PITAVASTATIN LOWERS PLASMA LEVELS OF COQ10 LESS THAN EQUIPOTENT DOSES OF ROSUVASTATIN OR ATORVASTATIN

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Background & Purpose

Coenzyme Q10 (CoQ10) is a fat-soluble quinone that participates in electron transport during oxidative phosphorylation. In the body to help preserve ATP stores, CoQ10 exists either in its oxidized form, ubiquinone, or in its reduced form, ubiquinol. These two forms affect bioavailability, transportability, and antioxidant activity. Statins block production of farnesyle pyrophosphate, an intermediate in the synthesis of CoQ10 (1). The reduction of CoQ10 following statin therapy is considered a possible mechanism for muscle-related averse events due to cellular ATP depletion and may be related to risk of incident diabetes (2). CoQ10 may be able to counteract various metabolic disturbances associated with insulin resistance as CoQ10 deficiency has been observed in patients with insulin resistance and diabetes. Recent meta-analyses have shown an increase in risk of incident diabetes following treatment with statins and is both dose-dependent and statin-dependent.

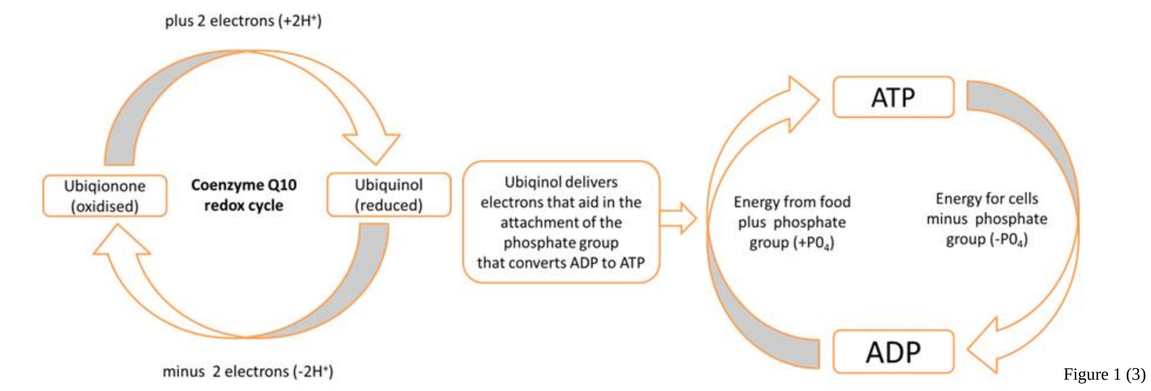

Figure 1 (3)

Lipoprotein Insulin Resistance (LpIR) is a new biomarker strongly associated with increased insulin resistance and potentially incident diabetes and may be an early indicator of type 2 diabetes risk (4,5,6).

Lipoprotein Insulin Resistance (LpIR) Score Parameters
Very-low-density lipoprotein (VLDL)
High-density lipoprotein (HDL) particles of average size
Low-density lipoprotein (LDL) particles of average size
Concentrations of large VLDL
Concentrations of large HDL
Concentrations of small LDL subclasses

Results

Comparable LDL-C reduction was noted among the 3 groups (Table 1), (p-value=0.2626), however, pitavastatin decreased CoQ10 levels (Table 2), in particular ubiquinol, significantly less than atorvastatin and rosuvastatin (p-value=0.0401). No statistically significant treatment difference was observed in ubiquinone levels (p-value=0.6988), however the significant change in ubiquinol (*p-value 0.0401) allowed total CoQ10 (**p-value 0.0697) to be marginally significant. No statistically significant treatment differences were observed in the metabolic or lipid measures. Among the lipoprotein particles and apolipoproteins, LDL-particle number showed a significant difference between treatment groups (p-value=0.0087); as subjects in the rosuvastatin arm exhibited the smallest decrease in LDL-particle number, while those in the atorvastatin arm exhibited the largest decrease. In the LpIR data analysis, the report found that although the mean LpIR did not change significantly from pre- to post-treatment for any treatment condition, both atorvastatin and pitavastatin did show non-zero decreases in LpIR.

