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Review Article

Is there a Role for Micronutrient Deficiency in the Pathogenesis and Complications of Type 2 Diabetes Mellitus? Facts, Controversies and Conclusions

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Abstract

Although a growing number of multiple level studies have found an association between micro-nutrient deficiency (MND) and incident type 2 diabetes mellitus (T2DM), a knowledge gap exists in the literature on how individual MND impacts the pathogenesis and complications of T2DM. This review provides current information based on recently improved research techniques on the mechanistic links between individual MND and pathogenesis and complications of T2DM.

A literature search was conducted using MEDLINE, SCOPUS and Embase Database. All relevant English language articles published up-to March 2019 were searched using related terms such as DM, IR, MND, deficiency of vitamins and minerals. This review has provided more insight into the intricate pathways of how MND could initiate the onset or worsen extant T2DM and complications including MND-induced oxidative stress (OS), inflammation and immune system dysfunction and leading to several metabolic aberrations such as disorders of tyrosine kinase activity during insulin signaling, glucose-induced insulin secretion, altered glucose transport, reduction in pancreatic insulin secretion, defective post-receptor insulin signaling and altered insulin-insulin receptor interactions.

Others include impaired cellular messenger, which is responsible for insulin signaling, disordered glucose homeostasis and decreased stimulation of glucose uptake and lipogenesis in adipocytes. Indeed, MND plays a significant role in the pathogenesis of T2DM. The various mechanisms heightened here could enrich our understanding of the adoption of better management protocols and preventive strategies for T2DM.

Keywords: *Essential Nutrients; Deficiency; Hyperinsulinemia; Diabetes Mellitus; Pathogenesis*

Introduction

The epidemiological data on diabetes mellitus (DM) are convincingly higher over the past decades in both developed and developing countries. DM is among the top 5 causes of death in most countries. It is responsible for over one million amputations each year, and a major cause of kidney failure in developed and developing countries and is responsible for huge dialysis costs. Worldwide type-2 diabetes mellitus (T2DM) is by far the most common type of DM and accounts for about 90% of DM in most countries including United State of America.

The rise in the number of cases of DM of different types has been blamed on the interplay between genetic predisposition and environmental inducements. Taken from the dimensions of diets and physical activity, with other covariates, most individuals are affected or have a higher risk for DM. Within the last two decades, numerous studies found alteration in micronutrients (MNs) status of patients with DM and in others, a concomitant deficiency in certain essential MNs have been co-related with the onset of DM and associated complications [1].

DM is characterized by a significant loss of important MNs due to the metabolic basis of the disease and its associated complications [2]. It is reasonable to infer that these MNDs could be the cause or the consequence of the metabolic deficiencies in DM, however this has been the center of research in different trials and intervention studies which is the scope of this discussion. To begin with, DM has been associated with antioxidant depletion and increased free radical production [3]. Also, it is evident that OS and endothelial cell activation, beta cell dysfunction, immune system dysfunction, inflammation, and insulin resistance (IR) may be relevant to the disease initiation, progression and its complications [4].

Over the passing decades, newer and better understandings in the prevention and management of DM have stemmed from detailed and pain staking studies and trials conducted. In almost all the studies reviewed and analyzed, a consistent finding has been the significant deficiency in many MNs with or without substantial antioxidant prowess. Such MNs are either classified as minerals or trace elements or vitamins (Table 1). In any case, though they seem micro in demand, they are macro in actions.

Classification of micronutrients based on their anti-diabetic mode of actions

Antioxidants	Immune modulators	Anti-inflammatory
Calcium, Magnesium	Iron	Manganese
Chromium, Manganese	Selenium	Copper
Copper, Selenium, Zinc	Zinc	Selenium
Co-enzyme Q_{10}, Vanadium	Magnesium	Magnesium

Table 1: *Minerals and trace elements with antioxidant, immune system modulating and anti-inflammatory activities.*

Methods

Search strategy

A search was conducted through Medline, Scopus and EMBASE database to identify English language articles published until March 2019 that explored the relationship between MND and T2DM using keywords such as “vitamins”, “minerals”, “T2DM“, IR”, “antioxidant”, “anti-inflammatory”, and immune system modulating vitamins and minerals.

