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Hypomagnesemia and diabetes mellitus: a bidirectional situation

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Introduction

Role of magnesium on health was first noticed approximately 400 years back, even before identification of magnesium as an element. A farmer in Epsom, UK observed healing of some skin conditions in animal and human by using water of well dugged by him during scarcity of water.[1] Since then news of importance of this water spread through out UK and named as Epsom salt. In 1755 Scottish chemist Joseph Black identified magnesium as an element and later on magnesium was isolated by Sir Humphrey Davy in 1808. Impact of magnesium remained ignored or overlooked even in the 21st century. At present there are lots of evidences where magnesium deficiency are found to have wide range of clinical manifestations and adverse effects on health. Surprisingly hypomagnesemia is not uncommon in general population even in apparently healthy individual and most of time the situation is underestimated.

Around 25 elements are considered essential for health in human among the ninety naturally occurring elements in this planet. Carbon, oxygen, hydrogen and nitrogen -these four elements out of 25 constitute 97% of body building blocks. Among the rest, 21 elements account 3% of all elements available in the body- 8 elements are anions and 13 are metals cations. Among the 13 metals calcium, potassium, sodium, magnesium -these four are major elements and rest are trace- metals. Meanwhile we can not easily recognize hypomagnesemia and assess readily due to apparent clinical manifestations though magnesium is neither commonly known, nor perceived, rather ignored. Approximately 40% of body magnesium is intracellular, nearly 60% are found in bone and teeth and less than 1% is present in circulation with very narrow range.[2]

Biochemically this forgotten electrolyte-magnesium is regarded as biologically chronic regulator of intracellular and intercellular process through synchronized bio-communication systems of proteins and enzymes. Complex cellular functions are catalyzed by nearly 500 enzymes known as kinases and ATP/ATPase pumps. magnesium play important physiological role in nearly 300 kinases in a single cell so these are called Magnesium dependent kinases. Magnesium is involved as co-factors in more than 600 enzymes and additional 200 as activator which are required in fundamental processes for energy production and nucleic acid synthesis.[3] Deficiency of magnesium impedes intracellular kinase's activities. Deficiency may present acutely or with chronic state. Presentation of clinical features may be latent or symptomatic. Most of the time presentation is vague and non-specific. More than 300 intracellular enzymatic reactions involving ATP-Mg or GTP-Mg are essential for many biological process such as glucose homeostasis, lipogenesis, protein synthesis, nucleic acid synthesis, methylation etc. Most prevalent divalent cation-magnesium is postulated as the underlying cause and progression of many medical conditions like metabolic syndrome, type 2 Diabetes Mellitus (DM) arrythmias, cardiovascular diseases (CVD).[4] In addition lots of clinical conditions like intractable electrolyte imbalance, hypertension, many neurological and muscular conditions, vit D activation, bone and osteoporosis, asthma ,eclampsia, gestational diabetes mellitus (GDM), skin conditions, migraine, depression. Sleep disorders ,cataract, glaucoma etc are thought to be associated with low magnesium.[5] Recently there are evidences hypomagnesemia is also associated as risk factors for polycystic overy syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).[6-9]

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Epidemiological evidences of hypomagnesemia and type 2 diabetes

Since 1940s it has been reported that hypomagnesemia were found to be strongly associated with type 2 Diabetes.[10,11,12] In a community study low magnesium(Mg) was found to develop 2 fold higher

incidence of type 2 DM than control in Caucasian people.[13] Inverse relation was revealed in several other studies with reduced serum magnesium and risk of type 2 DM.[14] Pham PC et al found 14 to 48% prevalence of hypomagnesemia in type 2 comparing with 2.5 to 15% in healthy control subject.[10] Montagagna M et al found higher fasting glucose value in people with hypomagnesemia.[15] Several other epidemiological studies revealed inverse association between risk of type 2 diabetes with low dietary magnesium.[16,17] Addressing the role of magnesium in type 2 diabetes was reviewed intensively from epidemiological studies and clinical trials by Rodriguez-Moran et al.[18] In that publication they also reviewed studies of implication of magnesium on glucose metabolism in non-diabetes subjects. More over hypomagnesemia was also found to be common in elderly non-diabetes subjects.

On the other hand diabetes itself may cause reduction of magnesium in our body through renal handling which was proved from mouse model.[19-21] Still a debate is there whether low serum magnesium and type diabetes may be the cause and consequence to each other. Low magnesium may lead to occurrence of DM, on the other hand DM in long run may induce hypomagne-semia.

