ileum. However, there is minimal absorption of magnesium via the colon. Magnesium absorption occurs through 2 transport mechanisms namely transcellular and paracellular pathway [9]. Transcellular absorption occurs through the action of Na⁺/K⁺ ATPase which establishes the Na⁺ gradient across the membrane. The gradient facilitates the exchange of magnesium with sodium at the basolateral membrane via the Na⁺-Mg²⁺ antiporter. Channel proteins called transient receptor potential melastin 6 (TRPM6) is also involved [9].

Synthesis of macromolecules such as proteins and nucleic acids is dependent on magnesium as a co-factor [18]. Cellular uptake of magnesium is via the magnesium channels and specific magnesium transporters. Intracellular concentration of magnesium is regulated through the activities of these transporters. Insulin increases magnesium uptake into the cells thereby increasing its level in the cytosol and decreasing its plasma level [19]. Research efforts are still ongoing to characterize the specific magnesium transporters involved in this [19].

Renal physiology of magnesium and diabetes

Magnesium wasting is a common occurrence in poorly treated diabetes as insulin regulates magnesium reabsorption in the renal tubules [9]. This is mainly because binding of insulin to its receptor in the renal tubules leads to increased incorporation of the magnesium channel protein TRPM6 in the cell membrane to enhance the reabsorption of magnesium. Apart from magnesium, it is also known that insulin stimulates reabsorption of other electrolytes, for example hyperinsulinaemia in type 2 diabetes stimulates the sodium-chloride co-transporter in the distal convoluted tubule and this may partly explain hypertension seen in this condition [9]. Insulin also stimulates the potassium channel Kir 4.1 which also plays a role in magnesium reabsorption causing hypomagnesemia and hypokalemia [9].

In addition, in a mouse with sodium-glucose co-transporter 2 (SGLT-2) gene knockout, there was affectation of magnesium absorption but clinical trials with SGLT-2 inhibitors have not shown any consistent abnormality of magnesium homeostasis

[9]. Glomerular hyperfiltration of magnesium and dysfunction of TRMP 6 due to oxidative stress have also been documented in diabetes [9].

Hypomagnesemia

This refers to the situation when the plasma magnesium is less than the reference range for normal people. The reference range depends on the laboratory and the assay type being used. Hypomagnesemia is not an uncommon finding among in-patients. The frequency of hypomagnesemia among hospitalized patient based on various studies ranges from 9% to 65% [17]. Patients admitted into the intensive care unit have higher frequency of hypomagnesemia compared with patients admitted to the general medical ward [17]. The documentation of hypomagnesemia in hospitalized patients is important because it is associated with increased mortality [17]. Therefore, hypomagnesemia should be checked in hospitalized patients especially the critically ill ones and an attempt should be made to correct the underlying pathology of the hypomagnesemia.

Common causes of hypomagnesemia include malnutrition, malabsorption, chronic diarrhoea, tubulointerstitial nephropathy, drugs such as loop diuretics, aminoglycoside, amphotericin B and cisplatin, chronic alcoholism and hyperaldosteronism [17]. Apart from diabetes mellitus, hypomagnesemia has also been linked with other diseases such as stroke, myocardial infarction, cancers and liver cirrhosis [20]. Most of the clinical presentations of hypomagnesemia are not specific and they include anorexia, nausea, vomiting, fatigue, tremor, agitation, behavioral changes, seizures, muscle fasciculations, arrhythmias [21].

Magnesium and insulin secretion

Magnesium plays a regulatory role in insulin secretion by the β cells of the pancreas [22]. A narrow intracellular magnesium balance is required for optimal insulin secretion by the pancreatic β cells. Normal insulin secretion involves the entry of glucose into the β cells which is rapidly converted to glucose-6-phosphate by an enzyme called glucokinase. Glucose-6-phosphate is ultimately metabolized to synthesize adenosine triphosphate (ATP). A rise in the intracellular ATP causes the ATP-sensitive potassium channels (K_{ATP}) to close. Closure of the potassium channels lead to the depolarization of the β cells leading to opening of voltage-gated calcium channels. This is followed by influx of calcium ions which eventually leads to insulin secretion.

Glucokinase enzymatic activity requires the presence of magnesium ions as a co-factor [22]. Therefore, magnesium deficiency can directly slow down the process of insulin secretion. In addition synthesis of ATP via glycolysis requires magnesium as a co-factor and magnesium deficiency impairs the rise in intracellular ATP in the β cells needed for insulin secretion [22]. In people with hypomagnesemia, the intracellular magnesium concentration is also low thereby blunting insulin secretion [23]. Moreover, calcium influx via the L-type Ca^{2+} channels is necessary for insulin secretion and this process is impaired in chronic hypomagnesemia [9].

Magnesium and insulin resistance

Insulin exerts its physiologic actions through two pathways namely, protein kinase B pathway and mitogen-activated protein kinases pathway [17]. The protein kinase B pathway mediates most of the metabolic actions of insulin. The pathway eventually leads to the translocation of the glucose transporter 4 (GLUT 4) from the intracellular compartment into the cell membrane, especially in skeletal muscle cells and adipocytes, thereby facilitating glucose entry into the cells. The protein kinase B pathway also regulates glycogenesis and lipogenesis [17].

