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EDITORIAL

Does a better vitamin D status help to reduce cardiovascular risks and events?

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Vitamin D is one and maybe even the most frequently used "drug" in the world as it is recommended as supplement during the early years of life from infancy onwards, and is also recommended systematically for all elderly subjects with little exposure to sunlight. This is mainly inspired by the essential role of the vitamin D endocrine system for bone health [1–3]. The vitamin D receptor and activating enzyme, *CYP27B1*, are both fairly generally expressed in most tissues and the vitamin D hormone, $1,25(OH)_2D$, also regulates a great number of genes, far more than needed for calcium transport. Therefore the question and hypothesis arise that the vitamin D endocrine system would have many extra-skeletal effects and that vitamin D supplementation may help to reduce the burden of nearly all major human diseases [1–3]. The cardiovascular system may well be such non classical target tissue for vitamin D action based on a vast and rapidly increasing number of publications and reviews in basic and clinical journals, and even in the lay press. Two manuscripts published in the present issue of endocrine add new data for this debate.

Ellis et al. [4] report that cardio respiratory fitness [measured by respiratory quotient (RQ) after moderate exercise and VO_2 max during a graded treadmill protocol] of women, aged 60 or more, is inversely correlated with serum 25OHD levels, albeit that this relation was only significant in Afro-Americans and not in Caucasians. The RQ data also suggest that a better vitamin D status was also associated with greater fat oxidation during sub maximal exercise. The study is however handicapped by the low number of subjects and by inconsistency between data in Afro-Americans and Caucasians. Moreover reverse causality is not discussed as it may well be that elderly women with greater habitual exercise have better VO_2 max and more exposure to sunlight during exercise. The second study tried to link carotid intima-media thickness (measured by ultrasonography and known to be a good surrogate marker of cardiovascular risks and events) with serum 25OHD and parathyroid hormone levels in a mixed population of vitamin D deficient (mean serum 25OHD of 13 ng/ml) patients recently admitted to a general hospital [5]. Carotid intima-media thickness correlated positively with age and body mass index, as expected, but not with serum 25OHD or parathyroid hormaone levels. There are many possible reasons for this lack of correlation including the low number of subjects with good vitamin D status and the complex mixture of patients.

These two studies are in fact a good example of what is presently known with regard to the link between vitamin D status and cardiovascular risks and events. Such a link is plausible as very severe vitamin D deficiency (such as in *Cyp27B1* null mice) or resistance (such as in Vdr null mice) is causing renin-mediated hypertension, decreased fibrinolysis and increased thrombogenicity [1–3, 6]. Systemic or cardiomyocyte specific Vdr knock out also causes cardiac hypertrophy and cardiac fibrosis. In vitro studies have also shown many beneficial effects of $1,25(OH)_2D$ on endothelial, smooth muscle or cardiomyocyte function [1–3]. A large number of observational cross sectional or prospective studies also linked a low vitamin D status with higher cardiovascular risk, events or mortality, especially for subjects with serum 25OHD levels below 25 ng/ml [7, 8]. The link between blood pressure and vitamin D status received great attention with mixed results as PTH was better linked with hypertension than 25OHD status [9]. The

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same conclusion was drawn with regard to cardiovascular diseases in a large meta-analysis by the same authors [10]. A low vitamin D status may also accelerate the cardiovascular problems of patients with chronic renal failure, especially as such patients frequently lack both the precursor 25OHD (for transforming into $1,25(OH)_2D$ in all cells of the body expressing *CYP27B1*) and $1,25(OH)_2D$. An analysis of human data is further complicated as vitamin D status influences parathyroid hormone levels (a well-known independent cardiovascular risk factor) and calcium intake alone may provide independent risks and benefits.

Too much vitamin D however may also be bad for the cardiovascular system as vitamin D toxicity is known to generate ectopic calcification in different tissues but especially in the vascular wall by stimulating the transition of endothelial or smooth muscle cells into osteoblast-like cells. So based on preclinical data and on many observational studies too little and too much vitamin D convey a cardiovascular risk in normal subjects as well as in patients with chronic renal failure. To formally proof causality and to define which levels of 25OHD provide the best protection, randomized controlled trials are needed. A meta-analysis of eight randomized controlled trials in hypertensive men and women demonstrated a small benefit of vitamin D supplementation on diastolic but not on systolic blood pressure [11]. Randomized controlled trials so have not yet provided formal proof of beneficial cardiovascular effects although a modest reduction in overall mortality has been observed after vitamin D supplementation [1–3, 6]. Such a beneficial effect of treatment with active vitamin D hormone or analogs in patients with severe chronic failure has been repeatedly reported but few of these studies fulfill the criteria of bona fide randomized controlled trials s. As obesity, diabetes and the metabolic syndrome are clearly linked to cardiovascular events and mortality, the relation with vitamin D status may be even more complex as vitamin D deficiency in mice induces resistance to diet-induced obesity while the opposite seems to be operational in humans [12]. So clearly more research is needed and several randomized controlled trials are in fact ongoing. In the meantime the best practical approach should be to implement what is proven based on evidence based medicine [1].

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