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ARTYKUŁ POGLĄDOWY / *REVIEW ARTICLE*

Vitamin D and statins: action in preventing cardiovascular events

Witamina D i statyny w zapobieganiu zdarzeniom sercowo-naczyniowym

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INTRODUCTION

Statins are widely used compounds in hypercholesterolemic patients reducing the risk of cardiovascular (CV) events. As a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are extremely effective at reducing low-density lipoprotein (LDL) cholesterol and have been demonstrated to reduce mortality and the risk of coronary heart disease (CHD) in a number of large primary and secondary prevention studies [1]. In recent years, however, a number of additional non-lipid-lowering, or «pleiotropic», effects of statins have been suggested as contributing to their efficacy in CV disease. Statins have been shown to reduce CHD events by as much as 37% in clinical trials, not only by lowering LDL cholesterol levels but also by other effects in inflammation, thrombogenesis, and arterial vasomotor function [2]. Moreover, an effect of statin on vitamin D metabolism has been suggested as an additional mechanism of action by which statins may exert pleiotropic effects [3].

Vitamin D receptors are present in a large variety of cell types including myocytes, cardiomyocytes, pancreatic beta-cells, vascular endothelial cells, neurons, immune cells, and osteoblast. Vitamin D has been shown to be important in many common diseases other than the well-understood rickets in children and osteomalacia and osteoporosis in adults. Vitamin D deficiency seems to predispose to hypertension, diabetes and the metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation [4]. A study of male health professionals showed a two-fold increased risk of myocardial infarction (MI) in subjects who were vitamin D deficient compared to those in the sufficient range [5]. In a different observational study, Pilz et al. [6] found that for an approximate 20 ng/mL increase in 25-hydroxyvitamin D, there was a 33% decrease in the risk of a fatal stroke. Furthermore, several studies have shown that an increased exposure to sunlight protects against CHD through production of 25(OH)D [7, 8].

It is extremely important, therefore, to establish the relation between statin and vitamin D level in CV disease prevention.

VITAMIN D METABOLISM AND ACTION

Vitamin D is photosynthesised in the human epidermis as a product of 7-dehydrocholesterol (7-DHC) irradiation with UVB. This process produces a previtamin D, which is thermo-converted to vitamin D_3 (Fig. 1). Excessive exposure to UVB results in degradation of vitamin D as well as previtamin D to

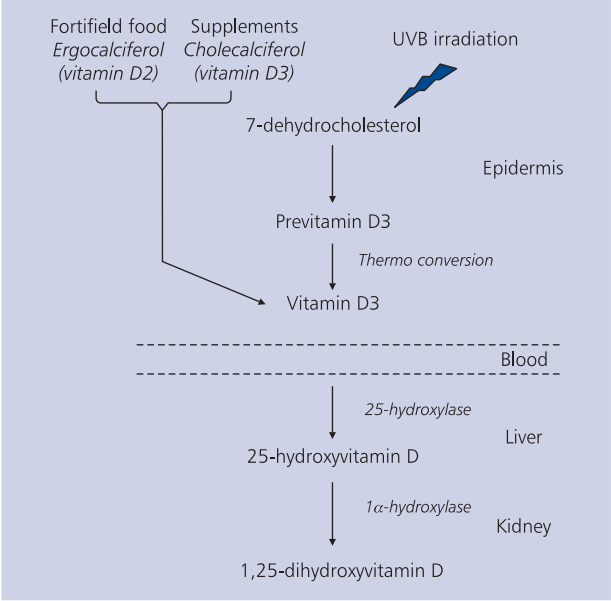

Figure 1. Vitamin D metabolism pathway

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inactive photoproducts. In a case of oral supplementation, vitamin D (D_3 and D_2) undergoes intestinal absorption, and is transferred with chylomicron remnants to the venal blood. Once in the circulation, vitamin D is taken up by the liver where it is converted to its first metabolite 25-hydroxyvitamin D (25-OHD, preferred blood level 75–150 nmol/L), which in turn is further hydroxylated in the kidney to form the active, hormonal form of vitamin D — 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The concentration of the hormonal form of vitamin D is in the picomolar range and is regulated by affecting its production and catabolism by such factors as calcium and phosphate ions, fibroblast growth factor 23 (FGF-23), and parathormone (PTH). $1,25(OH)_2D$ also feedback-downregulates its own production, at the same time downregulating PTH excretion by the parathyroid glands, and stimulating kidney 24-hydroxylase which conducts the first reaction of the catabolic inactivation of vitamin D [9, 10].

The so-called 'classic' action of vitamin D is focused on calcium and phosphorus homeostasis of the human organism. In response to a decrease in calcium concentration in the circulation, there is an increase in PTH secretion from the parathyroid gland. This powerful hormone acts to quickly replenish the blood calcium stores by rapidly switching the osteoclasts and osteoblast cells system into bone resorption mode, leading to mobilisation of bone calcium reserve and decreasing kidney calcium excretion. At the same time, PTH acts as an inducer kidney 1-hydroxylase which results in enhanced synthesis of $1,25(OH)_2D$ which in turn increases intestinal calcium absorption, further activates the osteoclast/osteoblast system, feedback-downregulates its own production, and stimulates an array of other catabolic genes involved in bone turnover. A decrease of phosphate concentration in blood serum stimulates 1-hydroxylase through the decreased concentration of FGF23, leading to an increased concentration of the hormonal form of vitamin D in the circulation. The increased $1,25(OH)_2D$ stimulates intestinal phosphate absorption and kidney phosphate retention, and bone resorption process to make up for the phosphate deficit in the circulation. Therefore, vitamin D acts as a bone protection agent only in a situation of proper supplementation of minerals and vitamin D itself.

