The effect of COQ2 gene (A>G)rs6535454) polymorphism on the occurrence of myopathy in statin-treated patients

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Abstract

One option that may affect how well patients tolerate their statin treatment is the COQ2 gene, which codes for the polyprenyltransferase (coenzyme Q2) enzyme. This enzyme aids in the production of coenzyme Q10 (CoQ10), whose depletion is triggered by statin medication and is regarded to be a contributing factor in the development of statin-related muscle symptoms. Therefore, statin-induced myopathy susceptibility may be explained by COQ2 gene polymorphisms. Myopathy is a prominent side effect of statins that leads to intolerance and ultimately the drug's discontinuation. The Imam Al-Hussein Medical City in Kerbala hosted the cross-sectional observational study. The trial's participants included 150 individuals who were atorvastatin users in total. A 40 mg atorvastatin tablet was administered once daily to all of the trial's participants, whose ages ranged from 30 to 65. Coenzyme Q10, lipid profile (cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein), renal function test (creatinine), creatinine kinase, and thyroid stimulating hormone were all measured in blood samples taken from patients who had given informed consent for genetic testing. In this work, COQ2 (A>G) was found using the Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS PCR) (rs6535454). In the Iraqi dyslipidemic patients , there is a significant effect of common polymorphisms (rs6535454) within the COQ2 gene, this poses a risk of developing myopathy associated with the use of atorvastatin.

KeyWords: myopathy, atorvastatin, COQ2 gene, Coenzyme Q10.

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Introduction

The treatment of high plasma total and low-density lipoprotein cholesterol levels typically involves the use of statins. Statins primarily function by interacting with 3-hydroxy-3-methylglutaryl coenzyme to stop the production of cholesterol. As a result of a reductase, the plasma concentrations of atherogenic lipoproteins are reduced(1,2). But using statins is associated with a wide range of adverse side effects, the most prevalent of which are muscle issues (myopathies and myalgia) (3,4). Statin-associated muscle symptoms (SAMS) were demonstrated to occur 1-2% of the time in research trials, but this percentage climbs to 15-20% in daily clinical practice(5). Due to the exponentially increasing number of patients undergoing statin therapy (almost 50% of US citizens over the age of 65 are taking statins), the number of persons in industrialized countries who are at an increased risk of SAMS may reach millions (6). Statin tolerance varies greatly from person to person, and a sizable genetic component is anticipated (5,7). Recent research suggests that common SNPs (rs6535454) in the COQ2 gene may be candidates for the emergence of SAMS (8-10). The production of CoQ10 involves the enzyme Coenzyme Q2 (COQ2, 4-hydroxybenzoate-polyprenyltransferase). It catalyzes the prenylation of para-ahydroxybenzoate. It is believed that CoQ10 concentration significantly contributes to the development of SAMS (7).

We looked at the potential impact of the COQ2 gene variant rs6535454 on the likelihood that SAMS would manifest in patients from Iraq receiving standard statin dosages.

Materials and methods

This prospective clinical study was conducted at Imam Al-Hussein Medical City/Cardiology Center and Al-zahraa Center from October 2021 to February 2022 with participants from the outpatient clinic in Kerbala, Iraq, and the College of Pharmacy at the University of Kerbala. The experiment included 150 participants who were using the statin drug atorvastatin. Ages 30 to 65, all trial participants had been taking atorvastatin 40 mg for at least six months. Patients with hypothyroidism, recent surgery, severe renal failure, liver failure, recurrent infection, numerous comorbidities, low body mass index, and several drugs were prohibited from participating in this experiment. The study's protocol was approved by both the Kerbala Health Directorate and the college of pharmacy at the university of Kerbala's ethical research committee. After being informed of the study's purpose and nature, each patient and the imam of Al-Hussain Medical City gave their approval.

