Effects of riboflavin and cobalamin levels on maternal metabolic homeostasis: a possible strategy to prevent gestational diabetes mellitus?

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ABSTRACT — Riboflavin deficiency increases body weight and fat deposition and decreases Glucose Transporter Type 4 (GLUT-4) and Glucokinase (GCK) expression. Cobalamin deficiency inhibits the conversion of methylmalonic acid (MMA) to succinyl-coA, causing MMA overload and consequent induction of lipogenesis and insulin resistance; in addition, it reduces the methylation of homocysteine to methionine, causing the accumulation of homocysteine which further enhances insulin resistance. Both riboflavin and cobalamin may prevent the onset of Gestational Diabetes Mellitus (GDM) in pregnant women.

KEYWORDS
Riboflavin, Cobalamin, Gestational diabetes mellitus, Insulin resistance, Homocysteine, Pregnancy.

RIBOFLAVIN AND COBALAMIN: TWO VITAMINS, MANY PATHWAYS

Riboflavin, also known as vitamin B2, plays a pivotal role in several biological pathways. In particular, it is a precursor for flavin mononucleotide and flavin adenine dinucleotide synthesis and, consequently, is required for proper functioning of numerous enzymes, including the ones of the oxido-reductase group. Thus, riboflavin has paramount importance for energy generation by aerobic cells, mitochondrial metabolism and fatty acid oxidation[1]. In addition, accumulating evidence suggests that riboflavin levels may modulate the proper function of nervous, cardiovascular, endocrine and immune systems, deeply affecting how they react in case of metabolic imbalance[2].

Vitamin B12 or cobalamin plays a fundamental role in neurological functions, DNA synthesis, and hemopoiesis. Some substantial sources of B12 include animal proteins, which are taken with diet and undergo gastric digestion and consequent release through the action of pepsin. Therefore, R-protein, secreted by the salivary glands, binds cobalamin and this complex transits to the duodenum. Due to the alkaline medium within the duodenum, R-protein is hydrolyzed and releases cobalamin, which becomes free to bind intrinsic factor (IF) secreted by gastric parietal cells. This last complex is absorbed by the mucosa of the terminal ileum, in a calcium-mediated fashion: after IF degradation, cobalamin is bound by transcobalamin-II and transported to the liver, where it is stored[3].

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From the biochemical point of view, on the one hand cobalamin is important as co-factor that enables the methylation of homocysteine to methionine, which is later activated into S-adenosyl-methionine that donates its methyl group to methyl acceptors; on the other hand, it allows the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Considering these important pathways, cobalamin deficiency may result in increased circulating levels of homocysteine, which are potentially harmful to vascular endothelium and neurons, and of methylmalonic acid (MMA), which can cause defective fatty acid oxidation, thereby promoting lipogenesis[4]. Apart from these widely known elements, accumulating evidence suggests that cobalamin is essential for cell proliferation during pregnancy: for this reason, recommended body stores in fertile women eating a mixed diet should be >1000 mg, whereas the total quantity required by the fetus is 50 mg. Nevertheless, low cobalamin concentrations have been reported in approximately 35% of pregnant women during the 3rd trimester[5].

Clinical and biochemical vitamin B12[6] and B2 deficiency[7] have been shown as highly prevalent among patients with both types 1 and 2 Diabetes Mellitus (DM) and other diabetogenic conditions. In addition, blood concentrations of vitamins B2, B6, C, niacin, and folate in blood were found very low in type 2 DM patients: considering the increased urinary clearance of these vitamins, the low observed levels are likely due to impaired reabsorption processes[8].

Based on the key role played in the modulation of the above-mentioned pathways and, most important, the possible detrimental effect of their deficiency on mitochondrial metabolism and fatty acid oxidation, in the current paper we aimed to offer an overview about riboflavin and cobalamin actions during Gestational Diabetes Mellitus (GDM).

RIBOFLAVIN'S EFFECTS ON INSULIN RESISTANCE AND DIABETES: POSSIBLE IMPLICATIONS FOR PREGNANCY

Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of type 2 DM: in particular, abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes. In this regard, it has been already shown that riboflavin supplementation in a mouse model of diabetes is able to significantly decrease fasting blood glucose, to allow a proper recover of CuZn-superoxide dismutase, catalase, glutathione reductase levels and, last but not least, to increase calcium levels and Glucose Transporter Type 4 (GLUT-4) expression[9]. These data clearly suggest that riboflavin could act as an antioxidant against oxidative stress, especially lipid peroxidation, protein carbonylation and oxidative DNA damage; in addition, the increase of calcium levels and GLUT-4 expression have paramount importance in improving glucose uptake and ameliorate peripheral insulin sensitivity.

