Review Article

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Cholesterol Reducing Drugs and its Effect on the Level of CoQ_{10}

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Abstract

The cholesterol lowering drugs are becoming popular among the society. As the society is suffering from obesity due to disturbed life style and increasing fast food habits. The Co-enzyme Q10 also termed as CoQ10 is located in the mitochondria of eukaryotic cells. It has the property of solubility in oil and it's like vitamin. The CoQ10 plays and important role in cellular respiration specifically in electron transport chain. The CoQ10 reactions results into the generation of Adenosine Tri-Phosphate (ATP). The maximum amount of energy of the body needs generated through this way. The organs having more energy requirements like heart, liver, kidneys have the elevated levels of CoQ10. It is evident that the cholesterol level reducing drugs also critically reduces the CoQ_{10}. The reduction of the CoQ_{10} level further shows adverse effects. The biosynthesis of cholesterol and CoQ_{10} has same point during the pathway. The therapy needs more in-depth research. The consideration and recognition of a drug as cholesterol level reducing drug will have more critical trials. The society will be really benefited if the drug is safe and have minimum or no side effects.

Keywords: Adenosine Triphosphate-ATP; Co-Enzyme Q10; Cholesterol Lowering Drugs; Obesity.

Co-enzyme Q_{10}

The Co-enzyme Q_{10} abbreviated as CoQ_{10} is present in mitochondria of eukaryotic cells. The co-enzyme is having the property of solubility in oil and it's like vitamin. The CoQ_{10} plays and important role in cellular respiration specifically in electron transport chain. The resultant of its participation leads to generation of Adenosine Tri-Phosphate (ATP). The maximum amount of energy of the body needs generated through this way. The organs having more energy requirements like heart, liver, kidneys have the elevated levels of CoQ_{10}. (Ernster L;Dallner G,1995)(Dutton P.L *et al,* 2000)

Beef mitochondrial CoQ_{10} was isolated during 1957. It is observed that in heart muscles its level is more due to high energy requirements. (Crane *et al* 1957)

The CoQ_{10} is available in 3 states i.e fully oxidized state called ubiquinone, semiquinone, ubiquinol. In human being the biosynthesis is the major source of CoQ_{10}. Deficiency of CoQ_{10} in humans may result because of reduced biosynthesis and increased utilization in body. Some chronic disease conditions like cancers, heart diseases also thought to be the reason behind reduction in the CoQ_{10} levels. The intake of 1200 mg/day is observed as safe level. The plasma CoQ_{10} level is assessable and it indicates the dietary intake status rather than the tissue level.

The mechanism of action of CoQ_{10} has enhancement in cardiac bio-energy, free radical hunter, anti-oxidant effect, improved endothelial effects and prevention of myocardial sodium-potassium ATPase activity. (Greenberg & Frishman, 1990)

The biosynthetic pathways of CoQ_{10} and cholesterol are same at some points. The mevalonate,

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which is the intermediary precursor of CoQ_{10} and suppressed by the cholesterol lowering drugs like statins.

CoQ_{10} biosynthesis occurs through steps like formation of benzoquinone, formation of isoprenoids side chain and joining of the two.

The patients on the treatment regimen of CoQ_{10} may develop the symptoms like nausea, Vomiting, Apetite loss and inflammation in stomach.

Carine Cleren *et al,* 2008 showed that the CoQ_{10} results in significant neuroprotective effects.

The physical state of CoQ_{10} is crystalline powder which is insoluble in water. The absorption of CoQ_{10} facilitates through micelle formation.

Cholesterol and its Biosynthesis

The free cholesterol and cholesteryl ester are the two forms of free cholesterol in tissues and plasma. Both forms in plasma transported in lipoproteins. In human beings the fats are absorbed as fatty acids from diet. These lipids then get transported across various tissue and organs for utilization and storage. The lipids were not soluble in water. Abnormalities in the metabolism of lipoprotein may cause hypo or hyper lipoproteinemias. The percent wise distribution of lipids in plasma is as under

Lipid	Percentage
Triacylglycerol	16%
Phospholipids	40%
Cholesterol	14%
Cholesteryl esters	36%
Long chain fatty acids	04%

The fats are less dense than the water and hence the density of lipoproteins reduces with increase of lipid proportion. The four major groups of the lipoproteins chylomicron, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high-density lipoproteins.

