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THE ROLE OF STATINS IN MYOPATHY AND THEIR EFFECTS IN OSTEOPOROSIS

EDITORIAL

The safety of HMG-Co reductase-inhibitors (statins) is of great interest to clinicians, policy makers and the public. Although myopathy is well documented as a side-effect of the statins, the increase in numbers of patients using this drug class may cause more of these case symptoms to be reported.[1]

Apart from their effect on the lipid profile, statins have other clinical effects. Some of these effects eg improvement in endothelial function is relatively well documented, but other effects require further studies to prove clinical significance. Animal, in vitro and some observational studies have shown positive effects on bone mineralization and reduction in bone resorption with the use of statins.[2,3]

This article will focus on the effects of the statins on muscles and bones, with specific focus on statin-induced myopathy and the possible role of statins in osteoporosis.

BACKGROUND

Statins as a class have been widely used for more than a decade and their safety and efficacy has been well documented. Researchers emphasize that statins are still the best drugs for treating elevated cholesterol thereby reducing the risk of heart disease, stroke and total mortality.[4,5]

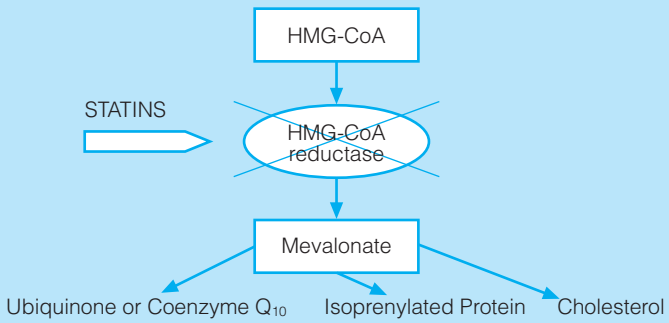
Statins have also been shown to improve endothelial function by increasing nitric oxide production through upregulation of nitric oxide synthase. Endothelial dysfunction is an early indication of organ injury after acute events like stroke, myocardial infarction, haemorrhage as well as chronic disease conditions such as hypercholesterolaemia and diabetes. It is a good prognostic indicator of cardiac events and mortality therefore an important target for intervention.[4]

In addition laboratory studies have shown that statins have a variety of other actions including antithrombotic, anti-inflammatory, anti-oxidant, vasodilatory and anti-proliferative effects.[4] However, large, prospective randomized trials are required to confirm whether these effects are clinically significant.

MECHANISM OF ACTION

Most cholesterol is synthesized in the liver, and statins work by inhibiting the formation of the enzyme involved in its synthesis. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase interrupts the conversion of HMG-CoA to mevalonate, a precursor of sterols and cholesterol. Mevalonate is a component in the biosynthetic pathway that is shared by cholesterol, ubiquinone, also known as coenzyme Q_{10} (CoQ_{10}), and isoprenylated regulatory proteins.[4,5] (**see Figure 1**). This inhibition results in a drop of intracellular cholesterol concentration in the hepatocyte, up regulation of LDL cholesterol receptors and ultimately an increased clearance of LDL cholesterol from the plasma.[6]

Figure 1: Mechanism of action of statins[5]



Source: Tomlinson S and Mangione K. Potential Adverse Effects of Statins on Muscle. J. American Physical Therapy, May 2005; Vol. 85(5):459 – 465)

Clinically, statins in combination with dietary therapy reduce LDL cholesterol and triglycerides and increase HDL by varying percentages depending on the type and strength of statin used. Regardless of the mechanism, benefits still remain pervasive, with statins' proven efficacy in lowering LDL cholesterol in a dose-dependent manner.[6]

Efficacy of statins varies from agent to agent and the choice of statin will depend on the number of cardiac risk factors a patient has, and the therapeutic goals for the patient.[6] Please refer to **Table 1** where the efficacy of atorvastatin in comparison with other statins is reflected. From this table it is clear that atorvastatin is a very potent statin. I*n terms of LDL-lowering effect*, Atorvastatin at a dose of 10mg/day can be considered "*therapeutically equivalent*" to simvastatin 20mg/day.

