

TRACE ELEMENTS AND VITAMIN D IN GESTATIONAL DIABETES

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Abstract. *Gestational diabetes mellitus (GDM), one of the most common pregnancy complications, is defined as glucose intolerance with onset or first recognition during pregnancy. Its prevalence varies worldwide in dependence on characteristics of the underlying population and applied diagnostic criteria. The etiology is multifactorial and not sufficiently elucidated. Available evidence suggests that the base of pathogenesis is relatively diminished insulin secretion coupled with pregnancy-induced insulin resistance. Modifiable and non-modifiable risk factors for development have been identified. Trace elements and vitamin D could be contributed to modifiable factors for prediction the risk in a large population. Essential trace elements in pregnancy are necessary to overcome systemic oxidative, metabolic and inflammatory stress. Evidence, still inconclusive, has been accumulated about the relation between higher incidence of vitamin D failure/deficiency during pregnancy and GDM. The lower level of 25-OH vitamin D could be associated with increased risk for anemia development, also including pregnant women. This review intends to provide an overview of the possible link between both vitamin D and trace elements as risk factors for GDM development.*

Key words: gestational diabetes, microelements, vitamin D status

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INTRODUCTION

The etiology of GDM is multifactorial and has not entirely been elucidated yet. Because of the increased prevalence, understanding the risk factors gains highlighted importance. Obesity (Body Mass Index, BMI > 30), race, family history of diabetes mellitus (especially in first-degree relatives), age older than 25 years, history of GDM in a previous pregnancy, polycystic ovarian syndrome are of major importance for the disease development [1]. Gesta-

tional diabetes has a natural course similar to that of type 2 diabetes (T2DM) with characterization by two main pathogenic factors: insulin resistance (IR) and an insulin secretion defect – a woman's pancreatic function is not sufficient to overcome the diabetogenic environment of pregnancy, thus leading to high blood glucose levels [2]. Different variables and unchangeable factors, affecting the size of IR, pancreatic B-cell dysfunction, and glucose homeostasis, are the subject of study in respect of risk and prevention of GDM and T2DM, considered to be two faces of

the same disease. The overweight, obesity, and age during pregnancy are the main modifiable risk factors for GDM, but identification of others is also of special interest [3].

Deeper knowledge on vitamin D status and the essential trace elements iron, copper, zinc and selenium as potentially modifiable risk factors of GDM and T2DM could assist the elaboration of prevention strategy with impact also on screening, diagnosis and subsequent treatment modalities of these diseases.

IRON

Iron has a dual nature in the human body. It is essential for life with a role in many metabolic processes as oxygen transport, cell growth, and differentiation, regulation of gene expression. On the other hand, the excess iron is highly toxic because it promotes oxidative stress. Recent knowledge determines hepcidin, a peptide hormone produced in the liver, as a key regulator of systemic iron homeostasis [4]. Hepcidin inhibits iron efflux to plasma by binding to and inducing the degradation of ferroportin, the only known iron exporter present in duodenal enterocytes, reticuloendothelial macrophages, hepatocytes, and placenta. The rate of hepcidin synthesis depends on circulating and stored iron, erythropoietic activity, oxygen tension, and inflammation. The interplay of these signaling pathways and relative strength of each signal are responsible for hepcidin expression [5].

Iron overload impairs the response to insulin in the liver, muscle, and adipose tissue [6]. Excess iron, once stored in the liver, interferes with glucose metabolism, causing hyperinsulinemia via both decreased insulin clearance and impaired insulin signaling. Insulin stimulates the intrahepatic iron accumulation by increasing the uptake of diferric transferrin via an enhanced number of transferrin receptors onto the cell surface while upregulating hepcidin expression directly [7]. Iron affects inhibitory effect of insulin on gluconeogenesis, reducing liver extraction and insulin metabolism. Increasing iron stores leads to peripheral hyperinsulinemia with both liver and muscle resistance.

Pregnancy is a unique physiological condition with elevated requirements for micro- and macro-elements. Maintenance of iron homeostasis is critical for mother and developing fetus because both deficiency and overload impair certain cellular functions. Prophylactic treatment with iron is questionable. Keeping an adequate iron level is important to prevent iron deficiency anemia with consecutive preterm birth delivery. High maternal hemoglobin as a result of iron supplementation would increase blood viscosity and

reduce placental perfusion with adverse pregnancy outcome. Stimulated dietary iron uptake requires particular attention because of iron potential to initiate overproduction of toxic hydroxyl radicals, thus, leading to cell death and oxidative tissue injury [8].