The cholesterol biosynthesis took place in the various tissues through acetyl-CoA which also act as precursor for various steroids like corticosteroids, sex hormones, bile acids and vitamin D.

The Low Density Lipoprotein (LDL) is important for the uptake of the cholesterol and cholesterol esters into many tissues. The High Density Lipoproteins HDL removes the free cholesterol from tissues transported to liver where it is eliminated from body. The removal of cholesterol may be as it is or after conversion to bile acids. Cholesterol is the main constituent in gallstones and plays a chief role in progression of atherosclerosis.

The cholesterol synthesized in body is about half of the body need (about 700mg/dl) and rest of the cholesterol is provided by the average diet.

The biosynthesis of the cholesterol took place through 5 steps.

1. Synthesis of mevalonate from acetyl CoA
2. Mevalonate losses CO_2 to form the Isoprenoids
3. Condensation of six Isoprenoids to form squalene
4. Cycalization of Squalene end up the product as the lanosterol
5. Cholesterol finally formed from the lanosterol (Robert K.Murray *et al.* 2003)

The CoQ_{10} and cholesterol biosynthesis share some point during pathway. The cholesterol level reducing drugs also adversely affect the CoQ_{10} level. This is the reason behind the generation of side effects of therapeutic use of the cholesterol level reducing drugs. Since the human being have the natural ability of biosynthesis of CoQ_{10} but deficiency may arise due to error in the biosynthetic pathways. At such event the supply of CoQ_{10} via medication may help for improvement.

Cholesterol Lowering Drugs

Statins and fibrates are the cholesterol level reducing drugs. Statins inhibit the Rac, a type of a small G protein. (K. Pahan, 2006)

The statins along with reducing of cholesterol level also deplete CoQ_{10} level. This will further results in weakening of heart muscles and immune system. The reports suggest that the CoQ_{10} protects the LDL from lipid peroxidation more effectively as cpared with the alpha-tocopherol. (Yamaonto Y *et al*, 1991, Stocker R *et al*, 1991) the cholesterol limiting drugs also known as Hypolipedemic drugs. There are many drugs that lower the cholesterol level. These drugs also show side effects. The drugs include Statin, Berberine etc.

Weijia Kong *et al* in 2004 in the study compared the drugs Berberine (BBR) and Statin. They observed that the Berberine have unique mechanism distinct from Statins. When the Berberine was administered orally to 32 patients suffered from high level of cholesterol for 3 months, the results observed that 29% showed reduced serum cholesterol level, 35% showed the reduced triglycerides and 25% showed the reduced LDL cholesterol level. In case of study with hamsters along with reduced serum cholesterol

level there were 3.5 fold increases in hepatic Low Density Lipoprotein Ribosomal mRNA and 2.6 fold increases in the Low Density Lipoprotein Ribosomal protein.

Teemu J. Murtola *et al* (2007) re-confirms the carcinogenicity of statins while study on Cholesterol-Lowering Drugs along with their effects as Prostate Cancer Risk. They found that the statin users were at more risk for development of prostate cancers as compared to other users.

Squalestetin I is a major hindering agent of cholesterol synthesis. The Squalestetin I is obtained from the fungi and it inhibits the squalene synthetase, an enzyme of mevalonate pathway without affecting the ubiquinone and dolichol. (Baxter A. *et al* 1992, Thelin A. *et al* 1992)

Ezemtmibe drug acts by block of cholesterol absorption. It is generally given with the statin. The drug Bile Acids Binding Resigns were used for the patients with high cholesterol level except triglycerides (TGs). The Nicotinic Acid shows its effects by slight increase in HDL level with decreasing the LDL, TGs and total cholesterol levels. Gemfibrozil and other fibrates reduce the triglycerides level by 20-30 %. Astrovastatin is widely used HMG-CoA reductase inhibitor. Niacin is a vitamin B and used as one of the cholesterol lowering drugs. It is observe that the niacin reduces the levels of both triglycerides and total cholesterol with increase in level of HDL.