MUSCLE TOXICITY

Statins are known to be associated with muscle toxicity, but there is no clear data to verify the extent of the problem in terms of both severity and frequency.[4] Cerivastatin (Baycol®), for example was withdrawn from the market by the manufacturer in 2001, following reports of severe adverse muscle toxicity and death.[5] The mechanism of statin myotoxicity is unclear[6] but there are several theories proposed, all of which are still under investigation. The following are some of these theories:[4,5]

- **Decrease in ubiquinone (CoQ_{10}):** Because statins inhibit the production of mevalonate, a precursor of CoQ_{10}, the synthesis of CoQ_{10} may also be inhibited. CoQ_{10} is involved in energy production via the mitochondrial respiratory chain. Thus decreased levels of CoQ_{10} could have adverse effects on muscles.
- **Decrease in isoprenylated regulatory proteins:** Mevalonate leads to the activation of regulatory proteins such as guanosine triphosphate (GTP)-binding proteins. These GTP-binding proteins are important in cell health and control of apoptosis (cell death). As statins inhibit the activation of these regulatory proteins, uncontrolled cell death may occur.
- **Cell membrane instability:** The reduction of cholesterol in skeletal muscle may cause instability of the cell membrane, with resultant muscle damage.

Myotoxicity by a statin appears to be **dose dependent and can occur suddenly, weeks or months after the drug has been initiated**.[5,6] Thus the risk of myopathy increases if the serum concentration of the statin increases. Factors that increase this serum concentration eg volume of distribution, drug metabolism and catabolism, can thus increase the risk of myotoxicity.

Factors that may increase the risk of myopathy include:[4,5,6,9]

- Renal and hepatic dysfunction
- Age especially if greater than 80 years
- Female gender
- Small body frame and frailty
- Hypothyroidism
- Multisystem disease
- Concomitant use of certain medication and alcohol
- Multiple medication
- Surgery
- Genetic factors

The combination of *statins with fibrates, specifically gemfibrozil, or nicotinic acid* has been identified as a potential risk factor

Table 1: Lipid Lowering Dose Ranges- Results from The CURVES Study[7]

Drug	Strength	Dose	% LDL-C reduction	% HDL increase	%Trigs reduction	% TC reduction
Lovastatin e.g. Lovachol®	10mg 20mg 40mg 80mg	10mg od 20mg od 40mg od 40mg bd	22% 29% 31% 48%	4% 7% 5% 8%	5% 12% 2% 13%	12% 21% 23% 36%
Atorvastatin e.g. Lipitor®	10mg 20mg 40mg 80mg	10mg od 20mg od 40mg od 80mg od	38% 46% 51% 54%	6% 5% 5% 1%	13% 20% 32% 25%	28% 35% 40% 42%
Fluvastatin e.g. Lescol®	20mg 40mg 80mg XL	20mg od 40mg od 80mg od	17% 23% 35%	1% 3% 8%	5% 13% 11%	13% 19% 20%
Pravastatin e.g.Prava®, Pranalip®	10mg 20mg 40mg	10mg od 20mg od 40mg od	19% 24% 34%	10% 3% 6%	3% 15% 10%	13% 18% 24%
Simvastatin e.g. Zocor®, Simvacor®, Adco-Simvastatin®, Simvotin®	5mg 10mg 20mg 40mg 80mg	5mg od 10mg od 20mg od 40mg od 80mg od	24% 28% 35% 41% 47%	7% 7% 5% 10% 12%	12% 12% 17% 15% 36%	17% 21% 26% 30% 36%

for myotoxicity.[5] However, recent recommendations support consideration of this combination in patients with elevated triglycerides and low HDL-C who are at high risk for developing coronary events.[5]

Warfarin (Coumadin), digoxin, amiodarone, diltiazem, cyclosporine, azole antifungals, and macrolide antibiotics or even grapefruit have been reported to interact with statins, therefore creating the potential for rhabdomyolysis.[5,6,8,9]

The majority of the drug interactions resulting in myotoxicity occur due to the inhibition of the CYP3A4 enzyme by the concomitant drug. The chance of interaction also depends on the type of statin used. Simvastatin, lovastatin and atorvastatin are predominantly metabolised by CYP3A4 and fluvastatin mainly by CYP2C9. Pravastatin, however, does not undergo extensive liver metabolism and no clinically significant plasma elevations are expected to occur with inhibitors of the CYP450 enzyme system.[6,8,9]

Renal and hepatic dysfunction, as well as diabetes and hypothyroidism also increase the risk of muscle adverse effects in statin users.[3,5]

Unfortunately, patients who may benefit the most from statin therapy are often the ones with co-morbidities, requiring multiple medications that put them at high risk for myopathies.[4,5,6]

To varying degrees, each of the lipid-lowering agents available can cause myopathy (**see Table 2 & 3**). The reported muscle complaints include myalgia, myositis and life threatening rhabdomyolysis.[1,5,6]

- **Myalgia** is muscle pain, aching or stiffness *without* elevated creatinine kinase (CK) levels and is the most common muscle complaint among patients.
- **Myositis** refers to inflammation of the muscle, resulting in myalgia-type symptoms with increased CK levels above the upper limit of normal (ULN).
- **Rhabdomyolysis** is muscle damage or breakdown due to severe inflammation. Rhabdomyolysis results in the release of the muscle cell contents (myoglobin) into the blood stream causing possible damage to the kidneys and other organs. CK levels are typically more than 10 times the ULN.