For each article selected the effect of the specific vitamin or mineral on IR and T2DM was considered. Articles with incomplete data, obvious methodology flaws, poor analytical methods and unadjusted covariates were excluded. In all 105 articles met the inclusion criteria and were considered in this review.

Pathophysiology of micronutrient deficiency-induced T2DM

Magnesium deficiency and T2DM

Magnesium (Mg) deficiency has been shown in different experimental and clinical studies to increase the propensity to glucose intolerance, DM, IR, atherosclerosis and coronary heart disease (CHD) [5].

Mg is an essential MN that abounds in significant amounts in living cells and has plasma concentration that is remarkably consistent in healthy subjects. It is a cofactor of many enzymes involved in glucose metabolism, especially those using high-energy phosphate bonds [6]. Mg deficiency provokes a cascade of several biochemical alterations and leading to many metabolic disorders such as in T2DM, hypertension and other cardio-metabolic diseases. It has also been reported that patients with hypomagnesemia can present with ischemic cardiac insufficiencies, vascular complications of DM and hypertension [7]. Additionally, hormonal, neurological, gastrointestinal, renal, and muscular dysfunction has been associated with hypomagnesemia.

Furthermore, Mg deficiency has been shown to cause endothelial cell dysfunction, inflammation, and oxidative stress, which are significant contributors to atherosclerosis and could further lead to diabetic complications [8]. Mg deficiency could contribute to pro-inflammatory, pro-thrombotic and pro-atherogenic environments that could lead to different cardiometabolic disorders [9]. Mg is believed to preserve membrane hyperpolarization and reverse potassium induced depolarization of smooth muscle cells [8]. On the other hand, low Mg reversibly inhibits endothelial proliferation likely through the up regulation of interleukin 1(IL-1). Additionally, the up regulation of vascular cell adhesion molecule (VCAM) and plasminogen activator inhibitor-1 (PAI-1) has been associated with Mg deficiency. The resultant leucocytes adherence enhanced increase chemokines secretion, cell permeability to lipids, low density lipoprotein-cholesterol (LDL-C) oxidation, vascular smooth muscle cells proliferation and migration and platelet activation [9].

There is a complex interplay between Mg deficiency and DM. It has been reported that hypomagnesemia state associated DM is caused by enhanced renal excretion [10]. Mg deficiency is associated with poor glycemic control and Mg supplementation has been shown in many studies to exert beneficial effects on glucose control in patients with T2DM and improves insulin sensitivity in non-diabetic subjects [11]. Additionally, Mg supplementation has been observed to prevent fructose induced insulin resistance (IR) and delay the onset of spontaneous T2DM in rats' models [12]. Inadequate intake of dietary Mg in diabetic patients may also cause hypomagnesemia [13]. In literature, it still remains inconclusive whether low plasma Mg is a cause or consequence of suboptimal glycemic control [14].

Synoptically, in a study conducted by Resnick., *et al.* [15], Mg levels were found to be reduced in non-insulin dependent diabetes mellitus (NIDDM) patients. Most specifically, Resnick., *et al.* [15] reported both intracellular and extracellular depletion of Mg in NIDDM. Hypomagnesemia may play a role in the development of retinopathy, altered platelet function, neuropathy, foot ulcers, albuminuria, and other problems frequently observed in T2DM patients [5,16]. It has also been linked to increase in abortion and malformation in diabetic pregnancies [17]. Mg deficiency in DM is not only link to the development and progression of the disease state but also the severity of the diseases. This notion was supported in a study by Pham., *et al.* [18] who opined that low serum Mg level could promote a rapid decline of renal function in patients with T2DM.

Additionally, Pham., *et al.* [19] found that subjects with serum Mg levels between 0.82 and 1.03 mmol/L had the lowest deterioration of renal function and best glycemic control. A number of other prospective studies of Mg intake and diabetes incidence have been conducted and reported [20].