Conclusion

Pitavastatin showed the smallest reduction in CoQ10 as well as greatest reduction in LpIR compared to atorvastatin and rosuvastatin. Pitavastatin may be preferred when considering statin therapy for patients needing potent LDL-C reduction, but at risk for developing diabetes due to impaired glucose tolerance or patients with drug induced muscle symptoms. LpIR could be a novel biomarker to measure insulin resistance in patients with type 2 diabetes to guide statin therapy. Further studies are necessary to determine the clinically relevant changes in levels of CoQ10 and in markers of insulin resistance and incident diabetes with statin therapy when considering treatment regimens.

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Hypothesis

In an adult, non-diabetic patient population with increased insulin resistance and dyslipidemia, pitavastin will lower CoQ10 less, particularly ubiquinol, and decrease LPIR more than equipotent doses of rosuvastatin or atorvastatin.

Methods

Single site double blind study of 134 patients randomized to pitavastatin 4 mg qd n=45), rosuvastatin 5 mg qd (n=44) and atorvastatin 20 mg/qd (n=45) for 12 weeks. The primary endpoint was to determine the difference in plasma levels of total CoQ10, ubiquinol and ubiquinone levels, before and after 12 weeks of therapy, between the three groups. Nine patients were excluded from the final analysis for not completing therapy. Non-parametric Kruskal Wallis tests were done to assess treatment differences in the change in CoQ10, ubiquinol, and ubiquinone from baseline. A secondary analysis of the data measured serum LpIR which is a known marker for risk of diabetes.

Tables of Results

TABLE 1: Select Lipid and Lipoprotein Changes Post Statin Therapy

	Atorvastatin		Pitavastatin		Rosuvastatin	
	Percent Change	Std.Dev.	Percent Change	Std.Dev.	Percent Change	Std.Dev.
HDL Cholesterol	-0.03	0.13	0.01	0.11	-0.01	0.11
LDL Cholesterol	-0.40	0.13	-0.38	0.01	-0.35	0.14
LDL-Particle	-0.42	0.14	-0.39	0.13	-0.32	0.16
Total Cholesterol	-0.29	0.10	-0.26	0.10	-0.26	0.10

TABLE 2: CoQ10 levels Post Statin Treatment

Raw Change	Atorvastatin			Pitavastatin			Rosuvastatin			ANOVA	K-Wallis
	N	Mean Change (mcg/ml)	Std.Dev.	N	Mean Change (mcg/ml)	Std.Dev.	N	Mean Change (mcg/ml)	Std.Dev.	p-value	p-value
Ubiquinone (mcg/ml)	42	-96.70	224.24	40	-110.42	136.29	36	-103.91	237.27	0.9544	0.6988
Ubiquinol (mcg/ml)	42	-624.39	669.45	40	-354.43	544.42	36	-538.52	709.53	0.1590	0.0401*
Total CoQ10 (mcg/ml)	42	-721.09	830.47	40	-464.85	571.37	36	-642.43	874.99	0.3090	0.0697**

TABLE 3: Mean of LpIR Levels Before and After Statin Treatment

	Atorvastatin	Pitavastatin	Rosuvastatin
Pre-Treatment	46.89	51.84	46.38
Post-Treatment	41.12	45.50	44.80
Treatment Effect	-5.85	-6.40	-1.57

References

1.Thompson, P. D., and L. Marcoff. "The role of coenzime Q10 in Stain-Associated Myopathy." JACC 49 (2007): 2231-7.
2. Munoz, A., et. al. (2014, Dec.). *Effect of statins (atorvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) on adenosine triphosphate (ATP) levels of 3T3-L1 adipocytes in presence and absence of Coenzyme Q10 (CoQ10).* Poster presented at the 2014 ASHP Midyear Clinical Meeting, Anaheim, CA.
3. Tang PH, Miles MV, DeGrauw A, Hershey A, Pesce A: HPLC analysis of reduced and oxidized coenzyme Q(10) in human plasma. Clinical chemistry 2001, 47:256-265.
4. Otvos et al. Circulation. 2006;113:1556-1563
5. Genuth and Kahn. Diabetes Care. 2008;31:1093-1096
6. Insulin Resistance and Pre-Diabetes. 2008. U.S. Department of Health & Human Services. NIH Publication No. 09-4893.

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