Another recent report[10] found that riboflavin supplementation induces functional changes in adipocyte-macrophage co-cultures and leads to a reduction in the intensity of their pro-inflammatory, pro-insulin resistance as well as their pro-diabetogenic activities. Conversely, suboptimal B2 levels increase body weight and fat deposition, decrease GLUT-4 and Glucokinase (GCK) adipose tissue expression, and increase expression of inflammatory markers, such as CCR5, interleukin-1β, and toll-like receptor 4. This appears extremely interesting since the reduction of obesity-related inflammation may orchestrate a positive effect on several associated syndromes, including insulin resistance, type 2 DM, and arteriosclerosis. The effects of low riboflavin levels may be due, at least in part, to its role for DNA methylation: indeed, a human-based analysis found that methylation of the HIF3A locus (codifying for hypoxia inducible factor 3 alpha subunit) is associated with higher body mass index[7]. Since riboflavin has been shown to protect against inflammation-induced cell damage and the development of insulin resistance in the non-pregnant state[9], it is possible to hypothesize a similar action even during pregnancy. In this regard, a recent study[11] highlighted that the supplementation of both riboflavin and myo-inositol (MI) is able to increase gene expression markers of insulin sensitivity and glucose uptake in a mouse model of GDM.

Considering that MI has already been demonstrated as a robust strategy for the prevention and treatment of GDM[12], its association with riboflavin may significantly enhance the insulin-sensitizing effects also in humans.

EFFECTS OF COBALAMIN LEVELS ON MATERNAL AND FETAL METABOLIC HOMEOSTASIS

Since early 80's, accumulating evidence suggested how metformin use had a significant impact on the concentration of cobalamin in patients with type 2 DM: in particular, a combination of alteration in small bowel motility (which stimulates bacterial overgrowth with consequential cobalamin deficiency), alteration in IF levels, interaction with the cubulin endocytic receptor and inhibition of the calcium-dependent absorption of cobalamin-IF complex at the terminal ileum may all decrease the level of this vitamin[13].

Recent data have clearly suggested an association between cobalamin deficiency and GDM[14]. Considering the above-mentioned pathways, cobalamin deficiency during pregnancy may account for the increased levels of homocysteine in maternal serum, as occur during GDM[15]. The identification of elevated homocysteine as a significant risk factor for the development of diabetes in women with previous GDM[16] further support this speculation. Thus, the incidence of GDM seems to be increased among women with cobalamin deficiency and adequate folate concentrations[17].

A possible biochemical background to underlie the association between cobalamin deficiency and GDM may be the decreased conversion of MMA to succinyl-coA, for which cobalamin acts as a rate-limiting coenzyme; this results in the accumulation of MMA, and may increase lipogenesis and insulin resistance[18].

Maternal cobalamin levels were found inversely associated with offspring's homeostasis model assessment-insulin resistance, triglycerides, homocysteine and positively with high-density lipoprotein-cholesterol[19]. In addition, the Pune Maternal Nutrition Study[18] showed that children born to mothers with low plasma vitamin B12 concentrations were smaller, more adipose and insulin resistant than children born to mothers with normal vitamin B12, especially if the mother had normal or high folate concentrations. Finally, low levels of cobalamin correlate also with an increased risk of neural tube defect, impaired neurodevelopment and altered risk of cancer in the offspring[20].

These data allow us to infer that low maternal cobalamin could be considered an independent determinant of adverse metabolic phenotypes not only for the mother but also for the offspring. Thus, the recent therapeutic approach of GDM with metformin, although promising, should be carefully evaluated taking into account the possibility of inducing maternal low levels of cobalamin (and related consequences for both mother and child) without a proper supplementation. Another extremely important point to address is the high risk of cobalamin deficiency in vegan/vegetarian women: in this population, indeed, the cobalamin deficiency may become overt during pregnancy.

CONCLUSIONS

Despite the lack of robust evidence in humans, the few available data suggest a key role of both riboflavin and cobalamin in several metabolic pathways. In particular, riboflavin deficiency seems to cause increased body weight and fat deposition, as well as decreased GLUT-4 and GCK expression in the adipose tissue. On the one hand, cobalamin deficiency inhibits the conversion of MMA to succinyl-coA, causing MMA overload and consequent induction of lipogenesis and insulin resistance; on the other hand, it reduces the methylation of homocysteine to methionine, causing the accumulating of homocysteine, which further enhances insulin resistance. Based on these elements, it is possible to hypothesize that maternal low levels of both riboflavin and cobalamin predispose to metabolic complications of pregnancy, including GDM. Thus, we recommend an appropriate supplementation of these two important vitamins for pregnant women, in order to prevent possible adverse outcomes.

Declaration of Interest

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper. The work was not supported by any grant/fund.

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