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A Molecular and Biochemical Study for Cholesteryl Ester Transfer Protein (CETP) Taq1B in Iraqi Patients with Hyperlipidemia

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Abstract:

Cholesteryl ester transfer protein gene contains some single nucleotide polymorphisms, which have been associated with serum high-density lipoprotein concentration and other lipoproteins. This study is done for determining of cholesteryl ester transfer protein polymorphism and evaluate its effect on serum lipid profile concentrations in some hyperlipidemic patients compared with healthy subjects in Salah Al-din governorate-Iraq. Blood samples were taken from (90) patients suffering from hyperlipidemia, and (70) samples that were apparently healthy controls. Serum lipid concentrations were measured by enzymatic assays. The polymorphism was genotyped using polymerase chain reaction restriction fragment length polymorphism analysis. The results showed that there was a significant decrease ($P<0.05$) in the frequency B2 allele, and B1B2, B2B2 genotype, and a significant increase ($P<0.05$) in the frequency B1 allele, and B1B1 genotype between patients and controls groups. There was a non-significant decrease in the levels of high density lipoproteins, total cholesterol, low density lipoproteins, and very low density lipoproteins levels, and non-significant increase in levels of triglycerides in individuals with the B1B1 genotype than in the B1B2 and B2B2 genotype. However, high density lipoproteins showed a significant decrease ($P<0.001$) between individuals with the B1B1 genotype and B2B2 genotype. Also, there was a non-significant difference in the levels of high density lipoproteins, total cholesterol, low density lipoproteins, and very low density lipoproteins levels, in individuals with the B1B2 genotype when compared with that of the B2B2 genotype.

Key words: CETP gene polymorphisms, Cholesteryl ester transfer protein, Hyperlipidemia, Lipoproteins.

Introduction:

Cholesteryl ester transfer protein (CETP), also called plasma lipid transfer protein, is a hydrophobic plasma glycoprotein that reduces the time required for transferring esterified cholesterol esters from HDL-C to chylomicrons, VLDL-C and LDL-C, in exchange with triacylglycerols. The CETP deficiency is linked to raised HDL-C levels and reduced LDL-C levels (1). The CETP is a key player in the metabolism of main blood lipoproteins. The CETP activities are highly affected by genetic factors. For example, individuals with homozygous CETP deficiency have high HDL-C levels and low LDL-C levels, and have no indication of premature atherosclerosis (2,3).

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Also, CETP gene polymorphisms, especially the TaqIB polymorphism seen in intron 1, is reported to be highly associated with CETP concentrations and HDL-C levels(4). Other studies reveal that this polymorphism is associated with the incidence of coronary artery disease (CAD) (5),(6). However, this polymorphism is not likely to be functional by itself, instead it represents a surrogate marker of functional variants of the CETP gene (7,8).

Hyperlipidemia is a common metabolic disease; it is a lipid abnormality where increase in levels of total cholesterol (TC), TG, LDL-C, while (HDL-C) are significantly low (9), (10).

The aim of this study: To date, there are no studies in Iraq about CETP gene polymorphism . For that, the objective of the present study is to find the role of the CETP Taq1B in association with plasma lipoprotein concentrations.

Material and Methods:

Blood samples were obtained from 90 patients with hyperlipidemia, and 70 samples from healthy

