



Invited Commentary

Serum 25-hydroxyvitamin D is associated with obesity and metabolic parameters in US children

Low serum 25-hydroxyvitamin D (25(OH)D) concentration has been associated with obesity and metabolic syndrome (MetS), but few studies have addressed these associations in the USA where the prevalence of vitamin D deficiency, obesity and related metabolic disorders in children is high. In an article in this issue of *Public Health Nutrition*, Fu *et al.*⁽¹⁾ present new exciting findings from a large cross-sectional, 'nationally representative' study which examined the associations between serum 25(OH)D concentration, obesity and metabolic parameters in 6311 US children and adolescents aged 6–18 years participating in the National Health and Nutrition Examination Survey 2001–2006. A unique feature that distinguishes their paper from other work in this area is that the authors have examined such associations according to gender. Multinomial logistic regression, with adjustment for potential covariates, found higher odds of obesity, abnormal waist circumference, abnormal HDL-cholesterol and high HOMA-IR (homeostasis model assessment of insulin resistance) score with deficient (<30 nmol/l) and inadequate (30–50 nmol/l) serum 25(OH)D concentrations, than with adequate concentration (>50 nmol/l). In gender-stratified analysis, Fu and colleagues found that low serum 25(OH)D concentration was associated with insulin resistance and abnormal HDL-cholesterol concentrations in girls, and with obesity in boys. There were however no associations with other metabolic parameters. These are interesting findings, where further research into possible mechanisms behind such associations is needed.

Vitamin D is known to play a significant role in the regulation of glucose homeostasis by stimulating insulin secretion from pancreatic β -cells in the islets of Langerhans^(2,3). Vitamin D is a fat-soluble vitamin that is distributed in various tissues of the body including the liver, fat and muscle⁽⁴⁾. It refers to two biologically inactive parent compounds: ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). Ergocalciferol is naturally synthesized from ergosterol in fungi and yeast when exposed to sunlight, whereas cholecalciferol is synthesized in the skin following exposure to UV light⁽⁵⁾. Animal-based foods, fortified foods and supplements are the main sources for ergocalciferol and cholecalciferol^(5–8). Both forms go through a two-step hydroxylation process. The first step takes place in the liver where ergocalciferol

and cholecalciferol are catalysed by 25-hydroxylase to produce 25-hydroxyergocalciferol (25(OH)D₂) and 25-hydroxycholecalciferol (25(OH)D₃; both termed calcidiol), respectively. The second step occurs in the kidneys and requires the $1\alpha,25$ -hydroxylase enzyme to produce the main biologically active hormonal form, 1,25-dihydroxyergocalciferol (1,25(OH)₂D₂) and 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃; both termed calcitriol)⁽⁵⁾, respectively. The biological action of calcitriol is mediated through vitamin D receptors (VDR) on pancreatic β -cells which belong to a large family of nuclear hormone receptors⁽⁹⁾. The active form calcitriol promotes intestinal calcium absorption and transcellular calcium movement by increasing ion permeability through the tight junctions⁽¹⁰⁾.

Low serum 25(OH)D concentration, which represents the sum of 25-hydroxyergocalciferol and 25-hydroxycholecalciferol (25(OH)D₂ + 25(OH)D₃), has been found to be associated with impaired glucose tolerance, immune dysfunction and cardiovascular risk in children⁽¹¹⁾. Childhood obesity has become a global health concern and one of the leading causes of many chronic conditions⁽¹²⁾ including metabolic syndrome, which refers to a group of risk factors related to the development of CVD in children and later in life⁽¹³⁾. Low serum 25(OH)D concentration is associated with obesity and MetS in children and adolescents⁽¹⁴⁾. These interrelationships raise two main questions: (i) Does low serum 25(OH)D concentration cause obesity and MetS or is it a result of these conditions? (ii) What are the possible causes of low serum 25(OH)D concentration and high risk of MetS in obesity?

Associations between 25-hydroxyvitamin D, obesity and metabolic syndrome

Many cross-sectional studies have well documented associations between low serum 25(OH)D concentration, obesity and MetS in children and adolescents. However, there is insufficient evidence to support a causal link. Therefore, low serum 25(OH)D concentration is likely to be a consequence rather than the cause of obesity and MetS. The findings by Fu *et al.*⁽¹⁾ are in accordance with a recent review which showed that low serum 25(OH)D concentration has been associated with cardiometabolic risk factors in children⁽¹⁵⁾. Low serum 25(OH)D concentration

has been found to be associated with MetS (low HDL-cholesterol/plasma adiponectin levels, dyslipidaemia, atherosclerosis, high systolic blood pressure) in obese children⁽¹⁵⁾. Kwon *et al.*⁽¹⁶⁾ reported a significant inverse association of baseline 25(OH)D concentration with serum TAG level at the 5-year follow-up in prepubertal children aged 7–9 years.