Blood samples were taking from eligible patients after getting their consent. All trial participants, who had fasted overnight, had their 5 mL of venous blood drawn in the morning. For the genetic testing, 2 ml was placed in an EDTA tube, and 3 ml was then added to the gel tube for the serum analysis. Serum was aspirated from the blood after it had been centrifuged at 3000 rpm for 10 minutes and utilized for analysis.Creatinine kinase (CK), Coenzyme Q10 (COQ10), renal function test (creatine), thyroid stimulating hormone (TSH), and lipid profile (total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL)) were the biochemical parameters that were measured for all patients. Genomic DNA was extracted from each blood sample using (Favorgen, china) genomic DNA extraction kit for blood, according to the manufacturer's instructions. The DNA was stored at - 200C until use. The SNP of COQ2 gene (rs6535454) was genotyped using conventional genotyping assays. PCR was run using specific primers created for the COQ2 gene. Based on the NCBI database, all gene information, sequence details, and SNP information were retrieved. Using specialist software, primer designs were produced. The statistical software for social sciences (SPSS) version 28 from IBM, US, was used to manage, process, and analyze the data of research participants after they were entered into a computerized database, checked for mistakes or inconsistencies, and finally analysed.

Results and discussion

Demographic characteristics for patients participated in the study showed that the age

categories reveals that the age group (48—65 years) are the higher percentage among other group. As shown in the table below, where females constituted 54% compared to males, in addition to that, BMI was the highest percentage among the group of overweighed people

Table (1): Descriptive of the Demographic and of the study population (n= 150).

Variable		N	%
Age (Years)	30 – 37 Years	16	10.7
	38 – 47 Years	35	23.3
	48 – 65 Years	99	66.0
Gender	Male	69	46
	Female	81	54
BMI Category	Normal weight	42	28.0
	Over weight	70	46.7
	Obese	38	25.3
Duration Treatment	1 – 24 Months	104	69.3
	25 – 48 Months	32	21.3
	49 – 72 Months	9	6.0
	73 – 96 Months	5	3.3
Smoking	Yes	41	27.3
	No	109	72.7
muscle cramps	Yes	47	31.3
	No	103	68.7
Weakness	Yes	60	40.0
	No	90	60.0
No Symptoms	Yes	49	32.7
Data Presented by numbers and percentage			

Genotyping of Gene (rs6535454)

Genetic polymorphism of gene for rs6535454, which observed were classified into three genotypes:

1. The major genotype group (AA) homozygous for the allele A.

2. The minor genotype group (GG) homozygous for the allele G.

3. The heterozygous (AG).

Table (2) and figure (1) summarizes the distribution of genotyping groups of rs 6535454 in patients

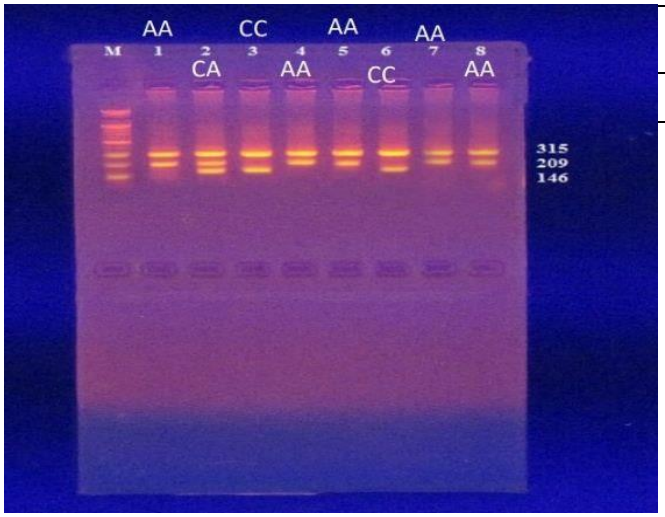

Figure (1): Genotyping of gene polymorphism rs 6535454.

Table (2): Distribution of gene polymorphism rs 6535454 different genotypes in Patients.

Variable	Group	Frequency	Percentage
Genotype	AA (wild)	63	42%
	AG (hetero)	37	24.7%
	GG (mutant)	50	33.3%
Data Presented by numbers and percentage			

In same way SNP rs6535454 differ from those expected under Hardy-Weinberg equilibrium (figure 2), number of observed vs expected were: {AA (63, 44.28); GG (50, 31.29); AG (37, 74.38) (goodness-of-fit x2 for Snip rs 6535454 gene = 22.234, P < 0.001} and therefore it was statistically significant table (3).

