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The Relationship between MCR4 and Lipid Profile in Metabolic Syndrome

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ABSTRACT

Background: Metabolic syndrome (MetS) is a multifactorial disorder marked by obesity, dyslipidemia, hypertension, and insulin resistance, which increase the risk of cardiovascular diseases and type 2 diabetes mellitus. Genetic factors, including polymorphisms in the Melanocortin-4 receptor (MC4R) have been linked to its development, especially regarding lipid metabolism and obesity. This study aimed to investigate the association between the MC4R (rs17782313) C/T polymorphism and lipid profile in individuals with MetS compared to healthy controls.

Methods: A case-control study was conducted with 150 Iraqi participants including 75 MetS patients and 75 healthy controls. Anthropometric measurements and lipid profile were recorded. Genotypic distribution of the MC4R (rs17782313) polymorphism was analyzed using ARMS-PCR. Statistical analyses assessed the correlation between MC4R polymorphisms, lipid profile, and risk of MetS.

Results: Patients with MetS showed significantly higher BMI, waist circumference, triglycerides, total cholesterol, and low density lipoprotein (LDL) levels when compared to controls. The TT genotype of MC4R (rs17782313) was more prevalent among patients (24%) than controls (12%), associated with increased risk of MetS (OR=2.81, p=0.024). The T allele was also more common in patients (40.7%) than in controls (26%) (p=0.007, OR=1.95).

Conclusion: Findings suggest a strong association between MC4R (rs17782313) polymorphism, lipid abnormalities, and MetS. The T allele and TT genotype may serve as genetic markers for increased susceptibility. Further studies are needed to clarify the molecular mechanisms behind therapeutic interventions targeting this receptor.

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Introduction

Metabolic syndrome (MetS) refers to metabolic problems that raise the danger of cardiovascular diseases and type 2 diabetes mellitus (T2DM). The condition is characterized by abdominal obesity, elevated blood pressure, and abnormal blood lipid level (1-4). Diagnostic criteria are determined using several scientific principles and suggestions. It affects over 25% of the global population, with prevalence rates ranging by age, gender, and ethnicity. In recent years, there has been a dramatic increase in instances, particularly among young

people (1-3). MetS is characterized by faulty lipid metabolism, including high triglyceride level and low high density lipoprotein cholesterol (HDL-C) (5, 6). These anomalies raise the risk of heart diseases by promoting atherosclerotic lipid profile (7, 8). Low HDL-C can raise the risk of cardiovascular disease (9, 10).

Genetic factors contribute significantly to obesity and metabolic syndrome, accounting for 40-70% of inter-individual variability (11). The gene encodes a receptor that regulates appetite and energy balance (12); while these receptors are found in the hypothalamus, which regulates hunger and satiety (13). Genetic alterations in the MC4R receptor can cause increased hunger, poor satiety, and overeating, leading to weight gain and metabolic Syndrome (14, 15). The Melanocortin-4 receptor (MC4R) gene encodes an important receptor involved in appetite regulation and energy balance. This receptor, which is mainly expressed in the hypothalamus, is critical for modulating hunger and satiety signals (16). Variations in MC4R can impair normal receptor function, resulting in increased hunger, diminished satiety, and a proclivity for overeating; all of which contribute to weight gain and obesity. A particularly relevant single nucleotide polymorphism, rs17782313, located in the gene has been tied to a higher body mass index (BMI) and an increasing danger of obesity, notably of European populations (17, 18). Aside from obesity, this mutation has been associated to MetS, which impacts lipid profile and overall metabolic health (19, 20). Given the link between genetics and metabolism, dietary choices, particularly the kind and quantity of fat consumed, may have an impact on MC4R polymorphisms. This emphasizes the importance of customized dietary interventions in managing and preventing MetS. By exploring these genetic and metabolic links, the team wants to get a deeper understanding of the mechanisms that underpin MetS and obesity.