In contrast to children and adolescents, low serum 25(OH)D concentration in adults is likely to be the cause of obesity and MetS. Gagnon *et al.*⁽¹⁷⁾ found that baseline 25(OH)D concentration was inversely associated with 5-year risk of MetS, fasting glucose, insulin resistance and TAG. Skaaby *et al.*⁽¹⁸⁾ reported that a 10 nmol/l increase in 25(OH)D level at baseline was associated with a decrease in LDL-cholesterol and TAG at the 5-year follow-up. Mai *et al.*⁽¹⁹⁾ found a significant association between lower serum 25(OH)D concentration and obesity in a follow-up period of 11 years. A 3-year follow-up study found a significant inverse association between baseline 25(OH)D concentration and MetS risk⁽²⁰⁾. The study by Black *et al.*⁽²¹⁾ found a significant inverse association of baseline 25(OH)D concentration with BMI only in young adult women aged 20 years compared with 17-year-old adolescent girls.

Causes of low 25-hydroxyvitamin D and metabolic syndrome in obesity

There are potential mechanisms which would explain why obese individuals are prone to have lower concentration of 25(OH)D and higher risk for MetS than their normal-weight counterparts. In obese adults, the lower serum 25(OH)D concentration could be due high sequestration of vitamin D in body fat tissues, less sunlight exposure or reduced absorption of dietary vitamin D^(22,23), which may lead to less bioavailability of vitamin D⁽²⁴⁾. Fu *et al.*⁽¹⁾ state in their article that inflammation is one of the potential mechanisms that explains the associations between 25(OH)D concentration, obesity and metabolic parameters. While it is a well-known fact that obesity is the major risk factor for developing MetS and CVD, visceral adipose tissue plays a critical role in the pathogenesis of MetS and its health consequences. Adipose tissue secretes various hormonal factors (adipokines) and inflammatory cytokines (IL-6, TNF- α) which act as pro-inflammatory mediators, leading to systemic metabolic dysfunction and adverse cardiovascular consequences. High numbers of stromal macrophages in visceral adipose tissue are thought to play a critical role in stimulating the secretion of inflammatory cytokines. Activation of adipocyte pro-inflammatory pathways reduces demand for TAG storage and increases NEFA levels, which can result in increased levels of insulin resistance in adipose tissue. Therefore, chronic inflammation appears to reside in obese adipose tissues⁽²⁵⁾.

Adipose tissue is the most important reservoir for 25(OH)D and can activate/deactivate 25(OH)D through specific hydroxylation processes. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, interacts with VDR, adaptor molecules and membrane receptors to regulate adipogenic genes involved in the regulation of cell differentiation, metabolism and calcium homeostasis⁽²⁶⁾. Abnormal serum 25(OH)D activation/deactivation ratio and a lack of VDR signalling in adipose tissue could lead to metabolic dysfunction⁽²⁷⁾. In addition to this, 25(OH)D-metabolizing enzymes were found to be differently expressed in subcutaneous and visceral adipose tissue in obese individuals. A cross-sectional study found that expression of the 1 α -hydroxylases CYP27B and CYP2J2 was reduced only in the subcutaneous adipose tissue of obese women⁽²⁸⁾. Of note, low serum 25(OH)D concentration in obese individuals may contribute to inflammatory dysfunction. The potential mechanism could be that low serum 25(OH)D concentration increases macrophage and monocyte cell surface expression of Toll-like receptors (TLR-2, TLR-4), resulting in increased pro-inflammatory cytokine production (IL-6, TNF- α)⁽²⁹⁾.

Conclusions

Low serum 25(OH)D concentration has been associated with obesity and MetS in children and adolescents, but the causal processes linking these interrelationships remain uncertain. Vitamin D deficiency and cardiometabolic risk factors have been reported to be higher in obese children than their normal-weight counterparts. The mechanisms underlying low serum 25(OH)D concentration and high risk of MetS in obese children are unclear, and it remains uncertain whether these lower concentrations might have negative health consequences. Although a systematic review of randomized controlled trials, case-control, cross-sectional and prospective cohort studies showed no beneficial effects of vitamin D supplementation on cardiometabolic risk factors among children⁽³⁰⁾, further studies are needed to determine whether vitamin D supplementation has any beneficial effects on metabolic parameters in obese children.

The study described by Fu *et al.*⁽¹⁾ concludes that low serum 25(OH)D concentration is associated with increased risk for obesity and MetS among US children and adolescents. These authors add new knowledge to the literature by highlighting gender differences in the association between serum 25(OH)D concentration, obesity and metabolic parameters. However, the direction of causality is not established, and the mechanisms underlying such associations are not clearly understood. Further studies are needed to better elucidate the causality and potential mechanisms underlying gender differences in these relationships.



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