CORRELATION BETWEEN DIFFERENT STATINS AND VITAMIN D LEVEL

Because of the convergence effect of statin therapy and vitamin D supplementation in many ischaemic heart disease prevention studies, scientists have been since the early 1990s investigating the pleiotropic effect of statins via the vitamin D metabolic pathway [11]. Surprisingly, observational studies have shown different statin influences on vitamin D serum levels depending on the type of statin administered.

In the STATIN-D study, there was a significant increase in 25-hydroxyvitamin D from 11.8 to 35.2 ng/mL with rosuvastatin treatment (10 mg/day), whereas no significant change in 25(OH)D was observed with fluvastatin treatment (80 mg/day) [12]. In the JUPITER study, rosuvastatin at doses of 20 mg/daily increased 25(OH)D in such a way that the participants on average went from deficient to sufficient in two months. The difference in CV risk between those deficient and sufficient in vitamin D in observational studies (described above) was similar to the risk reduction found in JUPITER [12, 13]. On the other hand, the study of Rejnmark et al. [14] found no effect of simvastatin (40 mg/day) on vitamin D metabolites status. As far as atorvastatin is concerned, Sathyapalan et al. [15] reported that its treatment (20 mg/day) increased by 47% 25(OH)D concentrations in patients with polycystic ovary syndrome.

PROPOSED MECHANISMS OF INTERACTION BETWEEN VITAMIN D AND STATINS

As we can see, the evidence for the importance of vitamin D status in terms of the risk of CV events is strong and growing. To translate these observations into molecular language, scientists have tried to come up with a hypothesis that could explain the similarity between the benefits of vitamin D and the benefits of statin therapy.

Cholesterol and 25-hydroxyvitamin D have the same precursor, namely 7-dehydrocholesterol, which is synthesised in a multiple-reaction pathway from acetyl-CoA with the hydroxymethylglutaryl-CoA (HMG-CoA)-reductase activity [16]. Levels of 7-dehydrocholesterol in the serum of healthy individuals are around 0.3 μM and are directly correlated with the activity of the HMG-CoA-reductase of the liver [17]. Statins, by reducing HMG-CoA-reductase activity, may decrease the level of circulating 7-dehydrocholesterol. This view is supported by cell culture experiments in which simvastatin treatment increased the expression of genes involved in cholesterol synthesis, including the Δ-7-sterol reductase [18]. Hence, it might be expected that there would be a reduction of 25(OH)D synthesis with statins, although the opposite was in fact shown in the described studies.

The hypothesis that the metabolic pathways of atorvastatin and vitamin D somehow cross is supported by the study of Schwartz [19]. There was reason to expect that increasing vitamin D metabolites might enhance the clearance of statin and its active metabolites and reduce the time-integrated statin concentration. In the Schwartz study, vitamin D supplementation indeed lowered atorvastatin and active metabolite concentrations, yet unexpectedly had synergistic effects on cholesterol concentrations.

A different influence on 25(OH)D level of each statin has to be stressed when we try to come up with a theoretical explanation. It has been proposed that differences in the bioavailability and pattern of liver uptake between statins may explain their different actions on vitamin D metabolism [11].

CYP3A4 catabolises 25(OH)D in the liver. Statins are extensively metabolised by CYP3A4 and CYP3A5. Thus, Yavuz et al. [11] have suggested that this CYP3A4 catabolic pathway may be responsible for the increased 25(OH)D levels with the statin treatment which are known to cause drug interactions by inhibiting the CYP enzyme system. Fluvastatin is a lipophylic statin compound, whereas rosuvastatin is a hydrophilic statin and has a relatively higher bioavailability. The hydrophilic rosuvastatin has a slow rate of diffusion across cell membranes, but is taken up rapidly by hepatocytes via active transporter proteins. Such differences may translate into different actions on vitamin D.

Finally, Grimes [20] has suggested that statins might act as vitamin D analogues and compete with vitamin D metabolites for its receptors. Although rosuvastatin does not appear to significantly bind to the vitamin D receptor, it does bind to the glucocorticoid receptor and the thyroid beta-1 receptor, both of which strongly bind both 25(OH)D and 1,25-dihydroxyvitamin D, which is also elevated by rosuvastatin.

CONCLUSIONS

Evolving data indicates that vitamin D deficiency is playing an important role in the genesis of coronary risk factors and adverse CV events. It seems to predispose to hypertension, diabetes and metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation. Overwhelming evidence supports the importance of vitamin D status in the pathogenesis and progression of CV disease.

The entire thesis set out above has tried to explain the observed interaction between statin and vitamin D serum level in CV disease prevention. Undoubtedly it is too complex, and no simple explanation is sufficient to fully molecularly describe the observations. In our opinion, the key to understanding the complexity of the interaction between statin and vitamin D lies in the fact that vitamin D supplementation decreases statin metabolites concentration. Although the study of Schwartz [19] involved a small number of patients, it focused the attention on the CYP3A4 enzymatic pathway. Large randomised controlled trials are needed to firmly establish the relevance of vitamin D status to vascular health and also statins' effects in reducing CV risk.

Conflict of interest: *none declared*

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