Table (3): Hardy-Weinberg equilibrium for rs 6535454 in patients.

Genotypes			Alleles		Hardy–Weinberg equilibrium X^2 test
			A	G	
Symbol	Frequency	%	0.5433	0.4567	37.940 P < 0.001 [S]
AA(Wild)	63	42			
AG (Hetero)	37	24.7			
GG (Hemo)	50	33.3			
Total	150				

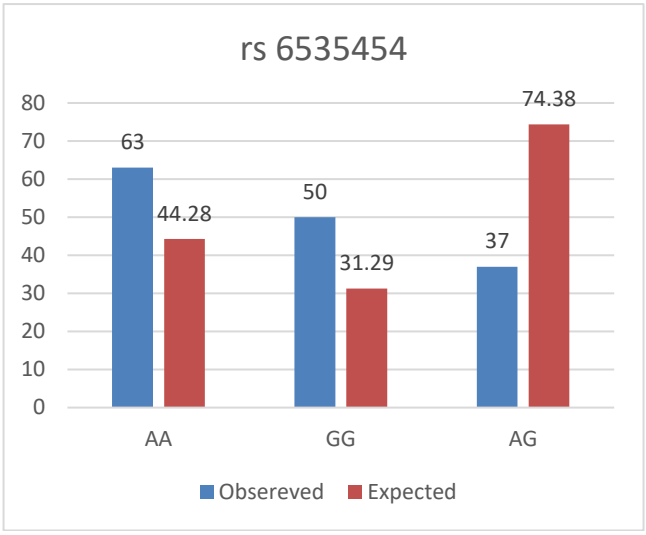

Figure (2): Observed (Obs.) vs expected (Exp.) genotype frequencies % of rs 6535454 gene among individuals' sample.

Relationship between demographic characteristics and rs6535454 SNP polymorphism.

To show the difference between demographic characteristics (mean) and rs 6535454 SNP (table 4), by performing a one-way ANOVA test to compare the mean age, weight, height, BMI, duration of treatment. A significant difference was found between mean weight of patient and rs 6535454 SNP, (p = 0.015), post hoc testing using LSD adjustment showed that the mean weight for the AA SNP (79.1±13.48) is higher than that AG SNP (71.35±11.63). No statistically significant difference was found among other mean of demographic characteristics (p > 0.05).A chi-square test was conducted between gender, smoking, and symptoms between rs 6535454 SNP, there was no statistically significant difference between them (p > 0.05).

Table (4): difference between demographic characteristic mean in rs 6535454 SNP.

Demographic parameters			Patient Genotype (N=150)			P value
			AA (N=63)	AG (N=37)	GG (N=50)	
Gender	Male		29(46%)	15(40.5%)	50(50%)	0.682 [NS]
	Female		34(54%)	22(59.5%)	25(50%)	
Symptom	Muscle cramp	Yes	22(34.9%)	9(24.3%)	16(32%)	0.54 [NS]
		No	41(65.1%)	28(75.7%)	34(68%)	
	weakness	Yes	25(39.7%)	14(37.8%)	21(42%)	0.924 [NS]
		No	38(60.3%)	23(62.2%)	29(58%)	
	None	Yes	22(34.9%)	14(37.8%)	13(26%)	0.448 [NS]
		No	41(65.1%)	23(62.2%)	37(74%)	
Results are presented as mean ± SD, or n= number of subjects and percentage, p<0.05 considered significantly different, [S]= Significant, [NS]= Non significant						

Effect of treatment with Statins on Lab. parameters having rs6535454 SNP.

To show the difference between mean of lab. Finding of (COQ10, CK, TSH, and Cr) between rs 6535454 SNP groups (table 5), by comparing the mean using a one-way ANOVA test. A statistically significant difference was found among mean of COQ10 between rs 6535454 SNP groups ($p < 0.001$). Post hoc testing using LSD adjustment showed that the mean COQ10 for the AA allele (14.40±6.98) is significantly higher than that of other 2 alleles. No significant difference was found between other mean of parameters and rs 6535454 SNP groups, ($p > 0.05$).