Recent biomarkers as serum iron, transferrin saturation (TfSat), serum ferritin, soluble transferrin receptors (sTfR), sTfR/ferritin ratio and serum hepcidin characterize complex relationship between iron status and the risk of GDM developing. The link iron – glucose is bidirectional: iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways [9]. Elevated serum ferritin is associated with impaired glucose tolerance and GDM [10]. It reflects iron accumulation in body's depots, proposed as a component of insulin resistance syndrome. Additionally, ferritin is an acute phase protein, and pregnancy is a pro-inflammatory condition. In GDM, this biomarker and BMI are independent predictors of carbohydrate tolerance disturbances in 2 hours Oral Glucose Tolerance Test (OGTT). Ferritin in mid-pregnancy correlates with a greater risk of GDM, independently of BMI and C-reactive protein (CRP), but no with OGTT results in early postpartum [11]. Increased TfSat, a measure for iron transport in the circulation, is associated with higher risk for GDM [12].

Inflammation significantly upregulates hepcidin by the mediation of interleukin-6 (IL-6), and also is responsible for largely increased serum ferritin. Iron, inflammation or both could be part of ferritin-insulin resistance axis. Other laboratory tests also assess inflammation: high sensitivity CRP and fibrinogen. CRP at mid-pregnancy correlates with GDM and inflammation is suggestive of the disease development [13].

The parameter sTfR reflects mainly the erythropoietic activity of bone marrow and is less influenced by the acute-phase response than ferritin. The data about the connection between sTfR levels in the first trimester and GDM risk is unconvincing. The sTfR/ferritin ratio offers greater sensitivity and specificity in the characterization of iron status than measurement of the individual members in the ratio ferritin/sTfR [14].

In high-risk pregnancies – associated with the inflammatory process, obesity and preeclampsia – higher serum hepcidin might cause an iron restriction in the mother, leading to anemia when persisting and to insufficient iron supply to the fetus [15]. In contrast, in true iron deficiency, serum hepcidin is lower than in normal iron status. Elevated hepcidin, significantly related to an increased GDM risk only during the second trimester, has been observed before the diagnosis. Diagnostic utility of serum hepcidin is determined

by the possibility of differentiation between true iron deficiency and functional iron deficiency in inflammation. Dynamic measurement of serum concentration of the peptide hormone over the progression of pregnancy, in combination with other parameters of iron status, would optimize trace element supplementation as periods and duration [16].

COPPER, ZINC, SELENIUM

The bioavailability of essential trace elements during pregnancy is dependent on physiological factors affecting the absorption, transport, and use in the relevant processes [17]. Pregnancy stimulates copper absorption due to increased activity of maternal enzymes – cytochrome oxidase for tissue respiration and superoxide dismutase as part of the antioxidative defense. Increased copper interferes with zinc absorption leading to lower zinc levels. Zinc and selenium demands are stimulated to ensure fetal nutrition. The essential minerals in normal pregnancy, particularly in the third trimester and at birth, are necessary to overcome systemic oxidative, metabolic and inflammatory stress that would result in a number of adverse conditions: spontaneous abortions, preeclampsia, gestational diabetes mellitus, intrauterine retardation [18].

Copper (Cu) is not only physiologically important for fetal development but also plays an interactive role in placental iron transport. Recently identified multicopper ferroxidase Zyklopen is involved in iron efflux from the placenta during iron transfer from mother to fetus. Copper is delivered to the fetus via specific placental transporters regulated by estrogen and maternal insulin levels [19].

Serum Cu and ceruloplasmin levels increase gradually in pregnancy. By the end of pregnancy, serum copper values are two-fold higher than in non-pregnant women. Serum Cu and ceruloplasmin could serve as sensitive indicators for the assessment of the course of pregnancy and placental function [20]. The increase of copper level with the progression of pregnancy may be partially due to the stimulated synthesis of ceruloplasmin, the major copper-binding protein, under the action of estrogen. Ceruloplasmin is an acute phase protein and the pregnancy, as a physiological proinflammatory condition, stimulates ceruloplasmin synthesis with a rise in serum copper [21]. The protein has antioxidant properties and is involved in the degradation of highly toxic hydroxyl radicals. The study of the specific enzyme activity of ceruloplasmin and copper/ceruloplasmin ratio would provide a more in-depth assessment of copper status in pregnancy in both norm and event pathology

[22]. Altered maternal copper levels may contribute to restriction in fetal growth or may lead to preterm delivery or premature rupture of fetal membrane.

Data about serum copper in GDM compared to normal pregnancy are inconsistent. Established significant positive association between fasting serum copper level and fasting serum glucose in GDM indicates that increased copper level could be directly linked to decreased insulin sensitivity [23]. Copper, like iron, is involved in glucose homeostasis as a pro-oxidant factor with the generation of free radicals.

The metabolism of iron and copper is closely interrelated, also in pregnancy. In the mother, iron deficiency results in an increase of liver copper. Corresponding increases in copper concentration and ceruloplasmin activity are also seen in the maternal serum. Lack of response to iron supplementation in some cases of pregnancy anemia implies at least that some of them could be a consequence of inadequate (low) copper intake. In this situation, the copper status should be considered [24].

Zinc (Zn) is an essential component of over 1000 proteins – antioxidant enzymes, metalloenzymes, required for carbohydrate and protein metabolism, DNA and RNA synthesis, cellular replication and differentiation, and hormone regulation.

