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## DO STATINS HAVE POTENTIAL AS ANTI OSTEOPOROTIC DRUGS AND CAN THEY BE USED FOR PREVENTION OR TARGETING OSTEOPOROSIS: A REVIEW

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### ABSTRACT

Inhibitors of HMG-CoA reductase enzymes, which are statins, are well known and much prescribed drugs for lowering of cholesterol and used for dyslipidemia. But, they have also been shown across various studies to stimulate bone formation. In bone cells, these inhibitors have been known to increase the gene expression of bone morphogenetic protein-2, thereby helping in osteoblastic differentiation, with some effects also on osteoclastic inhibition.

The findings that statins can increase bone formation and thereby mass of bone, can be helpful in preventing bone fractures and improving osteoporosis, which is a condition of marked bone loss. Hence, it is reviewed herein that HMG-CoA reductase inhibitors can be a great way, probably a futuristic drug for osteoporotic treatment and prevention.

**Keywords:** HMG-CoA reductase inhibitors, osteoporosis, osteoblasts, statins, bone metabolism, fracture

### INTRODUCTION

There has been a remarkable increase in the knowledge about osteoporosis since the past 25 years or so. Osteoporosis is seen to occur more in females than in males, although mortality is higher in men, which are caused by osteoporotic fractures<sup>1, 2, 3</sup>. Added to this, post menopausal women have a higher frequency of osteoporotic fractures and osteoporotic incidences<sup>4</sup>. Bone is a metabolically active organ in which mineral and organic components will be important to determine the mechanical function of skeleton<sup>5,6</sup>. Bone turnover is under the control of certain defined agents as well as processes, which regulate the formation of bones and also resorption of bone. These are two basic but important processes by which the bone remodelling is occurring. New bone formation is basically a function of the osteoblasts, agents

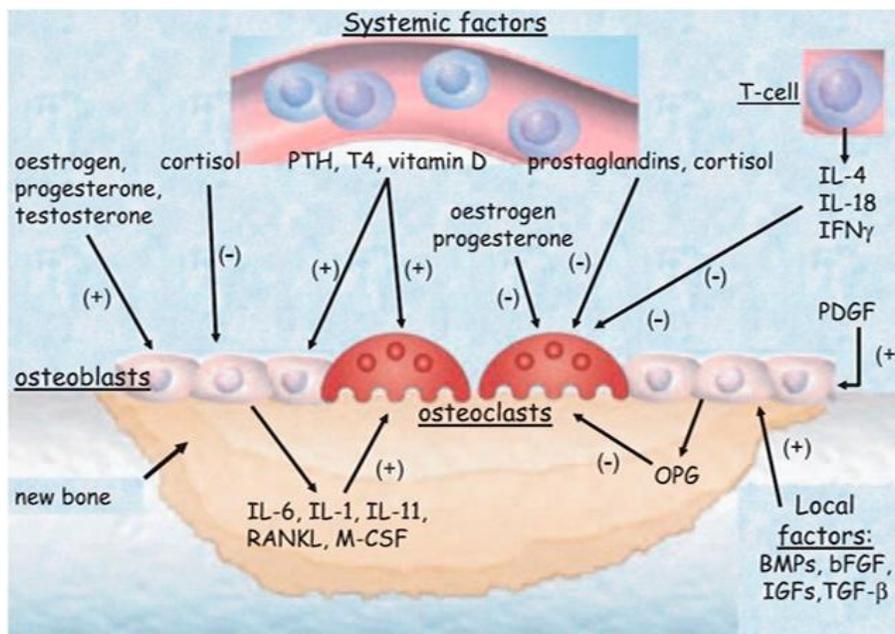
which act by increasing or decreasing the replication of cells in the lineage of osteoblasts, or modifying the differentiated function of the osteoblast. It would therefore be beneficial for stimulating the osteoblastic activity at local sites in bone by an oral anabolic agent, resulting in bone formation, where and when needed. Osteoporosis is defined clinically as reduced bone mass, to such a level where it will result in fracture, with minimal trauma<sup>7</sup>. This term will also suggest that there is parallel loss of both bone mineral and matrix that will render the mineralised bones incapable of withstanding minor trauma, without leading to fractures. Osteoporosis is a disease condition which is affecting about 30 million people in United States and about 100 million people worldwide. Unless the bone mass falls below 30% to 50% lower than the normal value, fractures do not occur.