Some evidence indicates that statin use can exacerbate the normal CK elevations seen after exercise.[4,5,6] A randomized controlled study by Thompson et al in 59 men with high LDL showed that CK levels increased by an additional 62% and 77% in patients receiving 40mg of Lovastatin after 24 and 48 hours post exercise respectively, as compared to the control group who received placebo.[5,9]

Statins share a common site of action but different cholesterol biosynthetic pathways depending on whether they are hydrophilic or liposoluble. Penetration of a statin into extrahepatic tissue increases with increasing lipophilicity.[9] These distinctions therefore account for the variation in muscle side effects among the agents.[6,9]

- **Hydrophilic statins:** Fluvastatin and Pravastatin are hydrophilic. They rely on a specific protein to transport them through the cell membrane.
- **Lipophilic statins:** The other statins are liposoluble. A transporter protein is not required to transport them through the cell membrane. Passage into the muscle cell may increase with the lipophilicity of the statin thus increasing its myotoxicity.[6,9] Cerivastatin was the most lipophilic statin until its withdrawal. Simvastatin and lovastatin are the next most lipophilic, followed by atorvastatin.[9]

In randomized controlled trials, the frequency and severity of muscle problems did not differ significantly between statin treated and placebo groups.[4] (**Refer to Table 3**)

Monitoring

The following are *recommendations* by The American Heart Association, American College of Cardiology and National Heart Lung and Blood institute on *the evaluation, monitoring and management of muscle complaints.*[8,9]

- Patients should be evaluated for muscle symptoms (i.e. muscle tenderness or muscle pain) before starting therapy.
- Baseline CK testing, with follow-up testing 6–12 weeks after therapy has been initiated and on each follow up visit.
- Baseline liver function test must be performed, with follow-up testing 12 weeks after starting therapy and thereafter annually (severe liver dysfunction can reduce hepatic metabolism thus increase risk of muscle toxicity).
- Patients should report any muscle discomfort or weakness, or brown urine upon which CK testing should be done.
- If muscle symptoms occur and if CK levels are above 10 times the ULN, statin therapy should be discontinued. In asymptomatic patients with these increased CK levels, the physician should seriously consider stopping the statin.
- If CK levels are between 3-10 times ULN then CK levels should be monitored weekly until there is no more concern or no more corrective action is needed. The statin may be continued unless there are progressive symptoms or progressive CK elevations on serial tests.
- In at-risk patients statin therapy is contraindicated before any surgical procedure and for some time post surgery.

However a slightly less conservative approach is followed by some physicians like Dr E.A Briton, director of the Metabolism Section of Cardiovascular Genetics, and associate professor at University of Utah School of Medicine: according to him CK levels vary from

Table 2: Reports of rhabdomyolysis to the FDA, January 1st 1990 to March 31st 2002[4]

Drug	Number of Reports	Reports of rhabdomyolysis due to drug (%)
Cerivastatin*	1869	57
Simvastatin	612	18
Atorvastatin	383	12
Pravastatin	243	7.3
Lovastatin	147	4.4
Fluvastatin	55	1.6
Total	3339	100**

* Discontinued
** Percentages do not sum to 100 because of missing data

Table 3: Toxicity Effects on Muscle in Major Trials[6]

Trial	Myositis		Rhabdomyolysis	
	Statin	Control	Statin	Control
Pravastatin Pooling Project (CARE, LIPID, WOSCOPS) N= 19,592	3	7	0	0
Lovastatin study (AECAPS/TEXCAPS) N= 6,605	21	21	1	2
4S Simvastatin randomized trial N = 6,605	6	1	1	0
Total N= 30,641	30	29	2	2

Legend:
CARE= Cholesterol and Recurrent Event trial, LIPID = Long Term Interaction with Pravastatin in Ischaemic Disease trial, WOSCOPS = West of Scotland Coronary Prevention Study, AECAPS/TEXCAPS = Air force/Texas Coronary Atherosclerosis Prevention Study, 4S = Scandinavian Simvastatin Survival Study