The element mimics and amplifies the pancreatic and peripheral functions of insulin. Alterations in zinc balance are related to T2DM. Zinc permits the formation of insulin-hexamers in beta-cells and partly regulates the beta-cell mass [25]. In other insulin-responsive tissues, i.e. muscle and fat, Zn shows insulinomimetic properties by affecting the insulin receptor signal transduction [26].

The importance of zinc to fetus growth is demonstrated by the active transport of zinc across the placenta into the fetal circulation resulting in higher cord blood concentrations than in the maternal circulation [27]. The requirement of Zn during the third trimester is approximately twice as high as that in nonpregnant women as a result of progressively decreasing in maternal concentration due to hemodilution and stimulated transfer to growing fetus [28]. Low maternal Zn may be associated with GDM, as well as preeclampsia, gestational hypertension, spontaneous preterm birth and infant birth weight.

Selenium (Se) is an integral component of several enzymes: formate dehydrogenase, glutathione peroxidase, selenoprotein P and W and the deiodinase. The element actively participates in the complex antioxidative defense through selenium-dependent glutathione peroxidases (GPXs) and other selenoproteins. Selenium deficiency is observed in various

diseases: diabetes mellitus, heart disease, autoimmune diseases and certain types of cancers [29]. Recently, research focus shifts from the link between Se and T2DM or obesity to Se and GDM. More important, Se might exhibit insulin-like properties, thus, takes part in the maintenance of normal glucose uptake, in the regulation of cellular glucose utilization and in reducing the severity of insulin resistance [30]. In pregnancy, hemodilution and an increased requirement for fetal growth, contribute to selenium depletion. Increasing of insulin resistance occurs in parallel with promotion of oxidative stress, more prominently in GDM. Over-consumption of antioxidants to overcome the oxidative stress could decrease selenium level additionally. Poor status of the trace element would result in aggravation of insulin resistance due to pregnancy, thus, leading to GDM. Some authors report increased selenium concentrations in GDM. In any case, the eventual significant association between serum selenium and GDM has not been evidenced strongly.

Vitamin D

Vitamin D deficiency is an increasing public health concern. The scientific evidence linking vitamin D deficiency with diabetes is growing large, but data about the relationship between vitamin D status and GDM are still controversial. Vitamin D deficiency appears to be associated with altered glucose homeostasis during pregnancy [31]. Supplementation with 1,25-dihydroxyvitamin D (1,25(OH)₂D) decreases glucose and increases insulin levels.

Normally, maternal physiological insulin resistance supports the fetus to absorb more nutrients. The findings of the link between increased risk of GDM and vitamin D deficiency are still biologically plausible. The active form of vitamin D-1,25(OH)₂D₃ regulates circulating glucose levels by modulation of insulin secretion via binding to vitamin D receptor. It promotes insulin sensitivity by stimulating the expression of insulin receptors and enhancing insulin responsiveness for glucose transport. Vitamin D regulates the balance between the extracellular and intracellular calcium pools in β -cell, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues. Vitamin D could have an anti-inflammatory effect in diabetes. Probably, the active form of vitamin D decreases expression of pro-inflammatory cytokines IL-6 and IL-1 and tumor necrosis factor α (TNF- α), involved in insulin resistance [32]. Vitamin D supplementation during pregnancy has beneficial effects on glycaemia, insulin sensitivity, insulin resistance and metabolic profiles [33]. Placenta has a capacity to synthesize active 1,25(OH)₂D linked to the placenta immune-modulatory function [34]. Con-

troversial results exist about the effect of vitamin D on insulin resistance on the base of the relationship between serum total 25(OH)D and homeostatic model assessment HOMA-IR.

The consistent relationship is established between vitamin D deficiency and increase in GDM development. However, well designed and randomized-controlled studies are necessary "to say that vitamin D replacement should be performed to prevent the development of GDM" [35]. A multivariate logistic regression analysis supports the data about vitamin D deficiency as a significant contributor for GDM (OR 1.387, $P = 0.019$) [36]. A large meta-analysis with 20 observational studies included reveals an association between maternal vitamin D insufficiency and a greater risk of gestational diabetes (RR 1.45; 95 % CI 1.15–1.83; $P < 0.001$) [37]. Some researchers fail to find a significant connection between vitamin D deficiency and risk of GDM [38].

Vitamin D and iron deficiency frequently co-exist. The interplay between iron and vitamin D metabolism may underlie that association. The degree to which molecular mechanisms might mediate these cross-talks has only started to be highlighted, and emerging data suggest that vitamin D affects iron metabolism by modulating erythropoiesis and hepcidin production [39]. In opposite, iron has been shown to modify the expression of fibroblast growth factor 23 (FGF23), the hormone as a key regulator of the renal production of 1,25(OH)₂D [40].

CONCLUSION

Investigation of the relationships between some essential trace elements and vitamin D status and typical laboratory indicators for women with GDM would contribute to a better understanding of the key role of trace elements and vitamin D for the effects of gestational diabetes as a complex metabolic syndrome, caused by a number of factors – genetic and modifier.

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