CHAPTER 4

VITAMIN D, FOLATE AND COBALAMIN IN OBESITY

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INTRODUCTION

The adipose tissue is considered as both a metabolic and an endocrine tissue. The evaluation of micronutrient status is important in obesity associated with excessive fat deposition, because in obese individuals the composition of the diet may be ignored. When excessive intake of macronutrients is combined with micronutrient deficiencies, the principle of sufficient and balanced nutrition will be impaired. (1)

Obesity and particularly morbid obesity are associated with nutritional, metabolic and biochemical variations such as an altered hormonal profile including vitamin D. (2,3) Obesity is a growing health problem both during childhood and adulthood periods of life and may lead to chronic and severe diseases in populations throughout the world. Its relation with metabolic syndrome (MetS) is well-established. (4-7)

Childhood obesity may lead to many clinically important sophisticated diseases such as diabetes mellitus, MetS, cardiovascular diseases and even cancer in adulthood. (2,7,8-11) Aside from genetic, socioeconomic, and cultural factors, nutritional factors are also important.

Micronutrients are required in minute amounts, however, they are of macro-importance in many reactions. Mutual interactions take place between the components of the metabolic reactions and minerals as well as vitamins. (12)

Vitamin deficiencies are common in obese individuals. This is confirmed by many studies concerning vitamin D, folate (vitamin B9) and cobalamin (vitamin B12) performed on both adults and children. Of them, cobalamin has been less evaluated in cases of obesity. (2,13,14) Within this context, the status of vitamin D, folate and cobalamin is under investigation. The aim of this paper was to review the profiles of these micronutrients during obesity and MetS in children and adults.

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VITAMIN D

Vitamin D is stored in adipose tissue. Due to its storage site, it appears to be closely associated with obesity. The involvement of vitamin D in macromineral status was investigated in overweight and obese individuals. (9,15-18)

Vitamin D is essential for bone structure, because it participates in calcium and phosphorus metabolisms, main macrominerals in the human body. The deficiency of this vitamin may interfere with human metabolic systems, particularly those of children. Vitamin D appears to play roles in cardiovascular and metabolic health. 25 – hydroxy cholecalciferol [25-hydroxy vitamin D, 25(OH)D] is associated with adiposity and cardiometabolic risk factors. The effect of vitamin D on cardiovascular risk factors such as oxidative stress and insulin resistance (IR) were also documented. (19-22) This vitamin exhibits important functions in immune system. (23)

Vitamin D is also related to magnesium and fat mass. Magnesium participates in vitamin D activation and function. This vitamin cannot be metabolized without sufficient magnesium levels. Low magnesium levels make vitamin D ineffective. (24-26)

In overweight and obese children, significantly lower magnesium levels were observed. Significant associations between magnesium and vitamin D levels were reported among students. (9,16,17)

Some foods rich in vitamin D are not sufficient to meet the recommended daily allowance of this vitamin. Vitamin D can be synthesized in the skin upon exposure to sunlight, which is an important source of this micronutrient.

It is interesting to note that adults and children living in countries both at high latitudes and quite close to equator may be under the risk of vitamin D deficiency. Besides, low socioeconomic status is introduced as an independent risk factor for poor vitamin D status. (27-32)

Vitamin D status is assessed using serum 25(OH)D concentrations determined by high-performance liquid chromatography. Vitamin D concentrations were evaluated as deficient (< 20.0 ng/ml), insufficient (20-30 ng/ml) and sufficient (> 30.0 ng/ml). (13)

Serum 25(OH)D declines with puberty onset. Children with both central obesity and suboptimal 25(OH)D (<30 ng/ml) before puberty-onset exhibit higher IR during puberty. Therefore, maintaining adequate 25(OH)D status before pubertal-onset is recommended particularly in obese children. (33)

Low serum vitamin D levels were reported among school children in Kuwait. (27) In a school-based survey performed on Saudi students, prevalence of vitamin

D deficiency was found as 49.5%. (31) In a study performed in Canada, 5.6% of children were vitamin D deficient. (30) In Spain, prevalences of hypovitaminosis D were 58.1%, 68.2%, and 81.1% among normal, obese and severely obese children, respectively. (29)