Source: Fine DM. Statin-Related Muscle Toxicity. J. Clinical Pharmacology. November/December 2003; 3(10): 554-560

day to day and *elevated levels of CK may have no correlation with statin-based myopathy*. He suggests a baseline CK level, but does not advocate routine CK monitoring. CK monitoring is recommended if a patient presents with symptoms of myopathy. His monitoring regimen is as follows:

- If patient has true myopathic symptoms but a normal CK level, statin therapy will be deferred.
- If the CK level is elevated but myopathic symptoms are equivocal, the level and degree of CK elevation will be taken into consideration to determine whether it is a true case of myopathy.
- If the CK is above 10 ULN in patients on a statin, statin therapy is stopped temporarily and lower doses or a change to a different statin is considered.[1]

Conclusion

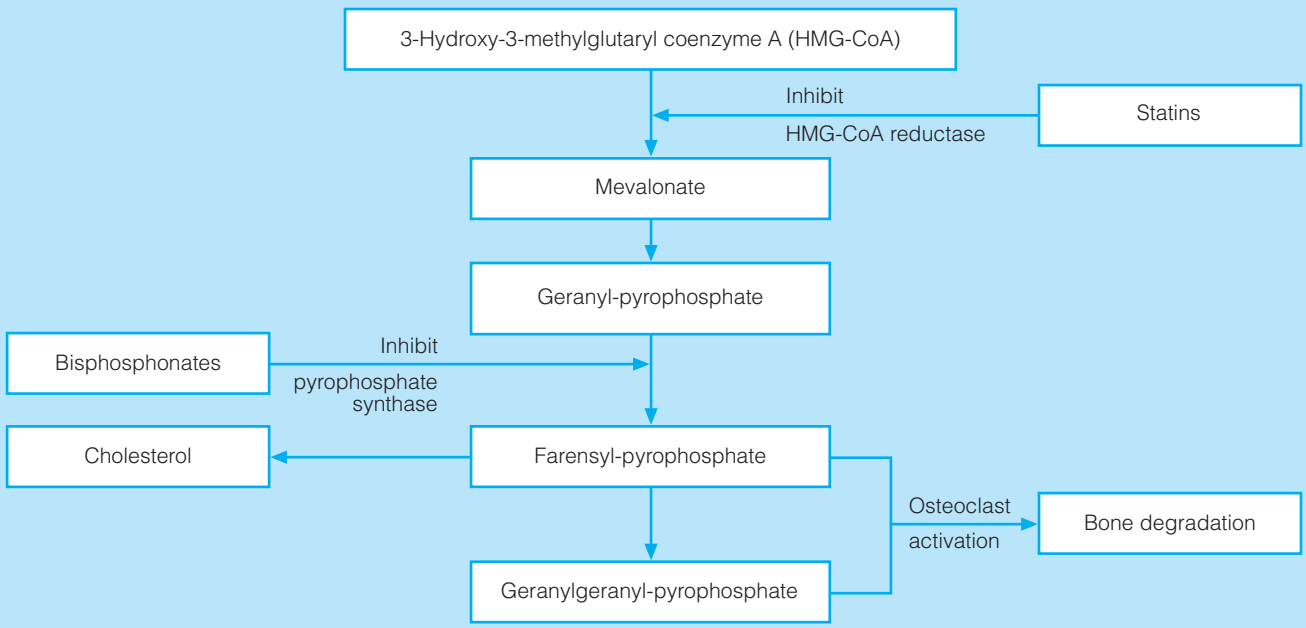
Patients should be properly evaluated before initiation of a statin, and closely monitored while using the statin.[9] Muscle problems increase with serum concentration of statin, and many factors can potentially influence this concentration.[4] Although statins are associated with various muscle side effects, these adverse affects are reversible upon withdrawal of therapy.[4,5]

STATINS IN OSTEOPOROSIS

It has been hypothesized that statins have an ability to improve bone health due to their interference with bone metabolism through various mechanisms. Two proposed mechanisms are:

- Statins may block the mevalonate pathway - the same pathway blocked by bisphosphonates further downstream through inhibition of farnesyl pyrophosphate (**see Figure 2**). Because of the reduction in mevalonate, activation of osteoclasts (cells responsible for the removal of bone) could be reduced.
- Statins may have an anabolic effect in bone, via the promotion of morphogenetic protein-2 (BMP-2), a potent anabolic agent.[2,3]