More specifically, a deficit in Mg can either be a product of Mg deficiency or depletion. Mg depletion on the other hand, has been associated with dysfunction of factors controlling Mg status such as intestinal hypo-absorption of Mg, reduced uptake and mobilization of bone Mg, sometimes urinary leakage, hyper-adrenoglucortism caused by increase adaptability to stress, IR and adrenergic hypo-receptivity.

Mg deficiency could affect both insulin and glucose mobilization enzymes/cofactors requiring Mg for enhanced actions. The underlying mechanisms by which Mg deficiency could be linked to the pathogenesis of DM are related in part to the disorders of tyrosine kinase activity during insulin signaling and glucose-induced insulin secretion, leading to insulin insensitivity in both adipocytes and muscle cells [21]. Furthermore, hypomagnesemia may induce altered glucose transport, reduced pancreatic insulin secretion, defective post-receptor insulin signaling and /or altered insulin-insulin receptor interaction [7].

Results from different studies conducted among different ages and gender showed that Mg intake may decrease the risk of developing T2DM. Meyer., *et al.* [22] in their studies found that the relative risk for incident T2DM was significantly reduced in their subjects with increasing Mg intake. Hence consumption of diets rich in Mg such as grains, fruits, and vegetables reduced the likelihood for developing T2DM. There are also studies that confirm that diabetics and non-diabetics with IR who are supplemented with Mg showed significant improvement in their IR state [23]. Although, in the viewpoint of the others, the notion that Mg supplementation could have beneficial effects in initiation, progression and complication in DM are rather not convincing, however, it could still be beneficial to include Mg rich food and supplements in the diet of diabetic patients.

In summary, Mg deficiency can affect both insulin action and glucose mobilization enzymes/cofactors requiring Mg for their actions.

Chromium deficiency and T2DM

Chromium (Cr) deficiency is a known cause of IR and T2DM. However, results from different studies revealed that Cr deficiency is reversible. For example, in their studies, Freund., *et al.* [24], showed that long term parental nutrition-induced Cr deficiency in patients can be reversed by Cr supplementation. In the passing decades more observational and interventional studies have been conducted to ascertain the efficacy of different Cr supplements in the management of metabolic disorders resulting from abnormal glucose and lipid metabolism. In these studies, different Cr formulations have been used (e.g., Cr picolate, nicolate, chloride and brewer's yeast) although no acceptable required dose has been established [25]. Evidently, the significant role of Cr in normal glucose metabolism is not debatable. In a study by Jain., *et al.* [26], trivalent Cr was found to inhibit protein glycolyzation and lipid peroxidation in high glucose treated erythrocytes. Increasingly, many studies have tried to find the answer to the research question: is Cr supplementation effective in managing T2DM? [27].

Different studies have brought forward divergent conclusions on the effect of Cr on glucose regulation. Additionally, there is a controversy as to whether dietary supplementation with Cr should be routinely recommended in subjects with documented deficiency [28]. Various designed clinical trials have provided evidence either in favor of [29] or against [30] the beneficial effects of Cr supplementation. It is worth noting that Cr losses are increased due to pregnancy, strenuous exercise, infection, physical trauma and other forms of stress [31]. Hence administration of Cr supplements on subjects with elevated blood sugar following a glucose load leads to a decrease in blood sugar level while hypoglycemic subjects responded to supplemental Cr by an improvement in hypoglycemic glucose value, increased insulin binding and alleviation of hypoglycemic symptoms [31].

On its toxicological profile, Lawson., *et al.* [32] opined that Cr supplementation does results in tissue retention, especially in kidney, although no pathogenic effect has been demonstrated.

However irrespective of inconsistent results from various studies, it is plausible that Cr supplementation could have beneficial effect on diabetic patients than in non -diabetic patients. In fact, reviews of literature by Ryan., *et al*. and Althius., *et al.* [33,34] all give credence to the opinion that Cr supplementation improves glucose intolerance, gestational diabetes and corticosteroid induced DM. Studies have shown that Cr bound to the oligopeptide chromodulin enhances the tyrosine kinase activity of the insulin receptor and inhibits phosphoserine phosphatase activity, and hence amplify the intracellular insulin signal pathway [35].

