Vitamin D and Epicardial Adipose Tissue

To the Editor

Gurses et al., in this Journal, showed that vitamin D deficiency is associated with a relevant increase in epicardial adipose tissue (EAT) in pre-menopausal women. This evidence should be apparently related to previous reports showing that vitamin D deficiency induces hypertrophy in cardiomyocytes, associated with decreased expression of the vitamin D receptor (VDR) suppressor of cytokine signaling 3 (SOCS3) and increased expression of inflammatory markers (IL-6, TNF-α, MCP-1/CCL2) in EAT. These data would suggest that vitamin D deficiency in EAT might play a major role as a pro-inflammatory factor and conversely vitamin D supplementation an anti-inflammatory and cardioprotective action. However, vitamin D supplementation did not give the expected effect on EAT thickness.

Honestly, vitamin D supplementation appears to have a wider spectrum of cardioprotective effects than previously suggested. In the paper by Gurses et al., the authors showed a negative correlation between serum 25-OH vit.D3 (calcidiol) and EAT thickness. Actually, low levels of 25-hydroxylated vitamin D3 were previously associated with slow coronary flow, endothelial dysfunction, and subclinical atherosclerosis. While an apparently strong correlation between EAT thickness and metabolic markers was shown, vitamin D intake was unable to produce a positive outcome. The role of EAT in these mechanisms remains to be fully elucidated and detailed understanding of the EAT immune microenvironment during inflammation might shed light on the role of epicardial adipocytes in the cardiac physiology. Adipocyte size in EAT seems to be negatively related with inflammation and metabolic syndrome, although on adiposity further papers reported contrasting results. In our recent study, vitamin D prevented lipopolysaccharide-induced inflammatory reduction of 3T3-L1 size and dampened the expression of pro-inflammatory genes. However, this in vitro study cannot be directly related to the different complexity of the whole organism, where circulating levels of calcidiol do not necessarily account for the rate of calcitriol activity in the different local cell microenvironments. Gurses et al. did not evaluate the epicardial tissue with respect to the adipocyte/pre-adipocyte ratio and adipocyte size, limiting their investigation to a transthoracic two-dimensional guided M-mode echocardiogram.

It would be very interesting to evaluate the pro-inflammatory profiles related to EAT thickness from surgical biopsies in order to ascertain if vitamin D supplementation might have a fundamental role in the EAT immune microenvironment. Therefore, the authors were not able to explain if EAT thickness was related to changes in the adipocyte size caused by inflammation or to an increase in the pre-adipocyte component, as a close relationship between pre-adipocyte and adipose tissue resident macrophages has been reported. Furthermore, the role of estrogen and VDR was not further addressed.

Despite the important and novel results shown by these authors in the study, it appears quite discouraging the difficulty in achieving best performance and promising outcomes with vitamin D dietary supplementation.

The main weakness of the study by Gurses et al. concerns the inability of exogenous vitamin D to revert EAT hypertrophy. Following treatment with the vitamin, the 25-hydroxylated form increased its serum level by about three-fold. Actually, in pre-menopausal women, health and quality of life may be impaired by “insufficient” plasma levels of vitamin D, calculated as 25-OH vit. D3 levels of ≤29 ng/mL, very close to the data reported in the paper by Gurses et al. (31.40 ± 8.60). This may even suggest that a serum level of ≤30 ng/mL 25-OH vit. D3 is insufficient to act on EAT thickness. Another puzzling issue is how much calcidiol is converted to the 1,25-dihydroxylated form [1α,25-(OH)2 vit. D3] by epicardial adipocytes. Taking into account that cholecalciferol induces gene expression of the main 25-hydroxylases in the adipocyte, this issue would deserve further investigation.

Growing evidence suggests that the vitamin D system has a range of physiological functions, with vitamin D deficiency contributing to the pathogenesis of several major diseases, including obesity, metabolic syndrome, and cardiovascular disease. Recent studies suggest that adipose tissue may be a direct target of vitamin D. The expression of both VDR and 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) genes has been shown in murine and human adipocytes. There is evidence that vitamin D affects body fat mass by inhibiting adipogenic transcription factors and lipid accumulation during adipocyte differentiation and furthermore exerts an anti-inflammatory activity; actually, some recent studies demonstrate that vitamin D metabolites also influence adipokine production and the...
inflammatory response in adipose tissue. Therefore, vitamin D deficiency may compromise the normal metabolic functioning of adipose tissue besides its effects on innate and acquired immunity. Given the importance of the tissue in energy balance, lipid metabolism, and inflammation in obesity, understanding the mechanisms of action of vitamin D in adipocytes may have a significant impact on the maintenance of metabolic health.

Conflicts of Interest

The author states that he has no conflict of interest.

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Salvatore Chirumbolo

Head of the Laboratory of Physiopathology of Obesity, Department of Medicine-Section of Geriatry, University of Verona, Verona, Italy

Address for correspondence: Salvatore Chirumbolo, Head of the Laboratory of Physiopathology of Obesity, Department of Medicine-Section of Geriatry, University of Verona, Italy, Policlinico GB Rossi, piazzale AL Scuro 10, 37134 Verona-ITALY

E-mail: salvatore.chirumbolo@univr.it

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