Materials and Methods

Of 150 people who took part in the present research, 75 subjects were classified as obese, while the other 75 served as healthy controls. The research protocol was approved by the Ethics Committee of the Biotechnology College at Iraq's Al Qadisiyah University, Iraq. Adults hailing from Iraq made up the entire sample for the research. Individuals with a BMI greater than 25 kg/m^2 and an age range of 18-67 years were classified as obese. The mean age of the participants was 42.96±8.61 years, and their mean BMI was 28.79±4.28 kg/m^2. People in good health with a BMI about 19.00-23.94 kg/m^2 (mean age of 45.82±9.76 years, mean BMI of 22.10±1.2 kg/m^2) served as the controls. The study did not include women who were pregnant or nursing. Questions regarding medical background, lifestyle, and potential dangers were presented to each individual. Physiometric measures, such as height, weight, waist circumference, and blood pressure, were taken from every individual who participated in the research (21). Participants were requested to fill out an informed consent form. For each subject, we used a precision of 0.5 cm for height and 0.1 kg for weight. The principle for BMI was weight in kilograms divided by squared height in meter. A sphygmomanometer, which measures blood pressure, was made of mercury. After fasting overnight, 3 mL of venous blood was provided and the serum was separated to evaluate the lipid profile. The Becman-Coulter system, an automated device that required only the placement of a blood tube and the pressing of a start button, was used to evaluate lipid markers such as triglycerides, total cholesterol, and HDL-C. To calculate low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C), the Friedewald formula was utilized. Genomic DNA from blood samples was taken out utilizing gSYAN DNA kit extraction kit (Frozen Blood) and a Nano drop spectrophotometer at (260/280 nm). There was a DNA concentration of 20 ng/µL.

Statistical Package for the Social Sciences (SPSS, Version 25, Chicago, IL, USA) was used to perform the statistical study. The proportions were employed to describe the obesity risk. To summarize categorical data, we used the number and ratio for all sociodemographic, behavior, anthropometric, clinical, and biochemical elements of the research. For continuous variables, we applied mean and standard deviation (SD). To inspect the change in covariates between high-danger and non-high-danger participants, an intergroup comparison was conducted using logistic regression. Pearson's chi-square test was employed for definite variables and independent-sample t-test was utilized for continuous data. MC4R rs17782313 was inspected in connection to biochemical variables, BMI, and demographic variables utilizing analysis of variance (ANOVA).

Results

The lipid profile (Triglycerides, Cholesterol, LDL-C, VLDL-C, and HDL-C) was compared between patients and control groups, and the results were shown in Table 1. Serum triglyceride level was 272.45±38.17 mg/dL and 148.6±12.19 mg/dL in MetS patients and healthy control groups, respectively. Patients had significantly higher mean values than healthy controls (p=0.001).

Table 1: Lipid profile (Cholesterol, Triglycerides, LDL and HDL) in MetS patients and healthy controls.

Group	Cholesterol (mg/dL)	Triglyceride (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	HDL (mg/dL)
MetS patients	292.30±47.7	272.45±38.17	164.13±22.6	54.58±8.56	60.09±12.4
	105.2-502.0	159.00-460.00	93.00-266.00	31.80-92.00	19.00-100.00
Control	159.59±15.7	148.6±12.19	124.01±12.7	29.51±3.54	51.88±5.90
	106.0-198.0	121.00-187.00	85.00-162.00	24.20-36.80	40.00-60.00
P value	0.001**	0.001**	0.001**	0.001	0.057

SD: Standard deviation; †: Independent T test: significant at $p>0.05$. HDL-C: High density lipoprotein cholesterol. LDL-C: Low density lipoprotein cholesterol. VLDL-C: Very low density lipoprotein cholesterol.

Serum cholesterol levels were 292.30±47.7 mg/dL and 159.59±15.7 mg/dL in MetS patients and healthy controls, respectively. MetS patients had significantly higher mean values than healthy controls ($p<0.001$).

The mean serum LDL-C level in MetS patients and healthy controls were 164.13±22.6 mg/dL and 124.01±12.7 mg/dL, respectively. MetS cases had significantly greater mean values than healthy controls ($p<0.001$). Though, HDL-C level di not significantly change between MetS subjects and healthy controls ($p<0.05$).

The distribution of MC4R (rs17782313) C/T polymorphism was determined using the ARMS-PCR method. This locus contains three genotypes of CC, CT, and TT. The wild type of homozygote genotype revealed solely C allele amplification with a 218 bp product size. The mutant type of homozygote genotype exhibited solely T allele amplification at 189 bp product size. In contrast, the heterozygote genotype demonstrated C and T allele amplification at 360 bp produce sizes, respectively (Figure 1). In all study groups, the genotype distribution remained consistent with Hardy-Weinberg equilibrium.

