



EDITORIAL

## Vitamin D deficiency (VDD): the culprit of cardiometabolic diseases? ☆,☆☆

### Deficiência de vitamina D (DVD): o responsável por doenças cardiometabólicas?

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It's commonly believed that vitamin D only plays a role in bone health maintenance and calcium phosphate homeostasis regulation. This limited recognition of vitamin D's function can be traced back to its discovery through the fight against rickets almost a century ago. Further studies revealed several other roles vitamin D plays in the human body; its importance in bone related health is merely the tip of the iceberg.

Until now, studies have highlighted that the receptor for vitamin D is quite ubiquitous, residing in almost all the major human organs, including the heart, brain, livers, kidneys, bones, urinary system, and parathyroid glands.<sup>1,2</sup> It's worth noting that vitamin D receptors are expressed in some seemingly unrelated tissues, for example, all kinds of immune cells, pancreatic  $\beta$  cells, neurons, as well as vascular smooth cells, epithelial cells, and cardiomyocytes in the cardiovascular system. Through those widely distributed receptors, vitamin D regulates the expression of over 200 genes directly or indirectly.<sup>3</sup> It partially explains why vitamin D deficiency has been reported to be associated with different kinds of diseases, such as hypertension, multiple sclerosis, colon cancer, and diabetes. Due to the gene polymorphism of vitamin D receptors, there is individual variation in vitamin D reaction. Recent progress in the study of the vitamin D

receptor regulating mechanism has greatly advanced the understanding of diseases related to this vitamin.

Among all research on the role of vitamin D beyond the bone system, the correlation between vitamin D deficiency (VDD) and cardiometabolic diseases has been a hotspot. Is there any causative relationship between VDD and cardiometabolic diseases? If so, which is the cause and which is the consequence? Although there is not yet a definitive answer, accumulating evidence clearly points to the close correlation between the two.

Research from different fields and perspectives provides evidence supporting the conclusion that VDD and cardiometabolic diseases are closely related. Firstly, combined results from the NHANES III cross-sectional study, the HPFS cohort study, and the NHS I research revealed a reverse correlation between serum 25(OH) D levels and blood pressure.<sup>4,5</sup> Another detailed randomized control study further confirmed that vitamin D lowered the systolic pressure, while leaving the diastolic pressure unaffected.<sup>6,7</sup> Secondly, the current knowledge of VDD and diabetes mellitus type 2 (DMT2) is largely derived from epidemic studies. A cross-sectional study indicated that serum 25(OH)D levels in DMT2 were dramatically reduced.<sup>8</sup> A cohort study demonstrated that low levels of 25(OH)D could be used as a biomarker to predict the development and progress of DMT2.<sup>9</sup> It is believed that vitamin D supplementation could regulate insulin sensitivity, and thus ameliorate insulin resistance and even benefit pancreatic  $\beta$  cell secretion.<sup>10</sup> It has also been demonstrated that adult VDD baseline levels are reversely correlated with ten-year risk of metabolic syndrome, and independent of factors such as gender, age, weight, season of the year, and smoking.<sup>9</sup> A cross-sectional study confirmed that VDD was linked to the development of metabolic

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syndrome in adults, young adults, and adolescents,<sup>11</sup> and that VDD was reversely correlated with five-year waistline, triglycerides (TG), fasting blood glucose levels, and insulin resistance. Additionally, a recent cohort study confirmed that proper 25(OH)D levels could largely reduce all-cause and cardiovascular mortality in patients with metabolic syndrome.<sup>12</sup> Lastly, cross-sectional and prospective cohort studies have observed a higher incidence of cardiovascular disease in the VDD population,<sup>13</sup> and VDD greatly increased the risk of cardiac death caused by heart failure and sudden cardiac arrest in White coronary angiography candidates.<sup>14</sup>

The abovementioned studies barely addressed children and adolescents, and Kelishadi et al.<sup>15</sup> explored the relationship among VDD, insulin resistance, and related cardiometabolic disease risk factors such as blood glucose, blood pressure, blood lipids, and obesity in obese children with vitamin D supplementation. The authors concluded that vitamin D supplementation was beneficial to cardiometabolic disease control in obese children and adolescents. This is the evidence regarding the correlation between VDD and cardiometabolic diseases in younger populations.