Insulin binds to the alpha-subunit in the insulin receptor bringing about conformational changes leading to auto-phosphorylation of the beta- subunit of the insulin receptor. In response to increase blood sugar, insulin level rises and Cr is mobilized from the blood to the insulin-dependent cells which are facilitated by transferrin. There is also a transfer of Cr bound to transferrin to apochromodulin, the low-molecular-weight Cr-binding substance. Apochromodulin, when fully activated is able to increase the activity of insulin receptor kinase and inhibits that of the insulin receptor phosphatase. The activation of insulin receptor kinase activity by Cr and the inhibition of

insulin receptor tyrosine phosphatase are responsible for the increased phosphorylation of the insulin receptor which is associated with increased insulin sensitivity.

Zinc deficiency and T2DM

Zinc (Zn^{2+}) is another essential MN that plays a contributory role in maintaining cellular homeostasis due to its influence on different biological processes. Zn^{2+} deficiency or invariably dysfunctional Zn^{2+} signaling has been implicated in a wide array of diseases including cancer, autoimmune diseases, cardiovascular diseases, neurodegenerative diseases and T2DM [36]. It is reported that Zn^{2+} plays a key role in the synthesis, secretion and action of insulin in addition to carbohydrate metabolism. Zn^{2+} availability and delivery to cells and tissues are tightly regulated by a family of proteins known as Zn^{2+} transporters [37].

Several studies have investigated and came to the conclusion on the mechanisms of insulin mimetic activity of Zn^{2+} on glucose and lipids metabolism [38]. Their conclusion therefore is that Zn plays a dynamic role as a cellular second messenger in the control of insulin signaling and glucose homeostasis. Zn^{2+} is said to mediate its insulin mimetic effect in parts through the inhibition of protein tyrosine phosphatases which increases the net phosphorylation of the insulin receptor and activates the signaling cascade [39]. It also includes the stimulation of glucose uptake and lipogenesis in adipocytes, tyrosine phosphorylation of insulin and insulin-like growth factor 1 (IGF-1) receptor and insulin receptor substrate-1 [39], activation of mitogen activated protein kinase (MAPKs) including extracellular signal regulated kinase 1 and 2 (ERK 1/2) and c-JUN-N-glycogen synthesis through the inhibition of glycogen synthetase kinase-3. Zn^{2+} therefore did not affect the action of insulin on insulin receptors but its action is post receptor either through the activation of receptor tyrosine kinase phosphorylation or activation of PI3K/Akt pathway leading to the activation of GLUT4 that increases glucose mobilization into cells [40].

The inhibition of protein tyrosine phosphatase by Zn under physiological condition involved Zn transport mechanism and has a widespread implication for understanding cardiometabolic disease progression [36]. Incidence of DM has been accompanied with hypozincemia and hyperzincuria [41]. Over the years research has been drawn to inclusion of Zn as candidate regimen in the management of T2DM and diabetic complications owing to both its known antioxidant and insulin mimetic prowess [42]. On the basis of the different results of both animals based observational and prospective studies conducted among type 1 and type 2 diabetics, the beneficial role of Zn supplementation was upheld in most studies [43] and doubted in few [44].

On the therapeutic efficacy of Zn supplements in diabetic humans, Jayawardana., *et al.* [45] conducted a meta-analysis of different studies. The review showed significant reduction in 2h post prandial blood sugar, LDL-C, total cholesterol, systolic blood pressure, after Zn^{2+} supplementation. Hence it was concluded that Zn^{2+} supplementation has beneficial effects on glycemic control and promotes healthy lipid parameters. In addition, Zn supplementation showed beneficial effects on diabetic neuropathy and nephropathy as reported by Farvid., *et al* [46].