Table (5): difference between Lab finding mean in rs 6535454 SNP.

LAB parameters	*COQ2 gene* rs 6535454 SNP (N= 150)			P value
	AA (N=63)	AG (N=37)	GG (N=50)	
COQ10	14.40±6.98*	10.23±5.6	8.63±3.68	**<0.001[S]**
CK	119.35±49.91	141.86±56.1	139.88±58.66	0.062[NS]
Cr	0.85±0.401	0.82±0.35	0.76 ±0.23	0.398[NS]
TSH	1.79±1.07	1.72±1.02	2.03±1.05	0.335[NS]
Results are presented as mean ± SD, p<0.05 considered significantly different, [S]= Significant, [NS]= Non significant				

Effect of treatment with Statins on lipid profile parameters having rs 6535454 SNP.

To show the difference between mean of lipid profile Finding of (Cholesterol, triglyceride, LDL, and HDL) between rs 6535454 SNP groups (table 6), by comparing the mean using a one-way ANOVA test. A statistically significant difference was found among mean of HDL between rs 6535454 SNP groups ($p < 0.046$). Post hoc testing using LSD adjustment showed that the mean HDL for the GG allele (43.78±12.59) is significantly higher than that of AA allele (38.52±9.01). No significant difference was found between other

mean of parameters and rs 6535454 SNP groups, ($p > 0.05$).

Table (6): difference between lipid profile mean in rs 6535454 SNP.

Lipid profile parameters	*COQ2 gene* rs 6535454 SNP (N= 150)			P value
	AA (N=63)	AG (N=37)	GG (N=50)	
CHOL	165.65±50.36	155.27±47.4	170.72±51.56	0.360[NS]
TG	173.08±84.38	140.19±49.7	156.88±64.99	0.080[NS]
LDL	88.25±37.68	83.23±33.92	95.45±38.77	0.303[NS]
HDL	38.52±9.01*	40.93±11.9	43.78±12.59*	**0.046 [S]**
Results are presented as mean ± SD, p<0.05 considered significantly different, [S]= Significant, [NS]= Non significant				

Estimation of risk in COQ2 gene rs 6535454 SNP in regarding to the lab. parameters:

The odds ratios of the detected genotypes of COQ2 gene rs 6535454 SNP in the levels of COQ10, Cr, CK, TSH, Chol, TG, LDL, and HDL in the myopathic patients treated with statin Table (7).The logistic analysis of the COQ2 gene rs 6535454 SNP of the myopathic patients concluded that the response to treatment (Statin) regarding COQ10 and HDL level was significantly related to the AA allele in comparison with GG allele (OR = 1.144, $p < 0.001$) and (OR = 0.951, $p = 0.019$) respectively. No other significant effect on other parameters $p > 0.05$.

Table (7): The odds ratios of COQ2 gene rs 6535454 SNP with levels of lab.parameters.

Variables	SNP	OR (95% CI)	p value
COQ10	**CC**	1.144 (1.061-1.233)	< **0.001 [S]**
	CA	0.985 (0.878-1.104)	0.794 [NS]
	AA	1[a]	-
Results are presented [S]; Significant, [NS]; Non significant, OR: Odds Ratio, CI; Confidence Interval, 1[a]; reference category			

The most frequent side effect of statin medication is myopathy, which can range from myalgia (muscle pains without an increase in creatinine kinase) to myositis (muscle symptoms with increased creatinine kinase level). Rarely, it can become severe enough to cause rhabdomyolysis, which can be fatal (muscle symptoms with marked elevation of creatinine kinase and myoglobinuria). According to the diagnostic criteria for myopathy and the type of investigation, the incidence of statins-induced myopathy reported in prior studies ranged from 5% to 20% (11).

