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Review

Vitamin and mineral deficiency and glucose metabolism – A review

Glaucia Carneiro [a,*], Blandine Laferrère [b], Maria Teresa Zanella [a]

[a] Department of Medicine, Division of Endocrinology, Universidade Federal de Sao Paulo, Rua Leandro Dupret, 365 Vila Clementino, 04025-011 Sao Paulo, Brazil
[b] New York Obesity Nutrition Research Center, Division of Endocrinology, Department of Medicine, St. Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY,USA

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SUMMARY

Background & aims: Zinc, magnesium and vitamin D are trace minerals and vitamins of importance to human biology and health and increasing evidences suggest that these minerals and vitamin play an important role in glucose metabolism. The aim of the study was to summarize the current evidences that links mineral deficiencies and alterations in glucose metabolism
Methods: A systematic review of PubMed database was conducted from September 1983 to September 2011 to identify literature related to zinc, magnesium and vitamin D deficiencies and glucose metabolism.
Results: Accumulating data from clinical studies suggest that zinc, magnesium and vitamin D deficiencies are independently associated with alterations in glucose metabolism. Deficiencies may increase risk of the development of insulin resistance and T2DM. However, there is inadequate evidence based data available to inform public health strategies.
Conclusions: Clearly, there is a need for further research, using well-designed studies and long-term follow-up, to fully demonstrate a causal role for these nutritional deficiencies in the development of insulin resistance and T2DM and the beneficial role of these vitamin and minerals supplementation in disorders of glucose metabolism, and/or in patients with or at risk of developing nutritional deficiencies.

1. Introduction

Vitamins, minerals and trace elements are essential factors and cofactors in many biological processes regulating directly or indirectly the body glucose metabolism. The accumulated evidence suggests that low plasma vitamin D, Zn or Mg concentrations are associated with impaired glucose metabolism and an increased risk of T2DM. The role of these vitamin and minerals in the pathogenesis of diabetes still remains to be explained.[1]

More than 70% of the American population uses some form of dietary supplement every day, of which vitamin and mineral supplements are the most commonly used.[2] The majority of them does not take their regular medication prescribed by the health care professional, but use these products without supervision. In this context, multivitamins and mineral dietary supplements are widely used in the United States, but there is insufficient evidence of their benefits and safety.

In this review, we summarize the current evidence from clinic-based, and interventional studies that links Zn, Mg, and vitamin D deficiencies to alterations in glucose metabolism and T2DM, and will briefly discuss the potential mechanisms that may play a role in this link.

2. Materials and methods

A PubMed database research was conducted to identify observational studies, prospective cohort studies and randomized double-blind placebo-controlled studies of the association among Zn, Mg and vitamin D levels and intake with insulin resistance and T2DM.

Terms and words used for the search included diabetes mellitus, type 2 diabetes mellitus, magnesium, vitamin D, zinc and deficiency. Searches were limited to studies in humans and to papers published in English.

In the second stage, all abstracts were examined to identify articles that described randomized double-blind placebo-controlled studies investigating nutritional intervention in people with T2DM.

In some studies, the assessment of the presence of vitamin deficiency was based on vitamin levels and in others on vitamin intake. Metabolic assessments have been more variable and have included levels of fasting blood glucose, insulin, and hemoglobin (HbA1c – a measure of glucose control over a 3-month period), and the

Abbreviations: Mg, Magnesium; Zn, Zinc; T2DM, Type 2 diabetes.

* Corresponding author. Tel.: +55 11 59040400; fax: +55 11 32871959.
E-mail address: glauciacarneiro@uol.com.br (G. Carneiro).

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estimation of insulin resistance by homeostatic model assessment (HOMA-IR; defined as the normalized product of fasting glucose by fasting insulin). In some studies, glucose tolerance was assessed by the oral glucose tolerance test (OGTT), a clinical tool that is used for the diagnosis of type 2 diabetes. Normal glucose tolerance, impaired glucose tolerance, or diabetes were defined using the ADA criteria.[3]

3. Results

3.1. Evidence from observational clinical studies

3.1.1. Vitamin D and diabetes

There is increasing evidence suggesting that vitamin D deficiency has adverse effects on glucose tolerance, insulin resistance, and the risk of diabetes mellitus, independently of the degree of obesity.

A total of 8421 men and nonpregnant women from the NHANES were prospectively evaluated for 20 years and the odds of having the metabolic syndrome decreased progressively across increasing quintiles of concentration of 25-hydroxyvitamin D (25(OH)D).[4] Another study from Third National Health and Nutrition Examination Survey also showed an inverse association between serum concentrations 25(OH)D and the prevalence of metabolic syndrome, but only in some ethic group population (non-Hispanic whites and Mexican Americans). The lack of an inverse association in non-Hispanic blacks may reflect decreased sensitivity to vitamin D in this race.[5]

In a prospective cohort analysis of data from the Nurse's Health Study, women were followed for 20 years to examine associations between vitamin D intake and risk for type 2 diabetes.[6] During 20 years follow-up, the relative risk (RR) of type 2 diabetes was lower in the group with the highest vitamin D supplementations (RR = 0.87 (95% CI 0.75–1.00); P for trend = 0.04). In contrast, the Women's Health Study showed that dietary vitamin D was inversely associated with the prevalence of metabolic syndrome in middle-aged or older women, but was not independent of total calcium intake.[7] It is worthwhile to observe that in the Women's Health Study, only women 45 years and older were evaluated. Therefore the differences found between vitamin D intake and diabetes may be more evident in young people than older people.