The molecular marker (M) ranged from 2000 bp to 100 bp. The CC homozygous wild-type exhibited only the C allele at 218 bp in the T-ARMS-PCR product, while the TT homozygous mutant displayed only the T allele at 189 bp. In contrast, the CT heterozygous genotype was characterized by the presence of both C and T alleles, appearing at 218 bp and 189 bp, respectively. Additionally, the outer internal control was observed at 360 bp in the T-ARMS-PCR product.

Table 2 shows the results of applying the Hardy Weinberg equation to the MC4R (rs17782313)C/T genotypes, CC, CT, and TT, and their distribution inside the control collection. Table 2 demonstrates that 45 of the 75 control participants had the homozygous wild genotype CC, 21 had the heterozygous CT genotype, and 9 had the homozygous mutant TT genotype. The observed distribution of control patients was dependent on MC4R (rs17782313) C/T genotypes and did not differ substantially from the expected distribution ($p=0.061$).

Table 3 shows the connection between the MC4R (rs17782313) C/T polymorphism and lipid profile level in MetS patients. Serum triglyceride level was 266.8±34.51, 275.31±33.2, and 297.36±36.57 in patients with CC, CT, and TT genotypes, respectively.

Patients with TT (mutant genotype) had higher mean level of serum triglyceride than additional sets, but the variance was not important ($p=0.502$).

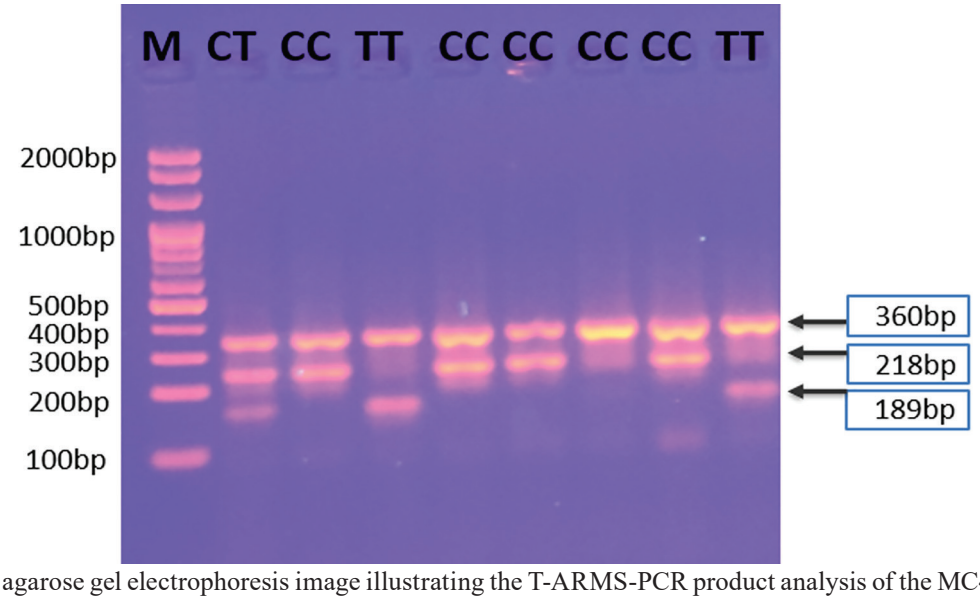

Figure 1: An agarose gel electrophoresis image illustrating the T-ARMS-PCR product analysis of the MC4R rs17782313 C/T gene.

Table 2: Hardy Weinberg equation.

Genotype	Observed	Expected	χ^2	*P*
Homozygote reference CC	45	41.1	5.563	0.061¥
Heterozygote CT	21	28.9		NS
Homozygote variant TT	9	5.1		

¥: Chi-square test; NS: Not significant at $p>0.05$; S: Significant at $p\leq0.05$

Table 3: The association between MC4R (rs17782313) C/T polymorphism and lipid profile levels in MetS patients

Lipid profile	ARMS-PCR			
	CC genotype n=32	CT genotype n=25	TT genotype n=18	*P* value
	Serum triglyceride level			
Mean±SD	266.8±34.51	275.31±33.2	297.36±36.57	0.502† NS
	Serum cholesterol level			
Mean±SD	277.71±42.02	301.45±46.47	284.63±47.7	0.668† NS
	Serum low-density lipoprotein (LDL) level			
Mean±SD	160.14±25.44	158.81±21.6	166.18±20.7	0.980† NS
	Serum high-density lipoprotein (HDL) level			
Mean±SD	58.47±8.5	60.37±12.7	59.00±11.9	0.971† NS
	Serum very low-density lipoprotein (VLDL) level			
Mean±SD	53.36±8.9	55.06±8.6	59.47±7.31	0.505† NS

n: Number of cases; SE: Standard error; †: One way ANOVA; NS: Not significant at $p<0.05$.