Few medications are as commonly used as statins, which successfully lower blood cholesterol levels and guard against a variety of cardiovascular illnesses linked to atherogenesis (12). Similar to how the statins' side effects, which mostly impact skeletal muscle, are common and severe enough to prompt one pharmaceutical manufacturer to pull cerivastatin from the market, few medications have caused as much controversy (13). However, despite ongoing concerns about their safety, statins are still frequently used. The common method by which these medications work. Mevalonate serves as a precursor for several chemicals, including dolichols and CoQ10, whose production is unintentionally hampered by inhibition of cholesterol metabolism at the level of mevalonic

acid (14). After just 14 days of treatment, atorvastatin significantly and rapidly decreased plasma CoQ10 levels, and this effect became much more pronounced after 30 days of treatment (15).

To the best of our knowledge, this is the first study that looked at the interindividual variability of the COQ2 gene, which is involved in statin-induced myopathy, in Iraqi patients who were on atorvastatin.

At atorvastatin 40 mg, demographic data for research participants showed that their ages ranged from 30 to 65, with the majority of patients falling into the (48 to 65) age category, or roughly 60% of patients. Major alterations in body composition brought on by aging, such as a progressive loss of muscle mass, strength, and quality coupled with an increase in fat content, can have a detrimental effect on older persons' functional status. Skeletal muscle changes are particularly significant because they are necessary for movement(16) .

Therefore, statin-associated adverse muscular reactions were statistically significantly more likely to emerge as people aged over 50 (17). This study disagree with previous study, where there is no significant association between age groups and statin related muscle symptoms. While it was agree with (18) , where they found no evidence of age-related changes, making the idea that older patients would be more at risk due to the prevalence of muscle symptoms in this group highly improbable.

The gender distribution was about 72.7% for male and 27.3% female, the result show that, 40.3% of 109 male and 80.3% of 41 female patients have muscular symptoms, these reveal that the female gender are more likely to occurrence of statin associated muscle problems Males are often physically stronger than females, which may be because they have greater muscle mass and less body fat overall. There are various causes for this, but hormones are by far the most significant. In men, testosterone helps enhance muscle strength and lean body mass or also increase muscle strength (19). These disagree with (20), which found that in regard to gender myopathy was more common in men than in women (31.4 percent vs. 22.6 percent), although it was in agreement with skilliving et al.(2016)(15) Which showed that female had a higher frequency than male (17 percent vs. 12 percent).

Obesity sets off a chain of events that includes larger adipocytes and more macrophages, more pro-inflammatory senescent cells in adipose tissue, elevated inflammatory markers, reactive oxygen species, insulin resistance, leptin levels, and decreased adiponectin. These events eventually lead to a loss of muscle mass and strength that is disproportionate to the relative increase in body size. As a result of the skeletal muscle's inability to move an obese person, muscle issues emerge (21).

Most of participant in study were over weighted (46%). There is a positive correlation between body mass index and adverse muscle reaction that caused by atorvastatin use. Several researchers reported obesity as risk factor (22). Whereas others discovered that a statin-induced myopathy is more likely when a person is fragile and has a small body size. (23). This study support the first observation, and it's also disagree with (23), where the lower BMI was statistically significant association with increase risk of developing muscle symptoms.

Mostly of the patients (about 69.3 %) were having a duration of treatment in range of (1-24) months. About 68.7% of the patients were reported to not having any muscle cramps while 60% were not having any Weakness. In statin-induced myopathy, the muscle pathology is non-specific, including fiber necrosis, degeneration, regeneration, and phagocytic infiltration. In certain instances, ragged red fibers, subsarcolemmal accumulations, lipid-filled vacuoles, and cyclo-oxygenase negative fibers are visible (24). Breakdown of the T-tubular membranes and subsarcolemmal fissuring are two examples of skeletal myocyte injury (separating the myo- filaments from the plasma membrane, but leaving the plasma membrane intact). These modifications take place even in patients who do not exhibit symptoms. (25).

On the other hand, research was done on the influence of pharmacogenetics on patients from South India who developed statin-induced myopathy. Statin therapy is constrained by

skeletal muscle toxicity brought on by increased systemic drug exposure. Up to 10% of statin-treated people may occasionally experience muscle pain or weakness (26).

Nearly 72% of the people under study were non-smokers, whereas 21% were active smokers. Smokers are less likely to engage in physical activity, which is secondary to the finding that they are less likely to experience muscle pain(27).