Figure 2: A potential link between statins and bone[3]



Mundy and colleagues were the first to report the ability of statins to promote bone formation. They confirmed these results by transdermally introducing lovastatin to rodents and the trabecullar bone in the rodents was increased by 57%. Similar but less dramatic results were observed in rodents which were given an oral daily dose of lovastatin over a period of 35 days.[10] Lovastatin enhances the synthesis of bone morpho-genetic protein 2 (BMP-2), which increases osteoblast differentiation and bone formation. Upon examination simvastatin, mevastatin**, and fluvastatin also demonstrated similar results when injected in murine skullcap bones.[3] (**Not available in South Africa)

Mundy's report paved the way for several other research groups to conduct observational studies on the association of statin use and the quality of bone in humans.[10] **Table 4** summarizes the key points of some of these studies.[2,3,11,12,13]

Discussion

Both animal and observational studies still show conflicting results on the effect of statins on the bone. Although statins may show an antiresorptive or anabolic effect on the bone, this probably differs among various statins depending on the potency of each statin.[12] Generally statins undergo a first-bypass metabolism in the liver, so only about 5% of the administered statin will be available in the peripheral circulation.[11] Furthermore, the lipophilicity of the statin plays an important role: pravastatin, which is water-soluble, does not enter cells easily and of all the statins may be least likely to have an effect on bone.[12]

Conclusion

Prospective randomized controlled trials are required to ascertain whether the statins do have beneficial effects on bone, and whether this effect is on the same level of magnitude as the effect of the drugs that are used specifically to treat osteoporosis.[12] Insight from the reviewed studies may however lead to the development of similar molecules that more effectively promote bone formation and inhibit resorption.[2]

Source: Gonyeau MJ. Statins and Osteoporosis: Clinical Review. J. Pharmacotherapy, 2005; Vol. 25(2):228 – 243. Available from http://www.medscape.com

Table 4: Studies on the effects of statins

Study	Population	No. of subjects	Duration of study (years)	Results	Conclusion
Cauley et al.[11]	Women on statin treatment compared to non statin users in WHI-OS (Women Health Initiative Observational Study)	79 on statin therapy for >3 years	3	Increase BMD in statin users vs. control: ▪ Hip = **0.87g/cm^2 vs. 0.84g/cm^2 (p=0.03),** ▪ Vertebra = **100mg/cm^2 vs. 0.98g/cm^2 (p=0.05**)	Statins increase BMD in statin users and the extent of increase varies from statin to statin; Atorvastatin & simvastatin users had higher BMDs than users of pravastatin, lovastatin & fluvastatin
Reid et al.[2,3,12]	Post hoc analysis of postmenopausal women treated with Pravastatin 40mg (4512) and Placebo (4502) (LIPID trial)	9,014	6	The number of fractures were essentially identical between the placebo & pravastatin groups: **HR 1.05 (0.8-1.37) with 95% CI OR 0.94 (0.77-1.16) with 95% CI; p=0.58**	Statins have no significant effect on fracture
Wang et al.[2,3,11,14]	Patients 65yrs of age and above. 1,222 patients with hip fracture vs. 4,888 control group	6,110	3	Chances of hip facture reduction: ▪ Statin use in prior 180 days = **OR 0.50 (95% CI 0.33-0.76)** ▪ Statin use in prior 3 years = **OR 0.57 (95% CI 0.4-0.82)** No significant fracture risk reduction in non statin users	Statins showed a positive effect on reducing hip fracture
Van Staa et al. [2,3,12]	Case control analysis of database of patients age 50yrs and above with fractures possibly related to osteoporosis vs. control group without fractures	> 80 000 + equal number controls. 950 current statin users	12	No statistical difference in incidence of fractures between statin users and non statin users: **OR 1.01 (95% CI 0.88-1.16)**	There is no association between statin use and bone fracture reduction
Women Health Initiative (WHI) LaCroix et al.[2,3,11,12]	Prospective observational study of postmenopausal women on statins vs. control; age 50-79yrs	>90 000 women 1,846 on statin; 85,870 on no statin	2-3	No difference in fractures rate was observed between groups. **HR 0.98 (0.6-1.62) with 95% CI**	No link between statin use and risk of hip fracture
Lupattelli et al.[13]	Postmenopausal women with primary hyperlipidaemia but without osteoporosis; no previous use of statins, steroids, HRT, thiazides, calcium, Vit. D or bisphosphonates	40	2	3.3% increase in spine BMD & 2.7% increase in hip BMD after 24 months on simvastatin	Simvastatin has a positive effect on the BMD
Meier et al.[2,3,11,12] (same database used by van Staa)	Nested case control analysis of research database. Patients age 50yrs and above some with fractures vs. control group	Database> 80 000 3,940 case patients; 23,379 control subjects	12	Reduction in fracture risk in statin users vs. control was: **OR 0.55 (95% CI 0.44-0.69)**	Current statin use has positive effect on reduction in fracture risk
Watanabe et al.[2,11]	Patients on statin treatment (fluvastatin or pravastatin) for more than one year period	20 (10 males; 10 females)	1	102.2 ± 0.7% *increase* from baseline in BMD of lumbar spine in patients on fluvastatin. Patients using pravastatin had 2% *decrease* in BMD	Fluvastatin showed a positive effect on bone formation, while pravastatin did not prevent bone loss
Chan et al.[2,3,11]	Observational case-control study of women above 60 yrs, some with fractures	3 675 (928 Reduced case patients and 2747 control subjects)	1	Recuced fracture risk in patients using statin: **OR 0.48 (95% CI 0.27-0.83)**	Fractures risk in patients on statin is significantly lower than in non statin users
Chung et al. [2,3]	Retrospective study of patients with type 2 diabetes mellitus, 36 on statins (lovastatin, pravastatin & simvastatin); 33 = control group	69	1.25	Increase of BMD: ▪ Femoral neck = **0.025g/m^2 (p<0.05)** ▪ Hip = **0.014g/m^2 (p<0.05)** ▪ Lumbar spine: non-significant decrease in statin users vs. control	Almost all statistically significant BMD increases in patients taking statins occurred in males, and can possibly be attributed to a decrease in osteoblast function