## DYNAMICS OF BONE & OSTEOPOROSIS

Bone mass is the net result of a balance between bone formation and resorption. This balance is mostly regulated by genetic as well as environmental factors. Genes regulating bone mass are vitamin D receptor gene, estrogen receptor gene, interleukin-6, transforming growth factor B and gene encoding type 1 collagen<sup>8,9,10,11</sup>. Environmental factors include nutritional status, exercise, drugs like glucocorticoids and contraceptive pills, neoplastic diseases such as myeloma, leukemia, lactation, parity, alcohol, smoking, weight loss and long hip axis length. Although the exact pathophysiology of osteoporosis is unknown, an imbalance between bone formation and resorption presumably causes bone mass to decline in adulthood and osteoporosis occurs when the amount of bone removed from the skeleton by bone resorbing osteoclasts exceeds the amount formed by osteoblasts during the coupled process of remodelling. Treatment of osteoporosis is aimed towards restoring this balance.

## BONE REMODELLING

Bone remodelling is well established throughout the literature and involves both systemic and non systemic factors. It is well known that in this procedure an important role is played by the system of receptor activator of nuclear factor kappa b ligand – osteoprotegerin 6, some cytokines and bone morphogenic proteins. Mesenchymal stem cells are pluripotent cells with a high mitotic index and are involved in the differentiation of adipocytes under the regulation of genes and transcription factors. Adipose tissue is considered as a separate endocrine gland, responsible for the secretion of adipokines such as leptin, adiponectin and hormones such as vitamin D<sub>3</sub>, estrogen, etc and in involved in the pathogenesis of some entities. Leptin is considered to exert a control over the RANKL/OPG axis by decreasing the expression of RANKL and increasing OPG to bring out pre-osteoblasts and mononuclear cells into the circulation.<sup>12,13</sup> There is diversion of adipocyte into an osteoblast, which is a multifactorial process regulated by various factors.



**Fig – 1: RANKL/OPG and other factors in bone formation**

Molecular biology and genetics reveal that both vascular and osteoblast biology have a common pathway of RANK/RANKL/OPG<sup>14</sup>. Mundy and colleagues in 1999 reported first that there was an anabolic effect of statins in human bone cells and cultured mouse. Simvastatin and lovastatin enhanced the expression of bone morphogenetic protein- mRNA<sup>15</sup>.

### **Statins as potential drugs for osteoblastic activities**

Several experiments have illustrated the effect of statins in bone metabolism *in vitro* and *in vivo*. Chan *et al.*<sup>16</sup> in 2000 demonstrated that there was negative effect of statin on bone repair. But in contrast, there were many other studies which showed beneficial effects. The administration of statins has anabolic effects on the bone by suppressing osteoclasts and promoting osteoblastic activities. Hence, statins can effectively work on bone formation and increase the bone mass density by inhibiting it, thereby helping in prevention of osteoporosis and aiding in fracture healing. Most of these studies have been done in different doses in animal models, apart from showing actions of cholesterol lowering in animals. Some also have shown remarkable increase in required growth factors such as TGF $\beta$ -1 and VGF or Vascular Growth Factor, possibly showing a path for the statins and bone interaction. There have been more studies in cell cultures, *in vitro*, which support the findings that statins have a potential mechanism on bone metabolism. There is expression in certain genes like BMP-2, COL1A1, Osteocalcin, etc while the RANKL gene is depressed are affected by statins, which might be the reason for the bone formation. In 2007, Hughes A *et al.*<sup>17</sup> found that the statins of hydrophobic nature and hydrophilic nature have inhibited osteoclastic action *in vitro*, while some other studies have shown lipophilic agents like simvastatin to have better action<sup>18</sup>. It was the pleiotropic effect of statins which led many