Newman TB and Hulley SB in their study published in 1996 the fibrates includes Benzafibrates, Ciprofibrate, Gemfibrozil, Fenofibrate and statin includes Atorvastatin, Lovastatin, Pitavastatin, Rosuvastatin, Fluvastatin, Mevastatin, Pravastatin, Simvastatin, Simvastatin+Ezetimibe, Lovastatin+ Niacin, Simvastatin+Niacin. They also observed that during 1985 – 1995 the prescription of the lipid-lowering drugs increased more that 10 times due to aggressively promotion by their manufacturers. The time required for the approval of the Lipid-lowering drugs may be 30 years+ by the FDA as the drugs were approved clinical trial dependent. During the trials the millions of asymptomatic people were given the medications. Cholesterol lowering drugs may increase non-cardiovascular mortality. The classes of the lipid lowering drugs like fibrates and the statins cause cancer in rodents.

Six year duration study of lipid influencing drugs as part of project among male survivors of myocardial infarction in was studied during 1975 as the Coronary Drug Project. (Coronary Drug Project, 1975) The projects concluded with the conclusion that the three lipid-influencing regimens out of the five lipid-influencing regimens studied the will need to be discontinued early because of adverse effects. Treatment with the clofibrate and niacin did not show any adverse effects studied.

The drugs studied were low dose and high dose estrogen, aspirin, clofibrate and niacin.

Bile Acid Sequestrants or the Resins

Bile acids are the breakdown product of cholesterol excreted into the intestine by the liver as bile. Out of the total bile acids the 90% will be reabsorbed from the intestine and used to make cholesterol in liver. Bile Acid Sequestrants or the resins hinder with this intestinal re-absorption by binding the bile acids in the gut and thus promoting their excretion from the body.

Cholesterol Absorption Inhibitors

Cholesterol absorption inhibitors act via obstruction of the assimilation of cholesterol at the brush border of the intestine and this will not affect the absorption of triglycerides or fat soluble vitamins.

These drugs have the benefit of not being absorbed and can help in lowering of cholesterol by about 20% on their own.

(www.cvtoolbox.com,2007)

Fibric Acid Derivatives

The fibric acid derivatives or Fibrates are the drugs like Gemfibrozil (Lopid), Fenofibrate (Lipidil micro, Lipidil Supra, Lipidil EZ), and Bezafibrate (Bezalip). They can reduce the triglycerides (35-50%) levels; increase the high density lipoproteins (HDL) levels (15-25%).

(www.cvtoolbox.com)

The drugs explained above have some benefits and some side effects too. The therapeutic use of any cholesterol level reducing drug is the method of choice as per the need of the patient. The physician may take proper care of the patient and prescribe as per the status of the patient.

Sources of CoQ_{10}

Sources of CoQ_{10} include meat and fish and in some amount found in nuts also. There is little or none is in grains, vegetables or fruits. The body has natural ability to synthesize CoQ_{10} hence when dietary source is not adequate it can be synthesize by body. Dietary intake through food is about 2-5 mg per day.

Benefits of CoQ_{10} as drug

The use of $CoQ_{10\ as}$ drug is beneficial in many diseases especially metabolic disorders. In case of diabetes it helps to improve function of endothelial cell lining of blood vessels. In case of high blood pressure it helps to lower blood pressure in some patients. In case of migraine headache CoQ_{10} proved more beneficial over the use of riboflavin. (http://www.coq10coenzymeq10.com)

The currently used lipid lowering drugs have effects as well as side effects also. The time required to establish a compound to be lipid lowering drug is more than three decades.

Conclusion and Discussion

It is evident that the cholesterol level reducing drugs also critically reduces the CoQ_{10}. The reduction of the CoQ_{10} level further shows adverse effects. The biosynthesis of cholesterol and CoQ_{10} has same point during the pathway. The therapy needs more in-depth research. The consideration and recognition of a drug as cholesterol level reducing drug will have more critical trials. The society will be really benefited if the drug is safe and have minimum or no side effects. The cholesterol level reducing drugs need to be taken with proper prescription only. The CoQ_{10} levels need to be monitored while on the cholesterol level reducing drug medication. Berberine drug need to be more deep investigation for side effects, depletion of CoQ_{10} level apart from other benefits. Combination of various cholesterol levels reducing drug as part of combination therapy also advantageous if implemented after serious study and clinical trials. Squalestetin I may also become useful as its do not have side effect in the form of CoQ_{10} level depletion. The best therapy out of the above describe drugs may serve better and can save more lives. At present the countries are facing the death due to hyper cholesterol level and its assimilation in arteries which supplies blood to heart muscles. The heart attack is caused due to low supply of blood to heart muscles. The world level organizations like World Health Organization W.H.O may come forward in this regard to formulate a good therapy for saving lives losses due to hyper cholesterol levels.

