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Dose PPP1R1A Polymorphism are Effected to Increased Risk of Heart Disease?

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Abstract
Apolipoprtein is the essential material for transport cholesterol and triglyceride in revers process and may play important role in lipid overload in body and involving the risk of cardiovascular disease (CVD). Although there are sufficient traditional risk factors for diabetes and heart disease, our understanding of the genetic risk factors is still lacking. A case-control research was carried out to determine how much of a role genetic factors have in relation to other risk factors. A 94 morbidly obese and 70 normal non-obese that matched in gender and age was collected. Measurements were made of biochemical variables, and polymorphism was genotyped using the polymerase chain reaction (PCR- RFLP). To evaluate the strength of the link between genetic and non-genetic factors, For the clinical parameter and odds ratio (OR), the mean, standard error (SE), and T test were calculated with a 95% confidence interval. The findings indicate that compared to non-obese individuals, morbidly obese individuals had increased levels of triglycerides, very low density lipoprotein, low density lipoprotein, blood pressure, and cholesterol. However, the value of high density lipoprotein between the two groups does not demonstrate any significant variations. The research found a substantial correlation between the genotype of PPP1R1A and morbidly obesity who are more at risk of DM type2 and heart disease (OR: 1.26, 95%CI: 0.91-1.60, P= 0.0003). However, more case-control research is necessary to draw a firmer conclusion.

Keywords : PPP1R1A, morbidly obese, heart disease, DM type2..

Introduction :
Dyslipidemia is common in obese and the common factors that connected to a high chance of developing coronary artery disease are lipids (1,2). Cholesterol is essential for human and have important functions in the body. It is the precursor for many compound such bile salts and steroid hormones and the substance responsible for the transfer of hydrophobic cholesterol molecules in blood are lipoprotein complexes(3,4). Cholesterol move from the digestive system to peripheral tissues for storage and from the last back to liver in revers by used the LDL-C and HDL-C respectively(5). Any defect in cholesterol transport pathway lead to keep free cholesterol that caused disrupted cell

function by effect on the fluidity of the cell membrane and can decrease the effect by convert it to biological esterified cholesterol(6-8).

The primary risk factor for coronary artery disease is a protein called apolipoprotein, which plays a significant role in determining plasma lipid levels in humans (9). According to the first proposed mechanism, apolipoprotein stimulates the activity of lipoprotein lipase, a vital enzyme in the breakdown of triglycerides, which improves the metabolism of TG-rich particles. In addition to its TG-lowering effect (10,11).

Other factors, such as Protein Phosphatase 1 (PP1), which inhibits the activity of protein kinases by dephosphorylating serine/threonine residues in target proteins, can raise the risk of cardiovascular disease. Research on human patients with failing hearts have shown a considerable increase in PP1 activity in the myocardium (14).

Cardiovascular disease is influenced by both genetic and non-genetic causes (15). Contrary to genetic variables, non-genetic risk factors for CVD have been proven, and these include obesity, type 2 diabetes, hypertension, dyslipidemia, and way of life. But the genetic factors is not clear yet(16-18).

So the aim of the study was to find out if there is a relationship between genetic factor and lipid levels in obese and effects them on heart disease.

Material and Method

The study population included 94 obese case participants and 70 non-obesity case participants who were frequency matched for age and gender. For two groups, national standards were used to assess weight and height, and BMI was calculated as body weight in kilograms divided by the square of height in (m2). Normal weight was defined as BMI 24.9, overweight as 25–29.9, obesity as 30–34.9, and severe obesity as 35+. All subjects had venous blood samples taken after a 12-hour overnight fast for genetic and biochemical investigation (18). All study participants' systolic and diastolic blood pressures were measured once. Triglycerides (TG), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol(VLDL), and total cholesterol (TC).

Genotype

The ROJE DNA extraction kit was used to extract genomic DNA from whole blood. Using the forward and reverse primers 5'-TGAAGGAGAAGGTGTCTGCGGGA-3' and 5'-AGGACGGTGCGGTGAGAGTG-3', respectively, RFLP PCR was used to determine the genotype of PPP1R1A. (19). The overall volume of the PCR mixture was 25 2L, made up of 12.5 L of master mix, 1 L from each forward and reverse primer, and 2 L (250 ng) of template DNA. A 10 minute denature step at 95 degrees followed by 30 cycles of 1 minute at 95 degrees, 40 seconds at 62 degrees, and 40 seconds at 72 degrees, with an elongation step of 10 minutes at 72 degrees, is the PCR condition. After electrophoresis in 3% agarose gel and digestion with HinfI restriction enzyme, the PCR product was analyzed.