subjects whose age ranged between 30-70 year. Venous blood 5 ml, obtained by venipuncture, was divided into two parts; first part for biochemical measurements of TC, HDL-C and TG levels by enzymatic colorimetric methods (11-14), the LDL and VLDL levels are calculated by Friedewald formula (15), when the triacylglycerol levels did not over 400 mg/ dL. The second part was for genotyping; blood samples were stored in EDTA tubes at (-20 °C) until genomic DNA extraction using manual method as descript in *Ali SM et al 2008* (16). The purity of genomic DNA was measured by determining the ratio of absorbance at 260 nm to 280 nm (A260/A280) while the high molecular weight and good quality were revealed by agarose gel electrophoresis. Only DNA samples with a purity range of 1.6 to 1.8 were used for polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) amplification, which was used to determine the genotype of the CETP Taq1B gene. A fragment of 535 bp from intron 1 of the CETP gene was amplified by PCR using these primers: Forward 5-CAC TAG CCC AGA GAG AGG AGT GCC-3, Reverse 5-CTG AGC CCA GCC GCA CAC TAA C-3. The 2X Go Taq green master mix was used supplied by Promega company (USA). The PCR was carried out in a total volume of 20 µL, containing10 µL of master mix, 4 µL of genomic DNA, 1 µL of each primer in addition to 4 µL of DNase/RNase free water. PCR cycling was performed with primary denaturation at 95°C for 5 min, thirty cycles were carried out for amplification consisting of 30 seconds at 95°C, 30 seconds at 63°C, and 45 seconds at 72°C. The reaction ended with additional five minutes of extension at 72°C. The resulting PCR products were visualized on a 2% agarose gel electrophoresis stained with red safe. A five µL of the PCR product was digested with 5 U of Taq I enzyme [New England, BioLabs, Inc.] at 65 °C for 1 hour and the digest was visualized on 2% agarose gel electrophoresis stained with red safe in the presence of 100 pb DNA ladder (Biolabs-England) as a molecular marker (17)**.**

Statistical analysis was conducted using SPSS-15 software. The mean ± standard deviation (SD) of serum lipid profile levels were calculated between hyperlipidemia cases and control group and among the genotypes of patients. The p-value was calculated using student's t-test, which are considered significant when $p<0.05$ and highly significant when $p<0.001$ and $p<0.0001$. Hardy–Weinberg equilibrium was used with the chi square test to compare the distributions of genotype and allele frequencies between hyperlipidemia patients and the control group. Pearson's chi-square test was used to compare the distributions of genotype and allele frequencies between primary combined hyperlipidemia cases and the control group (18).

Note: All samples were taken under the supervision of a physician and with the consent of patients in Salah al-Din Hospital, (Patients are volunteers).

Results and Discussion:

Biochemistry study

The levels of TC, TG, LDL- C, and VLDL-C were significantly ($P<0.001$) higher, and HDL-C significantly ($P<0.001$) lower in patient group compared with healthy group, as shown in Table 1. There are no significant differences between male and females groups, as shown in Table 2.

Table 1. The lipid profile of the patients and control groups.

Parameters	Control group	Patients group	*P* value
HDL-C (mg/dL)	51.7 ± 8.38	45.9 ± 12.6	0.001**
TC (mg/dL)	161.0 ± 11.2	228.0 ± 62.1	0.0001**
LDL-C (mg/dL)	71.3 ± 9.82	153.0 ± 37.5	0.0001**
VLDL-C (mg/dL)	32.3 ± 5.54	41.2 ± 17.6	0.0001**
TG (mg/dL)	74.7 ± 10.7	198.0 ± 78.2	0.0001**

*P<0.05 significant and **P<0.001 highly significant

Table 2. The lipid profile of the patients according to gender.

Parameters	Male	Female	P value
HDL-C (mg/dL)	47.6 + 15.9	44.8 + 8.67	0.29
TC (mg/dL)	231. + 57.7	225. + 65.8	0.63
LDL-C (mg/dL)	151. + 41.2	154. + 34.1	0.70
VLDL-C (mg/dL)	42.1 + 16.6	40.9 + 18.6	0.74
TG (mg/dL)	206. + 88.8	193. + 68.5	0.41

Genotype study: CETP TaqI B polymorphisms

More than one experiment was done to obtain optimal conditions through using different concentrations of the genomic DNA and the primer. The best results appeared at concentration (100ng) for the genomic DNA and (10pmol) for the primer, the required beam before cutting process was shown in Fig 1.

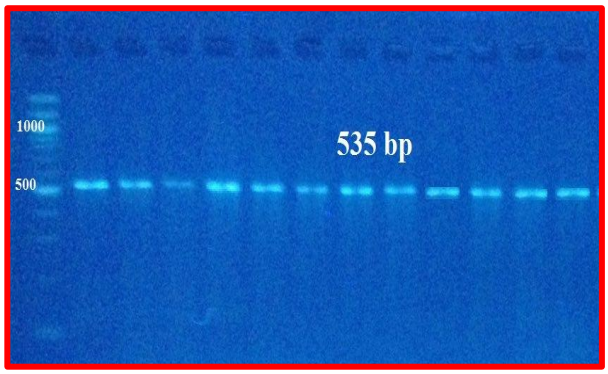

Figure 1. PCR product for CETP Taq1gene submitted to electrophoresis 2% agarose gel.

