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EDITORIAL

# Statins and Vitamin D

## Editorial to: "Increased Levels of 25 Hydroxyvitamin D and 1,25-Dihydroxyvitamin D After Rosuvastatin Treatment: A Novel Pleiotropic Effect of Statins?" by Bunyamin Yavuz et al.

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The diet-cholesterol-heart hypothesis dominated medical thinking for the latter half of the 20th century and it still persists. The diet component has so many inconsistencies that it is unsustainable [1–3]. It continues in popular folklore and government dietary policies but it seems to have been quietly dropped by most cholesterol-heart researchers. The original cholesterol-heart studies [4, 5] were undisputed at the time but the evidence is now not quite so clear. The Framingham study indicated that a significant relationship between high serum cholesterol and reduced life expectancy applies only to young men [6]. The assumption has been that a high cholesterol level is not just associated with coronary heart disease but is causative. The alternative view is that cholesterol is an expression of sub-clinical disease, but this has never been considered practically and all efforts have been made to reduce blood cholesterol. Generally speaking, these were unsuccessful in reducing coronary events but things changed with the arrival of the statin drugs, inhibitors of HMG Co-enzyme A reductase.

The first trial published was a secondary prevention trial, the Scandinavian Simvastatin Study (4S) [7]. This showed a significant benefit from statin therapy, as did the primary prevention study, the west of Scotland study (WOSCOPS) [8]. There was clear rejoicing among the adherents of the cholesterol-heart hypothesis who felt that these trials of "cholesterol-lowering" demonstrated a proof of the hypothesis [9]. Previous sceptics were converted [10], but without knowing the full story of the effect of statins. The more recently introduced ezetemibe certainly reduces blood cholesterol but no clinical benefit is demonstrated [11].

Statins have turned out to be enigmatic. They were more successful than anticipated and it was clear from the WOSCOPS study that the clinical benefit bore no relationship to cholesterol lowering [12]. In fact the authors suggested that statins might be acting in ways other than cholesterol lowering. At the time of introduction of statins, the only known chemical effect was HMG Co-enzyme A reductase inhibition, but it is now obvious that there are other effects as well, the details of which have not been characterised. There are many clinical benefits that cannot be explained on the basis of cholesterol metabolism. The benefits have a similarity to the clinical benefits of vitamin D in that it has been suggested that statins might somehow be analogues of vitamin D [13].

There is clearly a close relationship between statins, cholesterol and vitamin D. It is interesting to note that cholesterol and vitamin D have the same pre-cursor, namely 7-dehydrocholesterol. Statins inhibiting HMG Co-enzyme A reductase will inhibit the synthesis of 7-dehydrocholesterol, the pre-cursor of cholesterol. It might therefore be expected that there would be a reduction of vitamin D synthesis and it is perhaps strange that this has never been reported clinically. Early studies found that statins did not reduce the vitamin D level in the blood [14–16] and this was obviously reassuring. However, why should this be the case?

The paper by Yavuz and colleagues in this issue [17] explores this enigma in more detail. They demonstrate that rosuvastatin increases the blood level of vitamin D as 25-hydroxyvitamin D and also the activated hormone 1,25-dihydroxyvitamin D. This effect has also been found with atorvastatin [18]. The mechanism is unexplained and is far from clear.

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Ultraviolet light acting on the skin splits the 7-dehydrocholesterol molecule in a process which is physico-chemical and not biochemical. This occurs in the exposed skin of mammals and also in plankton close to the surface of the sea, thus entering the food chain to enable us to have dietary vitamin D from fish. 7-dehydrocholesterol is thereby transformed into pre-vitamin D, which isomerises into vitamin D as cholecaciferol. There is no other known way in which this miracle of evolution can occur. Do statins, through unknown mechanisms, lead to an increased synthesis of vitamin D, and if so, how? Or do they reduce the consumption of vitamin D?

Cholecalciferol is hydroxylated in the liver to form 25-hydroxyvitamin D, and further hydroxylation occurs in the kidneys (and also in macrophages) to form 1,25-dihydroxycholecalciferol. This is subsequently deactivated by further hydroxylation as part of homeostatic mechanisms, and possibly by photometabolic processes in the skin

There is a suspicion that vitamin D can be consumed, rather than just inactivated to prevent excessive blood levels. It has been observed that blood vitamin D levels are low in patients with tuberculosis and remain low throughout treatment, but increase afterwards without supplement [19]. Although vitamin D predisposes to tuberculosis, this study suggests that vitamin D is being consumed during the active inflammatory process, blood levels increasing when this process is complete. We know that statins have a beneficial effect in reducing infective or inflammatory episodes [20], in a similar pattern to vitamin D [13]. The mechanisms are unknown. Perhaps statins suppress the non-tuberculous inflammatory processes that would consume vitamin D as in tuberculosis, leading to an increase in blood levels of vitamin D as 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D.

This is clearly an exciting area and there is much research yet to be undertaken. The only registered clinical indication for statins is to lower cholesterol but it would appear that this is the least important of the clinical effects of statins. Their relationship to vitamin D and the health benefits of vitamin D are very significant and very important.

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