Several other cross-section studies have shown that 25(OH) vitamin D levels are significantly lower in T2DM compared to control subjects[8,9] (Table 2). A small cross-sectional study of 243 obese and overweight ambulatory adults in Auckland, New Zealand found that, in addition to a significant inverse association between serum 25-OH vitamin D level and weight and waist circumference, there was a weak inverse relationship with hemoglobin A1c.[10]

Two large cross-sectional observational studies (n = 799 and n = 5677) demonstrated that Serum 25-hydroxyvitamin D3 concentration was significantly lower in postmenopausal Italian women and in New Zealand Polynesians with newly diagnosed diabetes or impaired glucose tolerance, compared to controls with normal glucose tolerance.[8,9]

A 30 years prospective population-based study[11] demonstrated that 1-h glucose and area under the glucose curve during a standard 75-g oral glucose tolerance test (OGTT) were inversely associated with the serum concentration of 25-OH vitamin D in 142 elderly Dutchmen.

In summary the available human data are limited. Most observational studies are cross-sectional, whereas prospective studies have not measured 25-OHD concentrations. Also, the method for evaluation glucose metabolism was different among the studies. Although hemoglobin A1c and the glucose response during an OGTT were inversely associated with the 25-OH vitamin D concentrations,[11] results were conflicted between association of vitamin D concentrations and fasting glucose levels.[10]

3.2. Magnesium and diabetes

Table 1 summarizes the findings from the four-studies that have assessed magnesium intake[12–15] and from two-studies[16,17] that have assessed serum magnesium levels and glucose metabolism. In a prospective analysis, among 8502 women include in the Nurses' Health Study, comparing the highest with the lowest quintile of total magnesium intake, the observed RR for diabetes after 18 years was 0, 66 (95 % CI 0, 06–0, 73), adjusted for several risk factors.[12] Similarly, the Women's Health Study showed an association between greater magnesium intake and lower incidence of T2DM after 6 years only among women with BMI $\geq$ 25.[9]

In the Atherosclerosis Risk in Communities Study, a cohort of nondiabetic middle-aged adults (N = 12,128) followed for 6 years, a graded inverse relationship between serum magnesium levels and incident type 2 diabetes was shown in White but not in Black participants. Low dietary magnesium intake did not confer risk for type 2 diabetes.[14]

In a six-year prospective cohort study of 35,988 older women from Iowa, the dietary magnesium intakes showed a strong inverse association with the incidence of diabetes, after adjustment for potential nondietary confounding variables.[15]

In a cross-sectional analysis of 15,800 participants from the Atherosclerosis Risk in Communities (ARIC) study, the mean serum Mg levels were significantly lower in participants with CVD, hypertension, and diabetes, compared to those free of these diseases.[16]

Finally, the Mexican Diabetes Prevention Study showed that serum hypomagnesemia was independently associated with the development of IGT (impaired glucose tolerance), IFG (impaired fasting glucose) + IGT (impaired glucose tolerance) and type 2 diabetes, but not with the development of IFG.[17]

Observational studies have also showed that hypomagnesemia occurs frequently in patients with T2DM, especially those with poor glycemic control. Mather et al.[18] analyzed cross-sectional data from 582 T2DM and 140 controls and found that mean plasma Mg concentrations were significantly lower in patients with diabetes than in controls. Montagnana et al. performed a retrospective analysis of 7659 outpatients >35 years old and found that magnesium levels were significantly associated with FPG, only in patients with FPG > 7.0 mmol.[19]

Furthermore, the available data also have registered an inverse relationship between the ingestion of food rich in Mg and the risk of diabetes. A meta-analysis of 13 prospective cohort studies involving 536,318 participants and 24,516 cases, detected a significant inverse association between Mg intake and risk of type 2 diabetes in overweight (BMI > 25) individuals, but not in normal weight individuals (BMI < 25).[21] In summary, although Mg blood levels are associated with glucose metabolism in many studies,[13,16–19] the relationship between magnesium intake and glucose metabolism is unclear.[12–15,20] This discrepancy may be explained by gender. Negative association was found in the cohort which include male and female,[14] while a positive association between glucose metabolism and magnesium intake was observed in female cohorts.[12,13,15] Also, inverse association between Mg intake and risk of type 2 diabetes was found only in overweight people.[13,20]

3.3. Zn and diabetes

To our knowledge, only one cross-section large study looked at the association between current zinc levels and/or intake and the prevalence of diabetes. A cohort of 3575 subjects from north India, aged 25–64 years, including 1769 rural and 1806 urban were studied in this cross-sectional survey. Subjects were divided according to dietary zinc intake into low (<7.0 mg/day), moderate (7–15 mg/day) and high (>15 mg/day) intake groups and *highly sensitive colorimetric method*