The PCR products were further analyzed by standard RFLP. The presence of a restriction site for the enzyme TaqI in intron 1 was referred to as B1 and its absence as B2.

One fragment of 535 bp indicated the absence of the TaqI restriction site (B2B2 genotype); 2 fragments of 361 and 174 bp indicated the presence of the restriction site (B1B1); and 3 fragments of 535, 361, and 174 bp indicated heterozygosity for the restriction site (B1B2), as shown in Fig 2.

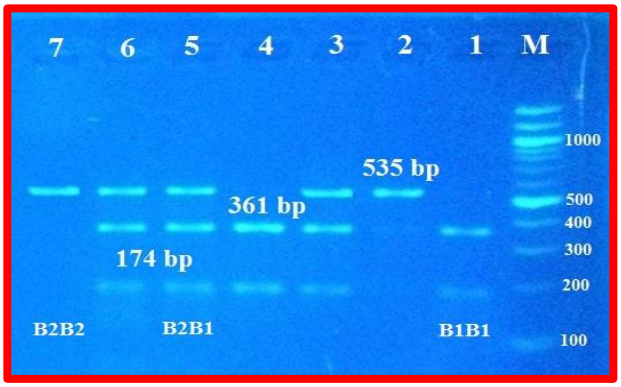

Figure 2. PCR amplification products for the CETP Taq1 gene polymorphism after restriction with the Taq1 enzyme. lane M: The DNA ladder (100-bp). Lanes 3,5 and 6: heterozygotic cases (B1B2 genotype) having 1 restriction site and 3 bands at 535 bp, 361 bp, and 174 bp. Lanes 2 and 7: Homozygotic B2B2 genotype cases with no restriction site and only 1 band at 535 bp. Lane 1 and 4: homozygotic B1B1 genotype case with 2 restriction sites and 2 bands of 361 bp, 174 bp.

The CETP/Taq1B genotype and allele frequencies in the patients and control groups were shown in Table 3. The genotypes B1B1, B1B2, and B2B2 were observed by the Hardy Weinberg equilibrium. Analysis of the polymorphism showed that the frequency of B1B2 and B2B2 genotype was significantly decreased in patients compared with the control. The B1B1 genotype was significantly higher in the hyperlipidemia patients group than the control group (P<0.0001). Also, B1 allele was significantly higher in the hyperlipidemia patients group than the control group (P<0.0001), and the B2 allele was significantly lower in the hyperlipidemia patients group than the control group (P<0.0001).

Table 3. Distribution of CETP TaqI B polymorphisms genotypes and alleles frequencies in patients and controls groups

Genotypes	Control group N=70	Patients group N=90	P value	$\chi 2$
B1B1	6 (0.08)	39 (0.44)		
B1B2	48 (0.68)	44 (0.48)		
B2B2	16 (0.22)	7 (0.08)		
	Allele			
B1	0.43	0.68	0.0001**	25.799
B2	0.57	0.32		

*P<0.05 significant and **P<0.001 highly significant

A large difference in the main types of dyslipidemia in different regions may be related to variance in economic growth, civilization, nutrition pattern changes in intermediate periods (19-22), and possibly genetic tendency. For example the cities that have experienced rapid economic growth like Beijing and other urbanized cities in China , could be accompanied by changes in diet and the style of life such as a higher intake of sodium and fat, reduced fiber intake, and lower physical activity. However, most village regions in china uneducated such remarkable economic growth, and have kept more traditional lifestyle and diet (23).

Several genes play a significant role in controlling the lipid metabolism and lipoprotein metabolism in the human body because of their central location in the lipid metabolism regulation. Alternation in lipid and lipoprotein concentrations has been revealed to be associated with the different genotypes and CETP mutations, in hyperlipidemic (24), or normolipidemic persons (25).

The B2B2 genotype was significantly lower in the patients group than in the control group, indicating a possible protecting role of this genotype. This was confirmed by the calculated odds ratio where subjects having the B2B2 genotype showed a decrease in risk of developing or appearing hyperlipidemia compared with the other genotypes, which means protection from hyperlipidemia (26).