Legend: HR = Hazard ratio, OR = Odds ratio

References

1. Medscape expert Interview with Brinton EA. Statin Therapy: Risks vs Benefit. Medscape Cardiology. 2004; 8(1). Available from http://www.medscape.com.
2. Cruz AC and Gruber BL. Statins and Osteoporosis: Can these lipid-lowering drugs also bolster bones? Cleveland Clin. J. of Medicine. 2002; 69(4).
3. Gonyeau MJ. Statins and Osteoporosis: Clinical Review. J. Pharmacotherapy. 2005; 25(2): 228 – 243. Available from http://www.medscape.com.
4. Bandolier Extra. Cholesterol and Statins. April 2004. Available from http://www.ebandolier.com.
5. Tomlinson S and Mangione K. Potential Adverse Effects of Statins on Muscle. J. American Physical Therapy. May 2005; 85(5): 459–465.
6. Fine DM. Statin-Related Muscle Toxicity. J. Clinical Pharmacology. November/December 2003; 3(10): 554- 560.
7. Missouri DUR Report. Statin Therapy. Drug Use Review Newsletter. October/November 2003; 8(6).
8. Bottorff M, Hansten P. Long-term Safety of Hepatic Hydroxymethyl Glutaryl Coenzyme A Reductase Inhibitors. Arch. Intern. Med. August 2000; 160.
9. White MC. HMG CoA reductase inhibitor-induced muscle toxicity: risk, monitoring, and management. Formulary. November 2002; 37.
10. Bauer DC. Update on the Skeletal effects of Statins. Available from http://www.medscape.com.
11. Edwards CJ, et al. Statins and Bone: Myth or Reality? Calcif. Tissue. Int. July 2001; 69.
12. Watts N. Bisphosphonates, Statins, Osteoporosis, and Atherosclerosis. July 2002. Available from http://www.medscape.com.
13. Lupatelli G, et al. Simvastatin Increase Bone Mineral Density in Hypercholesterolaemia Postmenopausal Women. J. Metabolism. June 2004; 53(6): 744-748.
14. Wang PS, et al. HMG-CoA Reductase Inhibitors and the Risk of Hip Fracture in Elderly Patients. JAMA. June 2000; 283(24): 3211-3216.

Contributor: Misela Vena
Editorial Advisor: Dr J Noble

MediKredit Integrated Healthcare Solutions (Pty) Ltd ("MediKredit") 132 Jan Smuts Ave, Parkwood, PO Box 692, Parklands 2121, South Africa

Tel: (011) 770-6000 Fax: (011) 770-6325
E-mail: Medifile@medikredit.co.za
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