Magnesium plays a role in the phosphorylation of insulin substrates and many enzymes involved in the protein kinase B pathway [17]. Magnesium deficiency decreases the phosphorylation of insulin substrates and diminishes the activities of various enzymes. This ultimately decreases the concentration of GLUT 4 incorporated into the cell membrane thereby causing insulin resistance and type 2 diabetes subsequently [17].

Hypomagnesemia and systemic inflammation

Insulin resistance has been associated with chronic low grade systemic inflammation [24]. Magnesium has been found to play a role in this inflammation-associated insulin resistance. The cytokines involved in the low grade chronic inflammation include interleukins (IL-1 and IL-6) tumor necrosis factor- α , plasminogen activator inhibitor-1 and vascular cell adhesion molecule-1. Hypomagnesemia has been reported to enhance the production of these cytokines thereby contributing to the inflammation-associated insulin resistance [24].

In the body, there are antioxidants such as superoxide dismutase, glutathione peroxidase and catalases [17]. These antioxidants protect the body from the deleterious effects of inflammation [25]. Magnesium is required by these antioxidants and magnesium deficiency can impair their functioning thereby making the systemic inflammation to fester.

Studies have suggested that low grade chronic systemic inflammation may be the link between obesity, metabolic syndrome on one hand and hypomagnesemia on the other hand [26]. A study found a higher frequency of hypomagnesemia in patients with type 2 diabetes and abdominal obesity compared with patients with type 2 diabetes without abdominal obesity [17]. Another study found a higher level of C-reactive peptide among type 2 diabetes patients with hypomagnesemia compared with type 2 diabetes patients with normomagnesemia further alluding to the link between hypomagnesemia and type 2 diabetes via systemic inflammation [27].

Hypomagnesemia and type 2 diabetes - The genetic link

Some important channels and transporters determine the entry of magnesium into the cells, hence its intracellular concentration. Studies have reported that single nucleotide polymorphisms documented in some magnesium transporters are associated with an increased risk of developing type 2 diabetes [28]. Moreover, ATP-sensitive potassium channel essential for the secretion of insulin has variants and the interaction of the variants with

hypomagnesemia affect the risk of developing type 2 diabetes [29-34].

Magnesium supplementation and insulin resistance

Animal studies have demonstrated that magnesium supplementation reduces insulin resistance in diabetic rats [35]. Even in obese rats who do not have diabetes, magnesium supplementation was documented to prevent diabetes mellitus in them [36]. These findings have also been replicated in humans.

Some researchers have looked at the effects of magnesium supplementation on insulin resistance in patients with type 2 diabetes and it has been found to be beneficial [30]. Even in overweight individuals who did not have diabetes, magnesium supplementation was equally found to reduce their insulin resistance [31]. Mediterranean diet and DASH (Dietary Approach to Stop Hypertension) diet which have been found to be beneficial in the prevention and treatment of patients with type 2 diabetes are also known to be rich in magnesium [32].

Apart from improvement in glycaemic control and insulin resistance, magnesium supplementation was also beneficial in the modification of other cardiovascular risk factors such as blood pressure and serum lipid profile [36]. A systematic review on randomized controlled trials on magnesium supplementation in individuals with diabetes and those at risk of diabetes demonstrated a beneficial effect of magnesium supplementation on glucose and insulin sensitivity parameters [37].

Hypomagnesemia and metformin

Metformin is a first line drug in the treatment of type 2 diabetes mellitus. Metformin has been found to be associated with chronic diarrhoea causing hypomagnesemia [33]. A study found an improvement in plasma magnesium and glycaemic control following discontinuation of metformin which had caused chronic diarrhoea and hypomagnesemia. However, in those who do not

develop chronic diarrhoea, metformin has been documented to improve magnesium status and glycaemic control in diabetic rats [34]. In addition, in a recently published animal study, diabetic mice developed hypomagnesemia but metformin did not alter magnesium homeostasis in the diabetic rats [38].

Hypomagnesemia, kidney disease, and diabetes mellitus

In post-transplant patients, researchers have documented hypomagnesemia which has recently been linked with the development of new-onset diabetes after transplantation (NODAT) [39]. Also, a retrospective study has documented a higher incidence of NODAT in patients with pre-transplant hypomagnesemia which is thought to increase insulin resistance in these patients [40]. A systematic review of the studies on the association between post-transplant hypomagnesemia and NODAT has also affirmed a link between hypomagnesemia and NODAT which is of great importance because of its association with allograft failure and mortality [41].

Discussion and Conclusion

The pathophysiology of type 2 diabetes is still not fully known. However, insulin resistance and β cell dysfunction play a crucial role in the pathogenesis of the disease. Magnesium is an essential mineral and it is needed for several physiologic functions in the body. Hypomagnesemia is commoner in patients with diabetes and it has been linked with the pathophysiology of type 2 diabetes mellitus. Hypomagnesemia is associated with defective insulin secretion, impaired insulin signaling and reduced activities of antioxidants. It has also been associated with chronic low grade systemic inflammation which has been linked with obesity, insulin resistance and type 2 diabetes. There is also a genetic link between hypomagnesemia and the risk of developing type 2 diabetes. Magnesium supplementation improves insulin resistance in diabetic and overweight but non-diabetic individuals.

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