The results in Table 4 showed that there was a non-significant decrease in the levels of HDL-C, TC, LDL, and VLDL-C, and non-significant increase in levels of TG in individuals with the B1B1 genotype than in the B1B2 genotype. This indicated that B1B1 and B1B2 genotype had no

effect on lipid profile parameters, which means this genotype does not cause the hyperlipidemia.

Also, the results in Table 5 showed that all lipid profile parameters levels were non-significantly different, except HDL-C which was a significant decrease between individuals with the B1B1 genotype and B2B2 genotype.

Table 4. Lipid concentrations of patients between B1B1 and B1B2genotype groups

Parameter	Mean ± SD B1B2 n = 44	B1B1 n = 39	P. value
HDL-C (mg/dL)	46.01 ± 8.81	43.0 ± 7.68	0.48
TC (mg/dL)	229.81 ± 62.46	222.79 ± 65.45	0.619
LDL-C (mg/dL)	153.11 ± 36.75	151.66 ± 41.65	0.867
VLDL-C (mg/dL)	42.93 ± 16.12	39.97 ± 19.50	0.452
TG (mg/dL)	*± 86.2 213.75*	182.10 ± 65.28	0.071

Table 5. Lipid concentrations of patients between B1B1 and B2B2 genotype groups

Parameter	Mean ± SD B2B2 n = 7	B1B1 n = 39	P. value
HDL-C (mg/dL)	51.4 ± 6	43.0 ± 7.68	0.004*
TC (mg/dL)	234.42 ± 45.12	222.79 ± 65.45	0.655
LDL-C (mg/dL)	156.28 ± 10.56	151.66 ± 41.65	0.774
VLDL-C (mg/dL)	38.57 ± 15.52	39.97 ± 19.50	0.858
TG (mg/dL)	201.42 ± 83.470	182.10 ± 65.28	0.493

*P<0.001 highly significant

The results in Table 6 showed that there was non-significant difference in levels of HDL-C, TC, LDL, and VLDL-C in individuals with the B1B2 genotype than in the B2B2 genotype.

Table 6. Lipid concentrations of patients between B2B2 and B1B2 genotype groups

Parameter	Mean ± SD B2B2 n = 7	B1B2 n = 39	P. value
HDL-C (mg/dL)	51.4 ± 6.0	46.01 ± 8.81	0.056
TC (mg/dL)	234.42 ± 45.12	229.81 ± 62.46	0.852
LDL-C (mg/dL)	156.28 ± 10.56	153.11 ± 36.75	0.823
VLDL-C (mg/dL)	38.57 ± 15.52	42.93 ± 16.12	0.508
TG (mg/dL)	201.42 ± 83.47	± 86.2 213.75	0.740

It is worth to mention that the differences were not statistically significant, possibly, because CETP activity in patients is lower than in healthy people. However, this was probably due to the patients were under effect of treatment, the environment of patients, and/or small study sample.

Our results disagree with the researchers who investigated patients with genotype B2B2 had a lower concentration of LDL cholesterol than those with genotype B1B1 and B1B2. It was also confirmed that polymorphism Taq1 of the CETP gene with a family history of hypercholesterolemia influences the reduction of atherogenic lipid profile due to a lower LDL concentration, and a higher HDL concentration. Also, it was observed in these patients the allele B2 was affecting factor for the occurrence of arcus cornealis, arteriosclerotic disease, and xanthomata (27). It has been proven that HDL-C is an independent risk factor for chronic heart disease (28). A growing body of evidence demonstrated that elevated levels of HDL-C may reduce chronic heart disease risk, and consequently contribute to elongate life expectancy (29). Moreover, this elevation in HDL-C was associated with B2 allele and B2B2 genotype, which was consistent with some earlier studies (30-34), but not others (35). It is widely established that B2 allele carriers show lower CETP concentrations and/or activity, leading to a dysfunction of the inverse cholesterol transport, causing an accumulation of cholesterol ester in HDL form and thus raising the levels of HDL-C(33),(36).