Both low vitamin D status and obesity have already reached epidemic levels in children and adults throughout the world. (27-29, 34-36) Vitamin D deficiency appears as a contributing factor in some diseases such as asthma and MetS. (37,38)

Vitamin D deficiency has already been emphasized during obesity and MetS. (39,40) Deficiency states may lead to improper mental functions. (10,41,42) Depressive disorders, learning difficulties, cognitive problems are some of the health problems, which may be observed in association with obesity. Vitamin D functions in the prevention of depressive disorders. Higher vitamin D concentrations are associated with better attentional functions. (10,13,43,44)

Relations between vitamin D and blood pressure values are also noteworthy. Vitamin D decreases the activity of renin-angiotensin-aldosteron system and lowers renin synthesis to reduce blood pressure. Vitamin D deficiency was highly prevalent in patients with hypertension as well as type 2 diabetes and was associated with higher systolic blood pressure (SBP). (45,46)

Typically, more attention was given to SBP as a major risk factor for cardiovascular disease for people over 50. In most people, SBP rises steadily with age due to the increasing stiffness of large arteries, long-term build-up of plaque and an increased incidence of cardiac and vascular disease. (47) Stronger relationships were reported between SBP and heart rate as well as muscle endurance than those observed between diastolic blood pressure (DBP) and these variables in obese women. (48)

Vitamin D deficiency may contribute to the complications of pediatric obesity. In a study performed on children, correlations observed between obesity indices-DBPs, vitamin D-triglycerides and low fasting blood glucose found in obese group were not detected in morbid obese group. These findings point out that some MetS components may arise during obese state prior to transition to morbid obesity. Following the determination of vitamin D deficiency prevalence, its associations with anthropometric measurements, blood pressures and triglycerides should also be evaluated before the development of morbid obesity. (13)

FOLATE AND COBALAMIN

Folate and cobalamin are closely interrelated micronutrients. They are well-cooperated. Cobalamin plays essential roles in transsulfuration reactions, hematopoietic system, and fat as well as protein metabolisms. Cobalamin deficiency leads to adipocyte dysfunction, fatty acid metabolism dysregulation, increased pro-inflammatory cytokine production, hematological, psychiatric and neurological problems, whereas enzymes of folate metabolism serve as targets during cancer chemotherapy. (49-53)

Cobalamin is stored in the body unlike other water-soluble vitamins excreted by way of urine. Serum cobalamin concentrations are measured by electrochemiluminescence immunoassay. Folate is analyzed by immunoassay analyzer. Values for cobalamin can be classified as low (< 148 pmol/L), borderline (148-221 pmol/L) and normal (> 221 pmol/L), respectively. Folate levels lower than 4 mcg/L point out deficiency state. (14)

Many studies reported concentrations as well as percent deficiencies of folate and cobalamin among the populations. However, data on both vitamins are inconsistent. (54)

Folate was introduced as a new biomarker of MetS, particularly during the screening of the populations. Low folate intake was reported as one of the predictors of MetS. It is important during the primary care of patients. Within this context, reduced folate levels were reported in MetS. Patients with MetS exhibit strong associations with low levels of folate and cobalamin. Serum concentrations of both vitamins were found to be inversely associated with MetS in Turkish women. (55-59)

Cobalamin deficiency is common in the elderly. Younger patients have better outcomes compared to older individuals during treatment with cobalamin. (60) In the elderly, an association between cobalamin status and high fat mass index was reported. (61) Another fat-based index, diagnostic obesity notation model assesment index, was reported as the most prominent index, which shows strong correlation with cobalamin concentrations in morbid obese children. A negative correlation existed between this index and the vitamin confirmed the association between cobalamin and obesity degree. (62)

Cobalamin levels of healthy individuals, women of childbearing age, obese people, pregnant women, those with gestational diabetes have already been investigated. (49,51, 63-68)

Since cobalamin participates in fat metabolism, cobalamin and folate supplementations during pregnancy may overcome the problem of gaining weight during this physiological state. Losing weight is difficult and obesity may lead to severe health problems. Cobalamin deficiency may also affect fetal development. (49-51) Both cobalamin and folate status were examined also for fetal and maternal health in obese pregnancies. (69) These vitamins were also considered following bariatric surgery. (70)

