Editorial article

Vitamin D deficiency: One more piece of the puzzle of cardiovascular risk in human immunodeficiency virus-infected patients?

Deficiencia de vitamina D: ¿una pieza más en el puzle del riesgo cardiovascular de los pacientes con infección por el virus de la inmunodeficiencia humana?

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Cardiovascular disease has become an important cause of morbidity and mortality in people infected with HIV. With the introduction of new antiretroviral drugs with a better metabolic profile than those employed in the past, the inflammation and immune activation associated with the virus have become increasingly relevant in the etiopathogeny of atherosclerosis. It is known that HIV replication can induce endothelial activation that favours the adhesion and activation of leukocytes and platelets contributing to maintaining a pro-inflammatory and procoagulant state. Although the replication of the virus has been considered to be the fundamental trigger of immune system activation, persisting inflammation and immune activation in patients on effective antiretroviral treatment (ART) has also been found in "elite controllers" (EC), or in people with undetectable stable viral load who are not on ART. This suggests that there are additional factors that trigger immune activation and could also be involved in the accelerated progression of atherosclerosis in people infected with HIV and with good virological control.

In addition to its effects on the bone and on calcium homeostasis, vitamin D could play an important role in the cardiovascular system. There are an increasing number of experimental and clinical studies that demonstrate that low vitamin D levels are associated with the development of cardiovascular disease through different mechanisms. Beneficial effects of vitamin D in the endothelial function have been described in smooth muscle cells and in the inflammatory and immune response. Data from in vitro and animal-model studies confirm that vitamin D induces an increase in the amount of nitric oxide released by the endothelium, an inhibition of the aggregation and adhesion of platelets and leukocytes, a reduction of oxidative stress, a relaxation of vascular muscle tone, and a reduction in the release of vasoconstrictor metabolites, an inhibition of the proliferation and migration of vascular smooth muscle cells, of the release of pro-inflammatory cytokines and a modulation of the inflammatory response. In addition, vitamin D could indirectly protect from atherosclerosis through the diminution of insulin resistance and the improvement of the lipid profile and blood pressure. All this leads us to consider that a low vitamin D concentration can constitute an additional cardiovascular risk factor.

Low plasma concentrations of vitamin D are frequent in the general population. In Spain, the prevalence of 25(OH)D values inferior to 20 ng/ml was 34% in a population cohort that included more than 1200 patients. Several observational studies support the association of vitamin D deficiency and cardiovascular disease. The retrospective analysis of an extensive population database that included more than 27 000 patients noted a strong association of vitamin D levels with coronary disease and acute myocardial infarction. Several prospective studies with a follow-up of up to 10 years have reported greater cardiovascular mortality and a greater number of cardiovascular episodes in subjects with the lowest levels of vitamin D, after adjusting for different confounding factors. However, in other studies, this association has not been confirmed after having adjusted for other risk factors.

In subjects infected with HIV, the frequency of vitamin D deficiency is very high, with figures that range between 60% and 88%. Even though there is no epidemiological data available for this population that shows greater incidence of cardiovascular episodes, studies exist that have found an association between vitamin D deficiency and subclinical atherosclerosis. In a case control study that included 149 patients infected with HIV, the lowest vitamin D concentrations were associated with a ten-fold higher risk of having carotid intima-media thickness (CIMT) greater than the median. In patients on stable ART, a significant correlation has been found between the vitamin D concentration and flow-dependent vasodilation (FDV), as a measure of endothelial function. Vitamin D deficiency, defined by concentrations of 25(OH)D<10 ng/ml, was independently associated with significant coronary stenosis measured with coronary CT angiography in 674 asymptomatic

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Afro-American subjects infected with HIV\textsuperscript{12}. The same study also found an independent association with coronary calcification\textsuperscript{19}. On the other hand, serum 25(OH)D concentration has been found to correlate negatively with insulin resistance\textsuperscript{14}.