However, most studies with beneficial effects included supplementation with other antioxidant vitamins and minerals as against Zn alone. Such as Cr [47], Mg [46,47], vitamin C and E [48], selenium (Se), niacin and manganese (Mn), copper (Cu), and other B vitamins [46,47] as against those studies using Zn^{2+} alone [43].

Selenium deficiency and T2DM

Selenium (Se) has also been shown to be beneficial in the management of T2DM. Some authors agree [49,50] and others disagree [51,52] on the beneficial role of Se in T2DM. According to Rayman and Stranges [50], although Se has both anti-diabetic and insulin mimetic effects, and its mechanism of action is to regulate the activities of seleproteins which are known to improve glucose metabolism, however, the relationship between Se and T2DM is undoubtedly complex and possibly U-shaped with possible harm occurring both below and above the physiological range for optimum activity of some or all seleno-proteins. Even Faghihi., *et al.* [52] shared a similar viewpoint and both recommended a cautious use of selenium supplements in T2DM. However, its inclusion among others in multi-mineral/multi-

vitamins preparations administered to diabetics may not be disputed. Additionally, other contemporary studies have shown that Se can also prevent cardiovascular diseases [53].

On the subject of high dosing and prolong duration of intake, Wang., *et al.* [54], opined that high Se impairs hepatic insulin sensitivity through opposite regulation of reactive oxygen species (ROS). Also, Zhou., *et al.* [49] found that high Se intake elevated activity or production of seleno-proteins including GPX1, NSrB1, SelS, and SelP. It is this up-regulation of seleno-proteins that possibly diminishes intracellular ROS and then dysregulate the key regulators of beta cell and insulin synthesis and secretion, leading to a chronic hyperinsulinemia which could be beneficial. Over scavenging the ROS such as H_2O_2, also attenuates oxidative inhibition of protein tyrosine kinase phosphatase and suppresses insulin signaling. High Se intake could affect expression and/or of key regulation of glycolysis, gluconeogenesis and lipogenesis.

Most interestingly on the other hand, epidemiological studies indicate that supra-nutritional Se intake and high plasma Se levels are possible risk factors for the development of T2DM, pointing to adverse effects of Se on carbohydrate metabolism in humans. Also, increase in plasma Se levels might be a consequence and cause of diabetes. The evidence and the molecular basis for this submission have been discussed extensively by Steinbrenner., *et al* [55]. Viewing the matter from both sides, the use of Se within moderate dose and period could still be recommended and most effective if co-administered with other potent diabetes management regimens.

Besides Se, a number of metal ions (vanadium, copper, zinc and cadmium) are known to trigger insulin mimetic effects by activating AKt and other kinases of the insulin signaling cascade such p70S6. It is postulated that PGC-1α serves as its molecular switch linking Se and carbohydrate metabolism [55].

Vitamins deficiencies and T2DM

Aside from minerals and trace elements with antioxidant, immune modulating and anti-inflammatory prowess that have been discussed, there are vitamins and cofactors that have been shown to possess similar mechanism of actions (Table 2).

Vitamins		
Antioxidants	**Immune modulators**	**Anti-inflammatory**
Vitamin A	Vitamin A	Vitamin A
Nicotinamide (β_3)	Vitamin β_6 (pyridoxine)	Vitamin β_6 (pyridoxine)
Riboflavin (β_2)	Vitamin β_9 (folate)	Vitamin β_{12} (cobalamin)
Vitamin C (ascorbic acid)	Vitamin β_{12} (cobalamin)	Vitamin β_9 (folate)
Vitamin E (tocopherol)	Vitamin C (ascorbic acid)	Vitamin C (ascorbic acid)
Omega-3fatty acids	Vitamin E (tocopherol)	Vitamin D (25-hydroxyvtamin D_3)
		Vitamin E (tocopherol)

Table 2: *Vitamins with antioxidant, anti-inflammatory and immune system modulating activities.*