However, there are some caveats in the research by Kelishadi et al.<sup>15</sup> Firstly, a control group of normal-weight children is necessary, since there was no data demonstrating that vitamin D levels in the obese children was lower than that of eutrophic children; this was assumed by the authors based on a previous result.<sup>16</sup> If there were no obvious differences of vitamin D levels between the subjects of the study and the eutrophic population, the rationale of vitamin D interference would be a concern.

Secondly, to meet the statistical analysis requirement, the authors carefully designed the experiment to guarantee that there were at least 20 samples in each group, and that there was positive result in each group. However, the authors didn't describe in detail the standards applied to decide which samples would be included, especially regarding the differentiation between simple obesity from secondary obesity that should be excluded. It's unknown whether vitamin D supplementation would be effective in secondary obesity patients, in whom VDD is probable. It was unclear why the authors chose obese children and adolescents aged 10 to 16 years old, and it is quite possible that the data accuracy and conclusion validity might have been compromised due to the inconsistency of the baseline for different populations included in the study. To define cardiometabolic risk factors and metabolic syndrome, the authors applied the latest cut-off points provided by the National Heart, Lung, and Blood Institute for the pediatric age group and the continuous value of metabolic syndrome (cMetS) score, as recommended by the American Diabetes Association and by the European Association for the Study of Diabetes for children and adolescents, respectively. It is a concern whether these standards are appropriate for the study and whether they reflect the true situation of the population of interest. Analyzing previous research on VDD and cardiometabolic diseases, it's natural to hypothesize that a small sample pool and improper sample selection are important reasons for the negative results obtained by the authors.<sup>17,18</sup> Therefore, if the authors had expanded their sample size and applied more stringent sample selection standards, they could have possibly observed the impact

of vitamin D to fasting blood glucose level and blood pressure, rendering their result more convincing and valuable to clinical and practical applications.

Moreover, the authors should have considered drug delivery and efficacy. Vitamin D capsules were orally administered in the study, and it is common sense that oral delivery is subject to potential absorption difficulty, thus affecting the vitamin D level of the study subjects and interfering with the results and conclusions. Furthermore, the authors should have taken into account the vitamin D supplement dosage, the frequency of administration, and the potential adverse effects of vitamin D.

Additionally, the length of vitamin D supplementation treatment and validity of the statistical analysis are potential factors that affect the study result. For example, it would have been constructive to compare within male and female sub-groups.

In short, due to all the caveats of the experiment design and analysis described above, although Kelishadi et al.<sup>15</sup> obtained positive data supporting their hypothesis that VDD is correlated with cardiometabolic diseases in younger populations, caution should be exerted when interpreting their results into practical applications. It would be better to first confirm their result with larger samples pools and more careful study designs if necessary. For instance, Kelishadi et al.<sup>15</sup> mentioned that there are several reports on the irrelevance of VDD and cardiometabolic diseases in different age populations. A similar result was reported by the author in another article.<sup>19</sup> By summarizing the available animal model or human research on this issue, regardless of the method used (simple observation or systematic random control study), a great discrepancy was observed regarding the final conclusion, i.e., it is still poorly understood whether there is causative relationship between VDD and cardiometabolic diseases. Better-designed, large randomized control trials of higher quality are necessary to further address the true role of VDD in cardiometabolic diseases.

To summarize, although there are limitations to the study by Kelishadi et al.,<sup>15</sup> their results are still valuable to the field and advance the VDD research by expanding the analysis to the younger obese population, which is more prone to cardiovascular diseases. It is a pioneering exploration on the benefits of vitamin D supplementation to insulin resistance and obesity-related cardiovascular risk factors in a non-adult population. Not only does it meet the current need to strengthen the study and prevention of chronic non-infectious diseases worldwide, it also opens a window to help pave the road for further study on VDD and cardiometabolic diseases.

## Conflicts of interest

The author declares no conflicts of interest.

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