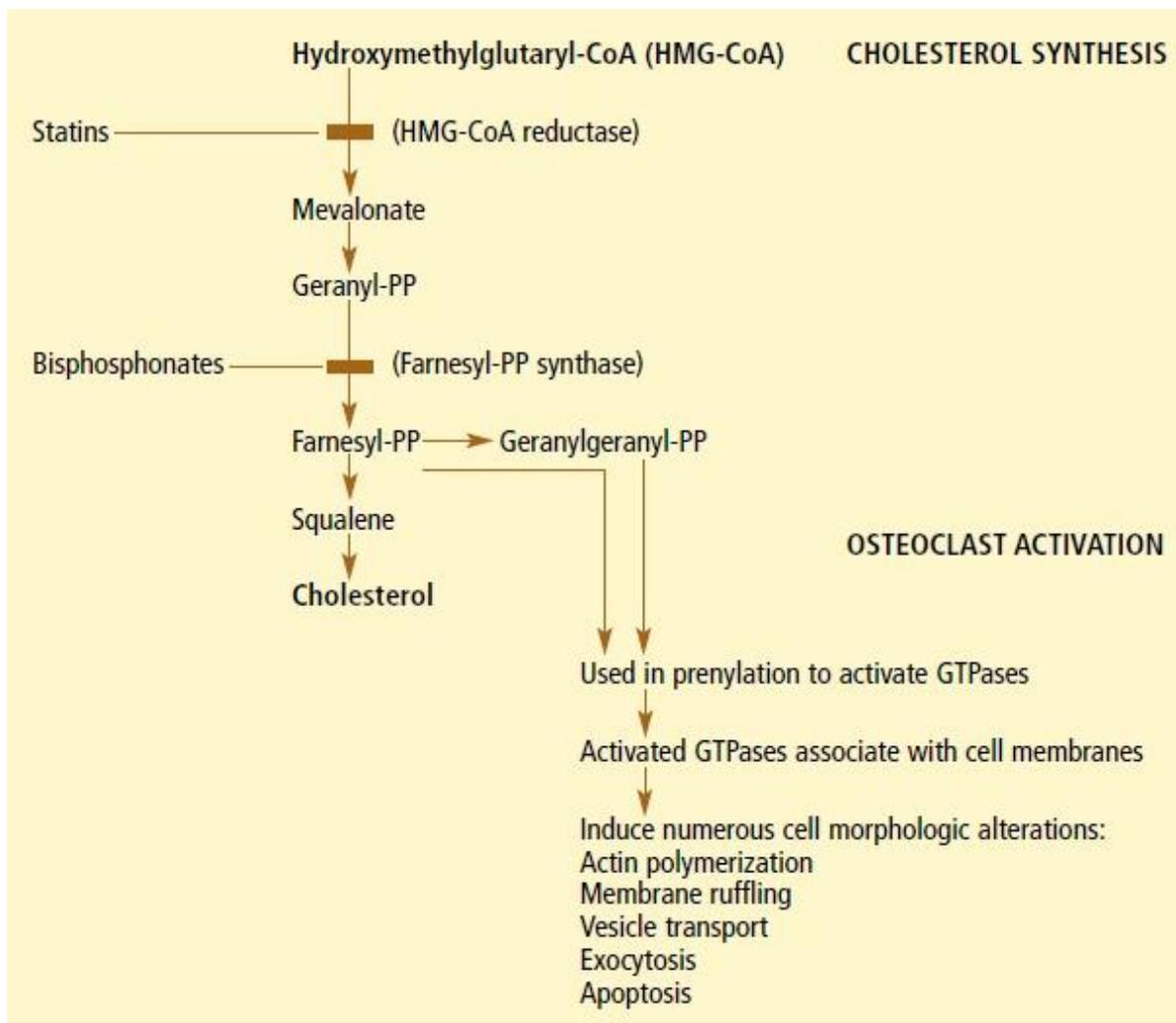
clinicians to study the use of statins in bone metabolism. A meta analysis by Uzzan *et al*<sup>19</sup>, found that statins have a positive effect on bone mass density in different bones of the body. It was concluded that there was statistically significant but modest positive effect of statins on BMD. More data is still needed to support the use of statins in prevention of bone fracture. Most of the literatures showed an increase in BMD and also in bone markers. All the available data from various literatures, starting from the experimental studies to the observational studies showed that there is surely some positive effect of statins on BMD. One meta analysis by Bauer *et al*<sup>20</sup> also showed the beneficial effect of statins on fracture risk. It was demonstrated by Chuengsamarn *et al*<sup>21</sup> that statins could inhibit bone resorption and stimulate bone formation, with a dual action on bone metabolism. It might be possible for statins to gain a position as a drug used for prevention and management of osteoporosis, so much so that statins is being frequently prescribed by clinicians for other treatments. Possibly in the future, drugs will be up in circulation, which will target the different pathophysiological and biochemical cascades as in statins with alterations of doses and could be used for different bone disorders like osteoporosis.