It is evident that vitamin C, E, nicotinamide and riboflavin, are beneficial in the management of diabetic complications owing to their antioxidant, anti-inflammatory and immune system modulating prowess [56]. Extensive studies have also found that vitamin D (VD) alone or with other potent MNs could affect the etiology and progression of both type 1 and 2 DM. For example, in randomized controlled trial by Afkhani-Ardekani and Shojaodinny-Ardekani [57], a significant decrease in FBS, triglyceride, LDL-C, glycosylated hemoglobin and serum insulin was found in the group of diabetic patients supplemented with 1000mg vitamin C. The dose of 500mg of vitamin C did not

produce any significant change in any of the parameters studied in T2DM patients. Low levels of serum vitamin C were closely associated with concomitant renal dysfunction and low-grade inflammation and also associated with diabetic nephropathy and retinopathy [58].

Biotin deficiency and T2DM

Another water-soluble vitamin-biotin has been shown to be effective in the management of T2DM. Over the forty years, Dakshinamurti and colleagues in their study found that development of IR in biotin deficient rats was resolved following biotin replacement [59]. This effect was attributed to the biotin-induced-hexokinase gene expression whose role is to increase hepatic glucose uptake. The few human based studies have shown beneficial effects in both obese and diabetic patients [60].

Thiamine deficiency and T2DM

Furthermore, moderate thiamine deficiency may affect glucose metabolism and aggravates diabetic complications On the basis that thiamine acts as a coenzyme for transketolase (tk), pyruvate dehydrogenase (PDHase), and α-ketoglutarate dehydrogenase complexes whose activities increase Kreb cycle activities and invariably improve intracellular glucose metabolism, Loung and Nguyen [61] reviewed different studies conducted on the impact of thiamine treatment in diabetes mellitus. In summary they found that thiamine and its derivatives have been demonstrated to prevent several biochemical pathways including increased flux through polyol pathways, formation of advanced glycation end products, activation of protein kinase C, and increased flux through the hexosamine biosynthesis pathway induced by hyperglycemia in DM. However, they still concluded that thiamine definitely has a role in the diabetic endothelial disease (micro and macroangiospthy), lipid profile, retinopathy, cardiopathy, and nephropathy. From these different studies, it is possibly that thiamine supplementation could modify the course of DM (type 1 and 2) by modulation of glucose metabolic pathways [62].

Vitamin D deficiency and T2DM

It is indisputable to state that vitamin D deficiency (VDD) can exacerbates the metabolic conditions in DM as deficiency in other MNs do. But does VD supplementation play a significant role in type 1 and type 2 DM? Divergent answers have been given to this question in many studies past and present. In a study conducted among 912 subjects (429 T2DM cases and 483 non-diabetic control), it was found that VDD was reported in T2DM (91.4%) and nondiabetic subjects (93.0%), its role in hemoglobin glycation and IR could not be established. It is worthy of note that depletion in VD status might not only be indicator of ill health but could also be an indicator of the individual lifestyle pattern ranging from indoor working with restriction to sunlight exposure, low visibility and poor dietary habits [63]. The use of VD supplementation in patients with T2DM have been investigated and reported by different investigators and analyzed in many reviews such as the one performed by Pittas., *et al* [64]. In some studies significant effect in diabetic patient was found following a consistent dose of VD supplement [65] while in others the effect was either said to be negligible [66] or not significant [67]. A twofold risk of newly diagnosed T2DM was found among elderly patients with low level of VD (< 50 mmol/L), after adjusting for many other confounding factors [68]. Another study among VD deficient T2DM patients found that supplementation with vitamin D3 caused a significant improvement in serum FBS, insulin and HOMA-IR, suggesting the IR ameliorating effect of VD [69].