Despite the large number of observational studies, to date, few randomised clinical studies assessing the effects of treatment with vitamin D supplements on arteriosclerosis and applying clinical response criteria have been conducted. These studies have shown no benefits from treatment with respect to the development of cardiovascular events, and the effects on other cardiovascular risk factors or on surrogate markers of atherosclerosis have been uneven\textsuperscript{15,16}. In a large clinical trial in post-menopausal women (The Women’s Health Initiative) who received treatment with vitamin D supplements and calcium over 7 years, no reduction was found in the incidence of cardiovascular disease 5 years after the intervention had ended\textsuperscript{17}. Treatment with vitamin D supplements over 12 months, accompanied by a program of weight reduction, diminished the concentrations of α tumor necrosis factor and triglycerides in subjects with overweight in a double-blind, placebo-controlled study\textsuperscript{18}. Unlike these studies, most of the randomised intervention trials that have assessed the influence of treatment with vitamin D on atherosclerosis have generally been of short duration. In two 12-week clinical trials, no benefits were found from vitamin D supplement in FDV or in the inflammatory biomarkers in diabetic patients\textsuperscript{19}, or in inflammatory biomarkers in patients with coronary disease, with the exception of the intracellular adhesion molecule\textsuperscript{20}. In a study in which daily doses of 2500 IU were used over 4 months, there were no changes in FDV, in the speed of the carotid-femoral pulse wave velocity, in the index of aortic increase or in CRP levels\textsuperscript{21}. Tests with a single oral dose have also shown negative results in healthy women and in patients with peripheral arterial disease\textsuperscript{22,23}. In contrast, other short-term tests have demonstrated an improvement in some of the surrogate markers of atherosclerosis, such as an increase in FDV in Afro-American adults with overweight\textsuperscript{24}, a reduction in the progression of aortic rigidity in young people of black race\textsuperscript{25}, a reduction of blood pressure in elderly women\textsuperscript{26} or an improvement in the lipid profile in women with overweight and obesity who presented an increase in the concentrations of HDL-cholesterol and ApoA-I, and in the LDL-cholesterol:apoB-100 ratio, in the adjusted analysis\textsuperscript{27}.

To date, only one small controlled clinical trial has been conducted with placebo in patients infected with HIV. In 45 patients with concentrations of 25 (OH)D<20 ng/ml, treatment with a daily dose of 4000 IU over 12 weeks slightly improved the plasma concentration of vitamin D and reduced total cholesterol and non-HDL cholesterol, but insulin resistance worsened with no changes in the endothelial function measured by FDV\textsuperscript{28}.

There is still uncertainty regarding the role played by vitamin D in cardiovascular disease and in the value of treatment to prevent it. Additional information is needed from appropriate randomised clinical studies to assess the role of vitamin D, preferably in the development of clinical events, or from well-validated surrogate markers of atherosclerosis, such as carotid intima-media thickness (cIMT). It is still unknown if long-term treatment or higher doses of vitamin D could have a favourable effect on the progression of atherosclerosis. Ideally, the effectiveness of the intervention on the plasma concentrations of vitamin D should also be measured to interpret the results of cardiovascular disease treatment. The information available is even scarcer in people infected with HIV. Since these patients have an immune activation status, pro-inflammatory and procoagulant conditions compared to those of the seronegative population, the effects of treatment with vitamin D on these mechanisms should be further studied. There is still little information about the effect of vitamin D on other cardiovascular risk factors such as blood pressure, lipid profile and insulin resistance in these patients.

In the new era of ART, concerns about comorbidities have replaced those of the infection and immunodeficiency control\textsuperscript{29}. Problems related to bone\textsuperscript{30} and the cardiovascular system are more frequent in people infected with HIV than in non-infected people, and the incidence of these problems is expected to increase as this population ages. For the moment, the treatment of comorbidities is similar to what is indicated in the general population. Treatment with vitamin D supplements is recommended in cases of deficiency, or if osteoporosis, osteomalacia or hyperparathyroidism exist. If vitamin D deficiency were to be confirmed as a real cardiovascular risk factor, additional treatment criteria could be considered that would contribute to bringing the prognosis of people infected with HIV closer to that of non-infected subjects.

References


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