Table (3) displayed the genotype and allele frequencies for rs 6535454. For both dominant and recessive models, the allele and genotype frequency distribution met the criteria for Hardy-Weinberg equilibrium ($p < 0.05$). For these polymorphisms of the study individuals, a significant difference was discovered. Based on the presence or absence of statin-induced myopathy, genetic data of the rs 6535454 polymorphisms were divided into two groups. The study found that the rs 6535454 polymorphism had genotype frequencies of 42 percent for homozygous wild genotype, 24.7 percent for heterozygous people, and about 33.3 percent for homozygous mutants. No explanation was provided. Additional research is needed to examine the other genotypes and to compare the plasma medication concentrations in patients receiving statin therapy (28).

An essential component in mitochondrial respiration is the enzyme coenzyme Q10. Primary CoQ10 insufficiency is a clinically and genetically variable syndrome that is thought to be autosomal recessive and is linked to myopathy(29).

In-patient on atorvastatin, reduction CoQ10 level is routinely observed (30) and a little decline in muscle CoQ10 has been recommended in some (31), but not other study (32). COQ2 encodes parahydroxy benzoate-polyprenyl transferase. Primary CoQ10 insufficiency and COQ2 have been linked (33).

COQ2 variants and in particular (rs6535454) (A>G) have been investigated, and have reported as shown in table (5) an association with statin induce myopathy by causing highly reduction in serum CoQ10 level particular in patients with homozygous mutant genotype (GG) which present in 50 patients with mean (8.63±3.68).

While in heterozygous genotype patients (AG) the COQ10 serum level mean was (10.23±5.6), it also decrease but less than (GG) patients. While the patients, which have wild type (AA) with mean (14.40±6.98) that have the ability to remain the CoQ10 level high and within the normal range. From the result the deduction was that the COQ2 gene polymorphism in (rs6535454) can increase the risk of atorvastatin induce myopathy.

The study was agree with (34), reported significant association between statin intolerance and SNP (rs6535454) ($p=0.047$). While disagree with Jaroslav et al. (2017), where there is no correlation between the chance of developing statin-related muscle issues and the common polymorphism (rs6535454) within the coq2 gene(35).

Based on creatine kinase level in table (5) the homozygous wild (AA) mean (119.35±49.91) and homozygous mutant genotype (GG) mean (139.88±58.66) and heterozygous genotype (AG) mean (141.86±56.1), the result show that in patients carry (GG) and (AG) genotypes there was elevation in creatine kinase level in compare with (AA) genotype in atorvastatin taking individuals.

Although this value did not rise to the extent that qualifies to be statistically significant, however, patients who have these genotypes are more sensitive to statin therapy, because the statin itself increase creatine kinase level by causing muscle damage and release this enzyme so, it exacerbated the condition.

In the genotype of the polymorphism of COQ2 SNP gene rs 6535454 was showed a statistically significantly different in the homozygous wild genotype (CC) ($p < 0.05$). (OR = 1.144 ; 95% confidence interval = (1.061-1.233) as shown in table (7). Myopathy has proven to be a difficult disease to understand and unfortunately all previous genetic links have not been replicated in larger studies. All variants known to be pathogenic or presented as of uncertain significance were analysed.

Conclusion and recommendation

There was a strong correlation between the CoQ2 gene found in Iraqi patients using statins and

lower CoQ10 serum levels, indicating that COQ2 genotypes have an effect on this parameter's levels and may therefore affect how well atorvastatin works.The homogeneous mutant genotypes and heterogeneous genotypes of the COQ2 gene are connected with significantly elevated serum creatine kinase levels.In conclusion to prevent the occurrence of myopathy with statin use we suggest to reduce the atorvastatin dose or change to another lipid lowering agents that have less effect on muscles.

To completely identify the impact of COQ2 genetic variant on Atorvastatin side effects, increase sample size, and use case-control studies rather than cross-sectional observational research in Iraqi hyperlipidemic patients using Atorvastatin.Research the effects of Coenzyme Q10 supplementation, a straightforward and alluring treatment, to see if it can completely or partially alleviate statin-induced myalgia in symptomatic patients.

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