References

1. Baxter, A., Fitzgerald, B.J., Hutson, J.L., McCarthy, A,D., Motteram, J.M., Ross, B.C., Sapra, M., Snowden. M.A., Watson, N.S., Williams, R.J. and Wrigth, C. J. Biol. Chem. 1992;267:11705-11708.
2. Carine Cleren, Lichuan Yang, Beverly Lorenzo, Noel Y. Calingasan, Andrew Schomer, Anthony Sireci, Elizabeth J. Wille and M. Flint Beal. Therapeutic effects of coenzyme Q10 (CoQ10) and reduced CoQ10 in the MPTP model of Parkinsonism, journal of neurochemistry 2008.p.1613–1621.
3. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360-81.
4. Crane, F. L, Hatefi, Y., Lester, R. I., & Widmer, C. (1957), Isolation of a quinone from beef heart mitochondria. Biochim Biophys Acta 1957;25:220–221.
5. Dutton, PL; Ohnishi, T; Darrouzet, E; Leonard, MA; Sharp, RE; Cibney, BR; Daldal, F; Moser, CC. "4 Coenzyme Q oxidation reduction reactions in mitochondrial electron transport". Boca Raton: CRC Press. 2000;p.65–82.
6. Ernster, L; Dallner, G. "Biochemical, physiological and medical aspects of ubiquinone function". Biochimica et Biophysica Acta 1995;1271(1):195–204.
7. Greenberg, S., & Frishman, W.H. Co-enzyme Ql0: a new drug for cardiovascular disease. J Pharmacol1990;30:596–608.
8. G De Pinieux, P.Chariot, M. Ammi-Said, F. Lourn, A.Astier,B. Jactot & R.Gherard(1996), Lipid Lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio, Br J Clin Pharmacol 1996;42:333–337.
9. http://www.coq10coenzymeq10.com/accessed on 20-11-2015.
10. K. Pahan.*Cell Mol Life Sci*. 2006 May;63(10): 1165–1178.
11. Teemu J. Murtola, Teuvo L.J. Tammela,Jorma Lahtela, and Anssi Auvinen, Cholesterol-Lowering Drugs and Prostate Cancer Risk: A Population-based Case-Control Study Cancer Epidemiol Biomarkers Prev 2007;16(11).
12. Thelin, A., Peterson, E., Hutson, J.L, McCarthy, A.D., Ericsson, J.and Dallner, G. Biochim. Biophys. Acta 1994;1215:245-249.
13. Robert K.Murray, Daryll K.Granner, Peter A.Mayes, Victor W.Rodwell, Harper's Illustrated Biochemistry,26th Edn, Lange Medical books/Mc Graw Hill Medical Publishing Division, New York. 2003.
14. Newman TB, Hulley SB. Carcinogenicity of Lipid-lowering Drugs, 1996;275(1):55-60.
15. Stocker, R., Bowry, V.W. and Frei, B. Proc. Natl. Acad. Sci. USA 1991;88:1646-1650.
16. Weijia Kong, jing Wei, parveen Abidi, Meihong Lin, Satoru Inaba, Cong Li, Yanling Wang, Zizheng Wang, Shuyi Si, Huaining Pan, Shakui Wang,

Jingdan Wu, Yue Wang, Zhuorong Li, Jingwen Liu and Jian-Dong Jiang. Berberin is a noval cholesterol-lowering drug working through a unique mechanism distinct from Statins, Nature Medicines 2004;10:1344-1351.

17. www.cvtoolbox.com, Cholesterol and Lipid Lowering Drugs. Continuing Medical Implementation® Inc. November 2007.p.3

18. Yamamoto, Y., Kawamura, M., Tatsuno, K., Niki, E. and Naito, C. In Oxidative Damage and Repair: Chemical, Biological and Medical Aspects (Davies, K.J.A., ed.) 1991.p.287-291, Pergamon, London.