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Commentary

Is vitamin D the missing link between childhood obesity and adenovirus-36 infection?

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It may seem irony that nutrition science historically pertained mostly to undernutrition and deficiency syndromes [1] but nowadays prevention, control and treatment of overnutrition, manifested as overweight and obesity, has become the main task of most nutritionists and related professionals [2]. This is because of the severe adverse consequences of obesity, including type 2 diabetes, cardiovascular disease and cancers, [3] and its considerable contribution in global burden of disease [4]. The causes of the obesity pandemic are many including inheritance [5,6]. Though the role of genes in development of obesity cannot be neglected [7], the upsurge of obesity prevalence during the last decades cannot be explained solely by genetics [8]. It is estimated that the occurrence of obesity, both in children and adults, has been tripled since about half a century ago. Just in 2016, some 40% of adults suffered from overweight with 13% affected by obesity [9]. The global prevalence of overweight in children under 5 years increased slightly from 4.8% in 1990 to 5.9% in 2018 [10]. In Iran, over 36% and 33% of adults are affected by overweight and obesity, respectively [11]. It is, based on strong evidence, deeply believed that obesity roots must be mostly sought in the environment [12-14].

A growing body of evidence suggests a determining impact for childhood obesity not only on the affected child's health but on his or her health status later in life. An obese child is more likely to become an obese adult and be affected by countless comorbidities [15]. In 2016, it was estimated that about 340 million children aged 5-19 years were either overweight or obese and in 2019 the number of overweight/obese children was estimated to be 38 million globally [9]. Though sex, parental weight status, maternal education and skipping breakfast are among the predisposing factors for childhood obesity [16], newly emerged evidence of the role of human microbiome on metabolism and obesity [17] has opened a new window to obesity research, *i.e.,* the possible role of microbial, and especially viral, infections in adipogenesis and obesity. Though the associations between several viral infections and obesity have been investigated [18], most studies in this area have examined the possible link between c-36 infection and adipogenesis [19]. Human adenovirus-36 (ADV-36) may induce host adipogenesis through the effect of viral E4orf1 gene on lipogenic enzymes [10,11]. Though some evidence arguably shows a link between ADV-36 infection and adipogenesis [20], this association is still controversial in humans. One meta-analysis study, for instance, did not confirm this association in children [21]. Moreover, the reported increase in prevalence of overweight/obesity just between 1980 and 2013 (27.5% for adults and 47.1% for children) [22] can barely be explained by ADV-36 infection. As a respiratory tract virus [23], ADV-36 must expectedly be more prevalent in economically poor countries, wherein hunger and underweight still is, and possibly continues to be, a problem [24]. It is noteworthy that not all ADV-36 seropositive subjects are overweight or obese [25,26]. Therefore, the key question is "what can modulate the association between ADV-36 infection and adiposity?". In an effort to find a reply to this question, we conducted a descriptive and comparative study on normal weight, overweight and obese children. We examined the association between body mass index, serum neutralizing anti-ADV-36 antibody and 25-hydroxycalciferol

(25(OH)D), the main indicator of vitamin D status. Our findings revealed a significant association between anti-ADV-36-Ab and weight status so that for each unit increment of anti-ADV36-Ab, the chance of increase in weight was 8.5 times (OR: 8.5, p=0.029). However, this association was disappeared when 25(OH)D was introduced into the model. Interestingly, for each unit increase in circulating 25(OH)D concentration, the chance of increase in weight reduced 5% (OR: 0.95, p=0.012) [27].

Vitamin D has so-called calcemic and non-calcemic functions including anti-inflammatory [28], antioxidant [29] and antiviral properties [30,31] possibly due to up-regulation of antimicrobial peptides such as cathelcidins (LL-37) and β-defensin 2 [30,32]. The key point is that there is an inverse relationship between vitamin D status and adiposity [27,33]. Therefore, with decreasing vitamin D status, there could be suboptimal immune response to the microbes, including ADV-36, and more adiposity. This notion needs to be examined by further studies both descriptive, including considering vitamin D status of the subjects, and well-designed clinical trials to investigate the effect of vitamin D supplementation on serum anti-ADV-36 antibody. Whatever the results will be, optimization of vitamin D status of children from birth is a necessity.

Finally, we deeply believe that the creation of each human body system has a philosophy beneath. The existence philosophy of the musculoskeletal system is undoubtedly using it to move. Our ancestor, hunter-gatherer Homo sapiens, was bare, therefore fully exposed to sun, and had to be extremely physically active to survive [34,35]. As a result, he was not affected by vitamin D deficiency, at least during sunny seasons, and never became obese, either [36]. During centuries that is like a blink in evolution, humans became covered by clothes and sedentary in life. Obesity and perhaps many other human diseases are, therefore, the cost of moving against the existence philosophy of our body systems.

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