Also, VDD was found to affect insulin synthesis and secretion in human/animal models of DM, suggesting its role in the etiology and pathogenesis of both types of DM. Furthermore, available epidemiological studies suggest a link between VDD in early life and later life onset of type 1 DM. Although a growing number of multiple level studies [70] found that adequate serum level of VD is beneficial in preventing the onset of both type 1 and 2 DM and that VDD is associated with diabetic complications. Haroon., *et al.* [71] on their part had a contrasting viewpoint on the beneficial effects of VD based on findings of studies they reviewed. Making further progress, the combination of VD with calcium in many studies and clinical trials has shown beneficial effects. For instance, a six month randomized placebo trial conducted among 95 adults with low serum 25-hydroxy-VD status (55mmol/l; with pre-diabetes or an AUSDRISK sure ≥ 15) who were at the risk of T2DM, showed that daily VD and calcium supplementation improved insulin sensitivity, insulin secretion, beta cell function, inflammation and metabolic endpoints.

Multiple micronutrient deficiencies/supplementations in T2DM

Although many studies with detailed experimentation on the prevention and treatment of DM have shown profound anti-diabetic activities of MN monotherapy, several recent studies have found multi-mineral/vitamin preparations to be more effective than therapy with a single MN. The co-administration of these multivitamins/minerals with standard therapy has been found to improve the clinical outcomes than when the standard therapy is used alone especially among individuals with higher odds for DM. These different MNs have been shown in different studies to exert a synergistic/additive action with each other in the management of oxidative stress, inflammation and immune system dysfunction which are the foundational basis for the initiation, progression and complications of DM (type 1 and 2). The use of standard therapy in combination with MN therapy could be beneficial even though they act through different channels; their individual mechanism of action could both be synergistic and additive and could promote the achievement of a common therapeutic goal.

Supporting this notion, Chen., *et al.* [72] found that the risk of hyper-homocysteinemia was 3 fold higher when the deficiency of vitamin β_2 or β_6 co-occurred with the deficiency of folate than the deficiency of either vitamin alone, suggesting the synergistic effects of either vitamin β_2 or β_6 and folate deficiency on the pathogenesis of hyper-homocysteinemia on one hand, and synergistic effect of adequate levels of vitamin β_2 or β_6 and folate in maintaining optimal serum-homocysteine level on the other hand.

To determine the effects of combined supplementation of chromium (Cr), vitamin C and vitamin E on oxidative stress in T2DM, a randomized blind placebo control study by Lai [73] conducted among diabetic patients showed that Cr supplementation in combination with vitamins C and E was more effective in minimizing oxidative stress and improvement of glucose metabolism in T2DM patients than supplementation with Cr alone.

Vitamin E acts as a lipid soluble antioxidant vitamin while vitamin C serves as a water-soluble antioxidant vitamin whose roles directly involve scavenging aqueous peroxyl radicals and indirectly regeneration of reduced vitamin E. As non-enzymatic antioxidants, vitamins C and E protect against the damaging effects of oxidative stress in diabetes through their anti-oxidative glycosylation and reduction of metabolic stress [73]. In a study reported by Ozkan., *et al.* [74], a combination of three antioxidant vitamins (vitamin C, E and alpha lipoic acid), also produced a more effective insulin activity in the brain tissues of experimental diabetic and non-diabetic rats than a single antioxidant vitamin.

On the contrary, in most studies, it is rather rare to find the deficiency of both vitamin C and E in diabetic and obese patients [75] and in others vitamin E supplementation did not show substantial significant effects on blood sugar control. These could possibly be due to the heterogeneity of the study participants or other underlying covariates. On the use of vitamin C supplements in T2DM, different studies conducted have arrived at different conclusions and the following had favorable outcome [76], thereby supporting the use of vitamin C in the management of diabetes and diabetic complications.

However, despite the contrasting view points from different studies, the use of vitamins C and E in the management of DM could ameliorates other underlying deficiencies that could affect blood sugar control than affect insulin synthesis and secretion owing to their proven antioxidant prowess.

Conclusion

Although varied results have been obtained in research studies of MNs in diabetic patients due to methodological issues, numerous established experimental, clinical and epidemiological evidences indicate that MND could have important implication in the initiation, progression and complications of DM. Likewise, co-administration of adequate pharmacologic doses of MNs with standard antidiabetic therapy has been found to improve the clinical outcomes of DM.

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