### **DISCUSSION**

Two recently elucidated pathways may explain how statins can be helpful in building up bone. The first mechanism is through the inhibition of mevalonate production. Many laboratories and researchers noted that cholesterol synthesis and osteoclast activation involved same biochemical cascade. The synthesis of cholesterol is done in plenty of steps. HMG-CoA is converted into mevalonate by enzyme HMG-CoA reductase. This enzyme is inhibited by statins. Then the mevalonate is converted to geranyl phosphate, which is in turn converted to farnesyl pyrophosphate by the enzyme farnesyl

pyrophosphate synthase, which is inhibited by bisphosphonate drugs. Then the cholesterol is synthesised<sup>22, 23,24</sup>. Osteoclasts use the intermediate molecules of farnesyl pyrophosphate and geranyl pyrophosphate from farnesyl pyrophosphate to modify and activate

the key intracellular proteins glutamyl transpeptidases and GTP-ase in a process called prenylation<sup>25</sup>. Bisphosphonates like alendronate and risedronate inhibit farnesyl synthase, preventing the formation of lipid products<sup>26</sup>.



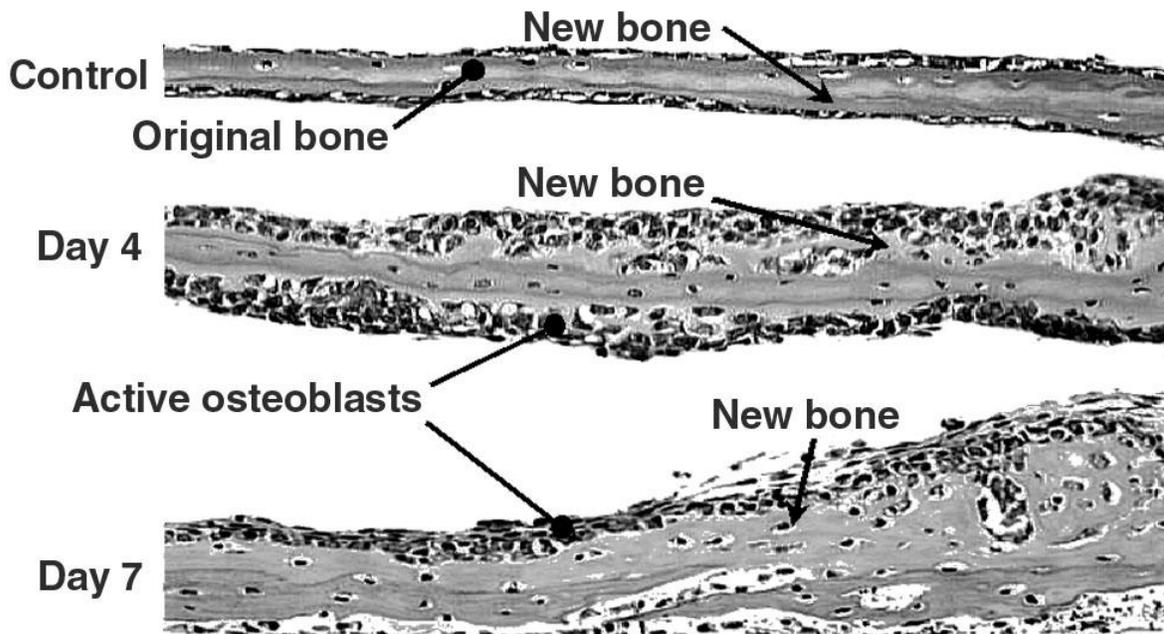
**Fig – 2 Interrelation of cholesterol synthesis and osteoclast activation**

Statins are as efficacious in not allowing osteoclast activation, even in experimental set ups, the action being due to mevalonate production. This will reduce the bone resorption and there is restoration of bone resorption and formation. In many clinical trials, it has been noted that fragility related fractures are reduced<sup>27, 28, and 29</sup>.