Mechanism of impaired insulin secretion by hypomagnesemia

There are several studies where insulin secretion were found to be reduced by hypomagnesemia comparing diabetes and non-diabetes patients.[22,23] Kostov K, Gunther T, Gommers LMM et al and Dastgerdi AH et al in their review articles described elaborately how magnesium play its role in every steps of insulin secretion as soon as beta cell is exposed by glucose.[22-25] In initial step of insulin secretion uptake of glucose by B-cell is done by GLUT2. Glucokinase is essential to convert glucose to glucose 6 phosphatase G6P. Rate of GK activity depends on ATP-Mg. Again closure of K-ATP channel is done through Mg ATP for binding to Kir 6.2 with SUR1 for membrane depolarization. Following increasing ATP and closure of K-ATP channels leads to activating Ca influx via L-type Ca channel. Hypomagnesemia decrease expression of L-type channel activities for insulin release from insulin containing vesicles. Atwater et al revealed that Cal/Mg ratio is also important in insulin release.

Mechanism of insulin resistance by hypomagnesemia

There are many clinical studies and reviews where hypomagnesemia is shown to be is associated with insulin resistance(IR) in peripheral tissues like liver ,muscle and adipose tissue in type 2 DM.[22,-25] Magnesium is essential for autophosphorylation of beta subunit of insulin receptor through binding Mg with tyrosine kinase and enhancing tyrosine kinase activity. Magnesium is also essential for activation of Ras-MAPK and PI3K/Akt kinase pathway for metabolic processes of glucose, fat and protein.[22] Magnesium is also required in increasing expression of GLUT 4 transporter. Several enzymes are needed in liver for gluconeogenesis and glycogenesis through glucose 6 phosphatase (G6P ase) and phosphoenolpyruvate carboxykinase (PEPCK) where Mg play vital role.[26]

More over adipocytes release proinflammatory cytokine and mediators IL1,TNF-alpha and free radicals which are thought to increase IR in type 2 DM. In rat model Mg deficiency was found to be associated with increased levels of IL1 and TNF-alpha.[27,28] Thus hypomagnesemia may cause increased IR indirectly by increasing proinflammatory products and reactive oxygen radicals, CRP.[29,30]

Insulin regulate magnesium homeostasis

It is found insulin regulate mg reabsorption from distal convoluted tubules in the kidney.[25] Gummers JGJ et al explained different mechanisms where magnesium homeostasis is maintained by kedney. Akt and PI3K require magnesium to increase the expression of TRPM6MG channel. Reduce insulin in type 2 DM has role in reduced activity of NCC transporter. There are also other mechanism postulated for regulating magnesium transport through insulin resistance. In earlier studies Mcnair P et al, Kostov K and Barbagallo et al found hypomagnesemia in older diabetic patient.[21,22,31] Paladiya R et al revealed more the uncontrolled diabetes and longer the duration of diabetes have lower the magnesium level.[32]

Supplementation of magnesium improve Insulin secretion and insulin resistance

There are a number of studies where different clinical studies showed that Mg intake is positively related in reduction of risk of DM. Rodrguez-Moran et al, El. Derawi et al shown oral supplementation of magnesium improve insulin sensitivity and metabolic control in type 2 diabetes.[33,34] Chacko et al found significant improvement of c-peptide concentration and fasting insulin level in overweight individuals by oral

magnesium supplementation.[35] One study also observed beneficial effects of magnesium on blood pressure, lipid profile in addition of glycemic status.[36] Interesting Mooren et al and Guerrero-Romero et al revealed improvement of insulin sensitivity in non-diabetic subjects.[37,38] Paolisso et al reported in his study Mg supplement increase insulin sensitivity in old subject with diabetes.[39]

Influence of magnesium on chronic vascular complications in diabetes mellitus

There are emerging evidences where we can explore serum magnesium deficiency is associated with development of micro-vascular and macro-vascular complications. Quite a number of studies revealed low serum magnesium in significant percentage of diabetic patient having retinopathy ,nephropathy and neuropathy comparing with patients without complications.[40-43] Even in newly detected type 2 diabetes with proteinuria, neuropathy and retinopathy were found to have serum magnesium deficiency.[44] There are few studies on relation of hypomagnesemia with cardiovascular events. Ceremuzynski L et al tried to show the beneficial effects of magnesium supplement on ventricular arrythmias and heart failure.[45] Singhal MK et al and Agrawal P et al revealed low serum magnesium in patients with coronary artery disease, peripheral vascular disease comparing patients without complications.[47]

Conclusion

Magnesium deficiency is clinically underdiagnosed but surprisingly easy to treat. We have convincing evidences in our hand about close relation of micro-nutrient like hypomagnesemia with incidence of type 2 diabetes and its progressions to both microvascular and macrovascular complications through decreased insulin secretion and insulin resistance. On the other hand it was shown serum magnesium is also reduced in longer uncontrolled diabetes through renal tubular loss. Adequate nutrition with magnesium supplementation can prevent diabetes, good glycemic control by improvement of insulin secretion, insulin sensitivity, reduced low inflammatory cytokines and oxidative free products release. We can get beneficial effects on cardiac dysfunction by supplementation of oral magnesium.

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