Statistical Analysis

Routine statistical analysis was done by using SPSS ver.16 software. To compared between healthy non-obese (control) and healthy morbidly obese (case) calculated OR and %95CI for genotype, and the conformity to hardy-Weinberg equilibrium (HWE) was tested, and differences between two group assessed by Chi-square test. The t-test, mean and standard error of mean calculated for clinical parameters such TC, TG, HDL-C, LDL-C, VLDL and the correlation between them and genotypes calculate by ANOVA test.

Result

In the study we evaluated the correlation of cardiovascular disease with PPP1R1A in morbidly obese. Furthermore to obtain definitive estimation of the correlation, compared between morbidly obese and non-obese groups through clinical characteristic and genotypes model, the overall results suggested that there was significant relationship between the clinical parameters and increase risk of CVD, that result shows higher levels of Apo-A1, Apo-A5, TC, TG, VLDL, LDL-C, SBP and DBP in morbidly obese cases than non-obese. In other hand shows not significant differences between two groups in value of HDL-C (18,21)as following in table 1.

Table 1 : clinical characteristic of study subjects (n=150)

Variable	Morbidly obese Mean ± SE	Non-obese Mean ± SE	p-value
Age (year)	34.06 ± 9.54	33.27 ± 9.49	0.0001
BMI(kg/m^2)	42.33 ± 0.66	22.42 ± 0.27	0.0001
TC(mmol/L)	197.92 ± 5.84	169.85 ± 2.72	0.0001
TG(mmol/L)	133.04 ± 4.66	97.22 ± 3.56	0.0001
HDL-C(mmol/L)	39.91 ± 0.61	40.66 ± 0.59	0.377
LDL-C(mmol/L)	128.05 ± 4.19	102.96 ± 2.11	0.0001
VLDL(mmol/L)	24.74 ± 0.77	19.62 ± 0.83	0.0001
SBP (mmHg)	13.07 ± 1.35	12.42 ± 0.79	0.0001
DBP (mmHg)	8.48 ± 0.77	8.13 ± 0.43	0.0001

BMI: body mass index, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 2 shows the distribution of polymorphism in morbidly obese and non-obese groups in co-dominant, dominant and recessive models. The outcome demonstrated that the genotype distribution for C677T in both the morbidly obese and non-obese groups did not depart from HWE. When compared to the morbidly obese group, the frequency of homozygous (CC) and heterozygous (CT) mutations in the control group was 27.03% and 66.22%, respectively (22-25). Thus, the (CC) and (CT) genotypes in the co-

dominant model showed strong statistically significant differences between the morbidly obese and non-obesity groups, OR 1.57,%95CI 0.88-1.62, P value 0.0001, and OR 1.26,%95CI 0.91-1.60, P value 0.0003 respectively, in other hand the result show statistically not significant relation in recessive model(26,27).

Table 2 : Association of morbidly obesity with MTHFR C677T to elevate risk CVD

characteristics	Morbidly obese (%)	Non-obese(%)	OR (%95CI)	P- value	Chi-Square
PPP1R1A					
Codominant model					
CC	20(27.03)	54(71.05)	1.57 (0.88-1.62)	0.0001	12.74
CT	49(66.22)	21(27.63)	1.26(0.91-1.60)	0.0003	10.06
TT	5(6.75)	1(1.32)	0.258(0.88-1.60)	0.082	1.52
Dominant model					
CC	20(27.03)	54(71.05)	1.57 (0.88-1.62)	0.0001	12.74
CT+TT	54(72.97)	22(28.95)	1.42 (0.88-1.63)	0.0001	11.76
Recessive model					
CC+CT	69(93.24)	75(98.68)	0.249(0.91-1.62)	0.094	1.84
TT	5(6.75)	1(1.32)	0.258(0.88-1.60)	0.082	1.52

BMI: body mass index, PPP1R1A: **Protein phosphatase 1 regulatory subunit 1A**, OR: odds ratio, CI: confidence interval.

This study provides the first concrete evidence of a link between the polymorphism PPP1R1A and cardiovascular disease incidence in the Iraqi population, which has one of the highest incidence and mortality rates worldwide. Although slightly elevated blood protein phosphatase levels appear to be a known risk factor for cardiovascular illnesses, the reality is that the many meta-analyses provide conflicting findings (28-31).

Our findings strongly imply that mutation is a risk factor for cardiovascular disease, highlighting the necessity of more research to fully comprehend the physiopathology of this association. However, more case-control research is necessary to draw a firmer conclusion.

Conclusion

In conclusion result shows that PPP1R1A SNPs were related substantially with obesity and therefore enhance risk of CVD in Iraqis population. The overall results suggested that there was significant relationship between the clinical parameters and increase risk of CVD, because shows higher levels of lipid profile in morbidly obese than normal non-obese cases. Finally we can say when a gene defect is present along with certain environmental exposures and lifestyle choices, disease risk may be increased.

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