B. Another mechanism which has statins affecting skeleton is that of activation of bone morphogenetic protein-2 promoter. This is a kind of protein which is a growth factor, which leads the osteoblasts into proliferating, maturing and thereby creating a new bone<sup>30</sup>. In an experiment, when lovastatin was injected into organ cultures of calvarial bones from the neonate mice, thrice a day for 5 days, volume of

bone increased by as much as 50%, in comparison to placebo. Histological studies

showed enhanced bone formation and osteoid accumulation.<sup>31</sup>.



**Fig – 3: Cultures of murine neonatal calvaria incubated for either 4 or 7 days in the presence of simvastatin at 1  $\mu$ M. Small amounts of new bone are present in control cultures whereas cultures exposed to simvastatin for 4 days show marked new bone formation and osteoblast accumulation. Cultures exposed for 7 days show further enhancement of bone formation.**

Although a number of recent drugs have shown to prevent osteoporosis and have been used in the treatment, not one of them has been shown to stimulate bone formation and increase osteoblasts activity. It was suggested that drugs which inhibit HMG CoA reductase, which are statins, many have such effects and reduce the risk of osteoporotic fractures.<sup>30</sup> Many other reports have also suggested such an anabolic bone effect, which might show a new path towards the treatment of osteoporosis.<sup>32</sup> To aid in the proof of such an action, it was stated that statins as a class of unknown bone anabolic agents acted through increased production of one of the important bone growth factors, which is Bone Morphogenetic Protein-2, which directly stimulates the osteoblastic activity and bone formation. Lovastatin was found to be stimulating the BMP-2 promoter, from among

30,000 natural compounds tested.<sup>33</sup> Many other subsequent studies have also demonstrated similar effects through fluvastatin, simvastatin and mevastatin.<sup>34, 35, 36</sup> These studies showed that the drugs inhibiting HMG-CoA reductase commonly utilised nowadays for lowering blood lipid levels, also stimulate bone formation activity by osteoclasts through the increase of BMP-2 expression, which is a proven differentiator of osteoblasts. Chuengsamarn et al also carried out many experiments in form of prospective randomised trials on the impact of simvastatin on osteopenic patients and found that bone formation marker and BMD was significantly higher than in the statin group and the difference of bone resorption marker was also significantly lower than in the statin group.<sup>37</sup>

## CONCLUSION

From such studies it can be very well concluded that simvastatin as well as other drugs in this particular group act as double therapeutic weapon by inhibiting the conversion of HMG-CoA to mevalonate, which is required for cholesterol synthesis and also inhibits the stimulation of osteoclastic activity. Also, there is increase in the stimulation of osteoblastic activities, providing enough evidence that the simvastatin has a promising role in fighting against osteoporosis. But still more studies are required to find the particular doses and the effect dosage and mode of administration of these statin group of drugs to make it commercially viable. Current therapies of osteoporosis treatment include estrogen replacement therapy, bisphosphonates and selective estrogen receptor modulators and all of them aim at blunting the resorption of bone remodelling. Based on previous findings it was found by Bauer and Cummings that large databases showed association between statin usage and skeletal status, showing relationship between statin use, bone mineral density and subsequent fractures.<sup>38,39</sup> Even a study on post menopausal women has come out which shows an increase in the bone mineral density who are taking statins<sup>40</sup>. It has been shown to have a protective effect against non pathological fractures among older women.<sup>41,42,43,44</sup> A similar story was involved with the use of Hormone Replacement Therapy or HRT, which was prescribed to ladies around 2000, without much long term studies. Statins are also being pushed nowadays for prevention of fractures. But, with the proper tests and long term studies, it will be coming out clearly, whether the benefits are worth making public.

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