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EDITORIAL

Vitamin B_{12} and diabetes risk—myth or reality

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The role of nutritional factors in contributing to diabetes risk has been the subject of research for several years. However, the focus on micronutrients particularly vitamins has been a more recent phenomenon. While most of the research has focused on vitamin D, the interest in vitamin B_{12} as a modulator of diabetes risk has been growing and the link reportedly getting stronger.

The question of whether vitamin B_{12} deficiency is associated with risk of future diabetes is an important question to ask in our country as a large section of our population is pure vegetarian and is thus prone to deficiency of this vitamin. In fact, vitamin B_{12} deficiency is widely prevalent in our country affecting 47% of our population [1]. A recent study from South India in urban individuals reported that the prevalence of absolute and borderline vitamin B_{12} deficiency was over 50% [2]. Vitamin B_{12} levels decreased as the level of glucose intolerance increased and the proportion of those with vitamin deficiency increased with increasing severity of glucose intolerance, more so among males and vegetarians [2].

The association of vitamin B_{12} deficiency with hyperhomocysteinemia [3] and other metabolic abnormalities such as insulin resistance and dyslipidemia [4] has been known for a while. Also, hyperhomocysteinemia has been well recognized as a cardiovascular (CV) risk factor [4]. A recent study from North India in rural subjects [5] found positive correlation of vitamin B_{12} levels and low HDL levels although the possible mediation by homocysteine could not be confirmed. Also, no significant relationship between vitamin B_{12} levels and any of the other lipid parameters and between hyperhomocysteinemia and any of the obesity or lipid parameters was found. Whether vitamin B_{12} could also mediate diabetes risk is not known and is currently being investigated.

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Evidence for a possible role of vitamin B_{12} deficiency in enhancing diabetes risk comes mainly from studies on pregnant women and their offspring and from studies using nutrigenetic approaches.

Studies from western India [6] suggest that low vitamin B_{12} levels in pregnancy are associated with obesity. These have focused our attention on the potential role of maternal undernutrition on maternal and fetal obesity and insulin resistance. The effects of low vitamin B_{12} levels on obesity and insulin resistance in pregnant women have been confirmed in a study from the UK [7]. Another study from the UK [8] has also shown that maternal vitamin B_{12} levels are associated with maternal obesity and risk of gestational diabetes mellitus (GDM). A more recent systematic review in 2019 [3] concluded that vitamin B_{12} deficiency could be associated with increased risk of GDM. The study included over 1810 pregnant women without GDM and 309 with GDM and showed that GDM patients had lower vitamin B_{12} levels than non-GDM subjects and that vitamin B_{12} level predicted GDM (OR 1.81). The results of these studies reinforce the hypothesis that there is a strong association between vitamin B_{12} and GDM risk. However, more studies would be required to clearly establish any causative link between the two.

Emerging evidence also indicates that vitamin B_{12} deficiency in the mother has a profound influence on fetal growth and development, and this fetal programming can result in increased obesity, adiposity, and insulin resistance later in life [6]. Studies in the Pune cohort suggest that maternal undernutrition is closely linked to fetal obesity and insulin resistance. These studies also describe the thin-fat Indian babies where the babies were thin but with higher levels of adiposity compared with babies of European origin. Over two-thirds of the mothers of these babies displayed vitamin B_{12} deficiency. Low B_{12} levels were also associated with a greater likelihood of adiposity and insulin resistance during childhood [9].Vitamin B_{12} is known to critically influence several cellular pathways particularly nucleic acid synthesis and gene methylation that is involved in the expression of genes. Some of these

pathways may be the basis of fetal metabolic programming that predisposes to insulin resistance in the offspring [6].

A study from South India examined the association of 2 FTO gene variants with greater predisposition to obesity in the CURES cohort and found that these were not only associated with a higher risk of obesity but also with a lower vitamin B_{12} concentration [10]. This interesting observation if replicated in larger studies will provide evidence for the hypothesis that vitamin B_{12} influences obesity and NCD risk by its effects on obesity-related genes. GWAS in Indians has shown that plasma B_{12} concentrations are regulated by newly identified population-specific variants in FUT6 gene [11]. A very recent study confirmed that vitamin B_{12} supplementation regulates several diabetes-associated genes such as TCF7L2, FTO, and CREBP/CBP through methylation of MiR21 and could thus epigenetically influence the risk of obesity, insulin resistance, and type 2 diabetes mellitus [12].

The relationship of vitamin B_{12} and metabolic traits was explored in healthy non-pregnant women in Indonesia by adopting a nutrigenetic approach [13]. Genetic risk scores (GRS) were derived using nine vitamin B_{12}–associated single nucleotide polymorphisms (SNPs) (B_{12}-GRS) and nine metabolic SNPs (metabolic-GRS). The B_{12}-GRS and metabolic-GRS had no effect on vitamin B_{12} levels and metabolic traits. However, the study did show a significant effect on HbA1C levels.

The study by Surendran et al. [14] published in the current issue is a similar nutrigenetic study in South Asians conducted in Sri Lanka. The authors constructed a vitamin B_{12}–related genetic risk score (B_{12}-GRS) based on 10 vitamin B_{12} SNPs and a metabolic trait–related genetic risk score (metabolic-GRS) based on 10 metabolic trait–related SNPs and examined the relationship of these risk scores to vitamin B_{12} levels and different metabolic traits in 109 Sinhalese adults. While there was a significant association of B_{12}-GRS to plasma vitamin B_{12} levels, the authors could not demonstrate any significant relationship between genetically mediated vitamin B_{12} levels and any of the metabolic traits. However, they found a significant interaction of B_{12}-GRS and dietary protein intake on waist circumference suggesting that low genetically mediated vitamin B_{12} levels could be associated with central obesity in the presence of lower dietary protein intakes. While these findings are interesting and open up novel possibilities of gene-nutrient interactions, they need to be replicated in larger studies which are appropriately powered before firm conclusions on such interactions can be drawn. Despite its limitations, this study highlights the need for focused research in the important area of gene-dietary nutrient interactions to understand the complexities of diet-related diabetes risk.

Whether low vitamin B_{12} levels could be causally related to enhanced cardiometabolic risk was evaluated by a unique Mendelian randomization (MR) approach [15]. SNPs identified by earlier GWASs to be robustly associated with vitamin B_{12} levels were analyzed by MR for any significant cardiometabolic risk. A causal relation of vitamin B_{12} was suggested with fasting glucose and beta cell function (HOMA beta) but not with any of the other cardiometabolic factors such as obesity, waist to hip ratio, body fat, HOMA-IR, HbA1C, or serum lipids. If replicated in larger samples, these findings could have major implications in understanding the role of vitamin B_{12} in diabetes risk.

Thus, a growing body of evidence points to a significant association of vitamin B_{12} and risk of diabetes. It would appear that besides macronutrients, recent research suggests that vitamins such as vitamin D and now vitamin B_{12} could also be key modulators of this risk. Larger studies looking closely at gene-environment interactions should unravel the mystery of what promises to be an important link between vitamin B_{12} and diabetes risk.

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