The mean level of lipid profile did not change significantly in patients with different MC4R (rs17782313) genotypes ($p<0.05$).

Discussion

MetS is a cluster of metabolic risk factors that can increase the risk of cardiovascular diseases and T2DM and is characterized by elevated blood pressure, abdominal obesity and abnormal blood lipid level (22, 23). Our findings revealed that patients with MetS had significantly greater level of dyslipidemia than healthy controls. MetS patients had significantly higher serum triglycerides, total cholesterol, LDL-C, and VLDL-C. These findings are consistent with the recognized MetS diagnostic criteria and pathogenesis. The dyslipidemic pattern is congruent with the findings of Grundy *et al.* (2019), who identified atherogenic dyslipidemia as a characteristic of MetS, defined by increased triglycerides and low HDL-C levels (24). Our MetS patients' triglyceride level was above the usual diagnostic criterion of 150 mg/dL that establishes hypertriglyceridemia as a significant component of the disease (25).

Our investigation indicated no important variation in HDL-C level between MetS patients and controls. This is in contrast to usual MetS presentations, which frequently showed low HDL-C level. Aguilar-Salinas *et al.* (2018) observed that HDL-C patterns differed between ethnic groups and may not always follow expected MetS patterns (26). These findings point to potential population-specific lipid profile changes that require additional exploration. Analysis of MC4R gene polymorphisms indicated significant associations with MetS risk. The TT genotype frequency was higher in MetS patients in comparison to controls, indicating a significant risk of disease ($p=0.024$). Similarly, the T allele was more frequent in metabolic syndrome patients ($p=0.007$), with an odds proportion of 1.95. Our finding is similar with a prior research by Loos *et al.* (2018), who found that the rs17782313 polymorphism at MC4R was substantially associated with obesity and metabolic disorders (27).

The MC4R gene was shown to be important for energy homeostasis and appetite, and its mutations have been correlated with monogenic procedures of obesity (28). Our results presented emerging evidence that common polymorphisms in or around the MC4R may influence MetS vulnerability. The Hardy-Weinberg balance analysis verified that the genotype distribution in the control group was within predicted bounds ($p=0.061$) and demonstrated the validity of our genetic findings. This shows that

observed genotype variances between patients and controls can be due to actual illness correlations rather than population stratification or methodological bias. Despite the substantial relationship between the MC4R rs17782313 polymorphism and MetS risk, we discovered no significant correlation between specific genotypes and individual lipid measures in the MetS patient population. Patients with the TT genotype had somewhat higher triglyceride level compared to CC and CT genotypes, although this variance was not statistically important (p=0.502).

Our findings are in consistent with the results of Chambers *et al.* (2020), who proposed that MC4R polymorphisms may influence MetS risk through processes that are independent of direct effects on lipid metabolism (29). The MC4R signaling system predominantly influenced energy balance via central mechanisms in the hypothalamus, with indirect effects on peripheral metabolism. Qi *et al.* (2021) postulated that MC4R genetic variations interacted with dietary variables to alter metabolic risk, which could explain the differences in lipid profile seen among genotypes of our study (30). The lack of substantial relationships between MC4R genotypes and lipid parameters in the MetS group suggests that once MetS is established, other factors may have a greater influence on lipid profile than MC4R genetic variation alone.

Conclusion

This study found a relationship between MetS, dyslipidemia, and the MC4R rs17782313 polymorphism. MetS patients had a very atherogenic lipid profile, with high triglyceride, total cholesterol, LDL-C, and VLDL-C. Genetic research revealed that people with TT genotype had a threefold higher chance of evolving MetS, whereas the T allele doubled the risk when compared to the C allele. However, MC4R variants had no significant effect on lipid profile in MetS patients, indicating that other metabolic variables play a more important role. These findings highlight the clinical value of genetic screening for early risk diagnosis, as well as the requirement for rigorous cholesterol management throughout MetS treatment. Future researches should look at gene-environment interactions and the molecular processes that link MC4R to metabolic disorders, paving the door for personalized prevention and treatment efforts.

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Authors' Contribution

DGK and SRM designed and directed the project, conducted the experiments, processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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