Others studied the effect of common gene polymorphisms participatory in HDL-C metabolism on HDL-C levels in individuals with normal levels of lipid. However, samples carrying allele B1 of the TaqI B polymorphism in the CETP gene have lower HDL-C levels compared to samples not carrying this allele. The combination of this allele significantly affected HDL-C levels (37). Moreover, the expression of human CETP in rats, a gene generally not expressed in them, results in hyperlipidemia and CAD, making CETP as a strong risk for CAD. The TaqIB polymorphism is the most studied CETP gene variant, and the B2 allele is shown to be associated with the lowest risk of CAD (3).

Many studies, however, confirm the fact that environmental factors (e.g., cigarette smoking, stress, alcohol drinking, malnutrition or inadequate nutrition, and low physical activity), apart from genetic factors, which play a role in the regulation of CETP concentration. The findings of *Hassanzadeh et al., 2009* (38) *and Kuivenhoven et al., 1998* (39) disagree with our results and showed a decrease in the TG level in B2B2 genotype in hyperlipidemic subjects.

Conclusion:

It is quite clear that there is a strong relationship between Taq1B gene polymorphism and hyperlipidemia among Iraqi people. This association was more a binding with HDL-C than other lipid profile.

Conflicts of Interest: None.

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دراسة جزيئية وكيموحيوية لبروتين الناقل لإستر الكوليسترول Cholesteryl Ester Transfer Protein (CETP) في المرضى العراقيين الذين يعانون من ارتفاع الدهون في الدم

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[3] قسم التحليلات المرضية، كلية العلوم التطبيقية، جامعة سامراء، صلاح الدين، العراق.

الخلاصة:

يمتلك جين البروتين الناقل لاستر الكوليسترول بعض الأشكال المتعددة لنيوكليوتيد وحيد والتي ارتبطت بتركيز البروتين الدهني عالي الكثافة والبروتينات الدهنية الأخرى في مصل الدم . تم اجراء هذه الدراسة لإيجاد الاشكال الجينية المتعددة للبروتين الناقل لاستر الكوليسترول Taq1B و تقييم تأثيره على تركيز الدهون البروتينية في مصل دم المرضى المصابين بارتفاع الدهون بالمقارنة مع مجموعة الاصحاء في محافظة صلاح الدين. تم جمع عينات الدم من (90) مريض مصاب بارتفاع الدهون، و (70) عينة من الاصحاء. وتم قياس تراكيز الدهون في مصل الدم بواسطة الاختبارات الانزيمية. تم تحديد النوع الجيني للأشكال المتعددة Taq1B باستخدام تقنية تفاعل البلمرة المتسلسل. أظهرت النتائج وجود انخفاض معنوي عالي ($P <0.001$) في تكرار كل من أليل B2، والتراكيب الوراثية B1B2، B2B2 ، وارتفاع معنوي عالي ($P <0.001$) في تكرار اليلB1، والتركيب الوراثي B1B1 بين مجموعة المرضى مقارنة بمجموعة الاصحاء. وكذلك وجود انخفاض غير معنوي في مستويات البروتينات الدهنية عالية الكثافة، والكولسترول الكلي، والبروتينات الدهنية منخفضة الكثافة، ومستويات البروتينات الدهنية منخفضة الكثافة جدا، وزيادة غير معنوية في مستويات الدهون الثلاثية لدى الأفراد الذين لديهم التكرار الجيني B1B1 مما كانت عليه في التكرار الجيني B1B2. وكانت جميع مستويات صورة الدهون ذات اختلاف غير معنوي ما عدا البروتينات الدهنية ذات الكثافة العالية والتي تنخفض بشكل معنوي ($P <0.001$) بين الأفراد الذين لديهم التكرار الوراثي B1B1 والتكرار الوراثي B2B2. أيضا، وجود اختلاف غير معنوي في مستويات البروتينات الدهنية عالية الكثافة، الكولسترول الكلي، البروتينات الدهنية منخفضة الكثافة، ومستويات البروتين الدهني منخفض الكثافة جدا، لدى الأفراد الذين لديهم النمط الوراثي B1B2 مما هو في النمط الجيني B2B2.

الكلمات المفتاحية: البروتين الناقل لاستر الكوليسترول، الاشكال المتعددة لجين Taq1B، ارتفاع دهون الدم، الدهون البروتينية.