Many studies on folate and cobalamin were performed on adults with MetS. (57-59) However, to the best of authors' knowledge, less attention was paid to the roles of folate and cobalamin in childhood obesity and MetS. (14) There are controversies on the association between body mass index (BMI) and cobalamin status. (61, 71-76)

Obese children and adolescents are risk groups for low cobalamin levels. Therefore, deficiency state should be handled in obese children. (77) Increased BMI was associated with decreased cobalamin levels in children. (78) About one third of obese adolescents had a low or borderline cobalamin status. Folate levels did not differ among the groups with low, borderline and normal cobalamin status. (79)

Associations between increased BMI and reduced cobalamin were observed in the early stage of pregnancy. (80,81) Children born to mothers with low cobalamin levels appear to develop higher adiposity and IR. (82) In a similar manner, cobalamin concentrations were significantly lower in obese children and were negatively associated with the severity of obesity. (78) In another clinical report, lower concentrations of cobalamin in obese were observed than those in overweight and normal weight individuals. (83) However, for instance, an association between cobalamin status and BMI or body composition was not found in the elderly. (61)

Folate and cobalamin levels appear to be linked with some cancers. Low cobalamin increases gastric cancer risk. (84) Erythrocyte folate levels were reduced in pancreatic cancer. (85) Status of both vitamins were also investigated in pediatric cancers. (86)

However, there are some controversial findings related to cobalamin as well as vitamin D status in terms of breast cancer. Unexpectedly, associations of increased breast cancer risk with higher vitamin D and vitamin B12 concentrations were reported. (87-89)

Deficiency state end-products of both folate and cobalamin may interfere with the expected profiles of MetS components. The alterations in MetS components may affect cobalamin metabolism and also its associations with anthropometric measurements. Further increases in folate and cobalamin deficiency in MetS associated with the increased folate as well as cobalamin deficiency metabolites may add to MetS parameters. (14)

An interesting functional association may exist among folate, cobalamin and obesity, which in turn gives rise to MetS. Experimental studies have pointed out that supplementation with methyl donors such as folate and cobalamin may prevent transgenerational amplification of obesity suggesting that DNA methylation mechanisms are involved in this process. (90)

Blood pressure is related to this complicated network of folate, cobalamin and obesity. This may be explained by the collaborative work of folate and cobalamin as coenzymes in the methionine regeneration from homocystein. This couple may have synergistic effects on blood pressure or endothelial function. (91,92) Increases in blood pressure have been shown to be reduced by folate and cobalamin administration. (93)

Elevated concentrations of homocystein and reduced folate as well as cobalamin concentrations are significantly correlated with coronary artery diseases. (94,95)

CONCLUSION

Both severe obesity and MetS may be life-threatening health problems in adults. Childhood obesity also requires attention, because it may be the predictor of some severe diseases during the future life of the child. Due to cobalamin's role in fat metabolism, deficiency state of this vitamin may interfere with lipid and energy metabolisms. Folate contributes this process because of its close association with cobalamin. The contribution of vitamin D deficiency to the development of obesity and MetS is well known. Therefore, the investigation of the network among these three vitamins and obesity as well as MetS will be interesting. (62)

Obesity has been associated with increased risk of accelerated cognitive decline and dementia, which suggests underlying neurobiological changes. (96) The impact of MetS on cognition and brain functions is also being investigated. (97)

Folate and cobalamin are associated with cognitive disorders and learning difficulties. The antidepressant effects of vitamin D are known and the deficiency state affects mental functions negatively. Vitamin D, folate and cobalamin deficiencies are, all, related to impaired cognition. (14, 98-102) In recent reports, close associations have been found among vitamin D, folate, cobalamin, obesity, brain volume and white matter. (103,104)

Under the light of these information, both childhood and adulthood obesity are in close association with MetS, the most probable consequence of severe obesity. Cardiovascular and cognitive alterations are health problems commonly observed in obesity. Vitamin D, cobalamin, and folate appear to contribute to these derangements. Considering the fact that deficiencies of all of these vitamins are common among the populations, encouragement of supplementation is expected, in the first instance, to be able to overcome the development of obesity, which in turn may lead to severe obesity and MetS.

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