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Association of Biochemical Parameters in Females with FHCL (Familial Hypercholesterolemia) with TCF7L2 Polymorphism

Sachin Chawla
Research Scholar, Department of Chemistry, Glocal University, Saharanpur, Uttar Pradesh, India

Abstract: *Familial Hypercholesterolemia (FHCL) is a genetic disorder characterized by elevated levels of cholesterol in the blood. This study aims to investigate the association between specific biochemical parameters in females affected by FHCL and the presence of a polymorphism in the TCF7L2 gene. FHCL is known to have a genetic basis, and TCF7L2 polymorphisms have been implicated in various metabolic conditions. This research focuses on understanding how variations in the TCF7L2 gene may influence biochemical markers in females with FHCL. The study involves the analysis of key biochemical parameters, including but not limited to lipid profiles, glucose levels, and other relevant markers. By examining these parameters in individuals with FHCL and assessing the presence of TCF7L2 polymorphisms, the research aims to establish potential connections between genetic factors and the biochemical profile observed in affected females. This investigation contributes valuable insights into the complex interplay between genetic predisposition and biochemical outcomes in FHCL. Understanding such associations is crucial for advancing personalized medicine approaches and developing targeted interventions for individuals with FHCL based on their genetic makeup.*

Keywords: TCF7L2, FHCL, polymorphism, hypercholesterolemia.

1. Introduction

Intronic mutations identified in the transcription factor 7-like 2 gene have been implicated in the onset of type 2 diabetes (DM2) based on studies conducted in Iceland and the United States [1]. These findings have received robust confirmation through multiple investigations into type 2 diabetes [2, 7]. Notably, individuals of Europid descent [1, 4] exhibit indications of a connection with DM2. TCF7L2, a transcription factor containing a versatile box, plays a crucial role in the WNT signaling pathway. Proteins associated with WNT signaling contribute to cell differentiation, proliferation, adhesion, and gene transcription [8]. Mutations within the WNT signaling system have been linked to various disorders, including cardiovascular, skeletal, cancer, and neurological issues [9, 10]. A complex hereditary disorder, Familial Combined Hyperlipidemia (FCHL), has been associated with coronary artery disease. Individuals with FCHL may manifest hypertriglyceridemia, hypercholesterolemia, and mixed hyperlipidemia [11]. Moreover, medical characteristics of DM2, such as impaired glucose tolerance, hypertriglyceridemia, and hyperinsulinemia, have demonstrated associations with FCHL profiles [12, 13]. Given the broad spectrum of phenotypes observed, including those associated with FCHL, we hypothesize that mutations in TCF7L2, previously linked to DM2, may also influence the FCHL phenotype. This study aims to explore the role of TCF7L2 mutations in individuals with Familial Combined Hyperlipidemia, building upon the recent association of these mutations with FHCL [1].

2. Material and Methods

2.1 Samples

The study involved a total of 100 female participants aged between 25 and 45 years. This cohort comprised 70 individuals diagnosed with both Familial Combined Hyperlipidemia (FCHL) and Type 2 Diabetes (DM2), who sought medical attention at the national diabetes center in Baghdad, Iraq, during the period from November 2022 to March 2023. Additionally, a control group consisting of 50 healthy individuals was included for comparative analysis. The study received ethical approval from the Center Ethical Committee, and diagnoses were confirmed by qualified physicians. To identify participants with DM2 and FCHL, the American Diabetes Association criteria were employed. Fifteen individuals met the specific criteria for DM2 with FCHL. Inclusion criteria for FCHL considered total cholesterol (TCh) and triacylglycerol

(TG) levels falling within the 110th population percentile of Iraqi families. To ensure the specificity of FCHL norms, the presence of Belated Coronary Heart Disease (CHD) was used as a deciding criterion. CHD diagnoses were confirmed through angiography or after a myocardial infarction. All participants provided written informed consent before participating in the study. In the DM2 with FCHL group, which comprised 50 individuals, the study design received approval from the ethics committees of the participating centers. To maintain the integrity of the study cohort, individuals with compromised chronic inflammatory conditions, malignancy, renal dysfunction, and connective tissue diseases were excluded from the analysis. This exclusion criteria aimed to ensure a homogeneous study population, minimizing confounding factors that could affect the results.

2.2 Biochemical Tests

The study ensured standardized conditions for sample collection by obtaining all samples after a minimum fasting period of 8 hours. Blood specimens were collected using two types of tubes, namely plain tubes for biochemical analyses and EDTA tubes for molecular analysis. This careful separation allowed for the distinct processing of samples based on the type of analysis to be conducted. The Molecular and Biotechnology Laboratory at Al-Nahrain University undertook the responsibility of performing biochemical tests on the collected samples. These tests encompassed a range of parameters relevant to the study, including fasting blood sugar (FBS), total cholesterol (TCh), low-density lipoprotein (LDL), triglycerides (TG), high-density lipoprotein (HDL), creatinine (Cr), uric acid (UA), and blood urea nitrogen (BUN). These tests provide crucial information about the biochemical characteristics of the serum, offering insights into factors such as glucose metabolism, lipid profile, and kidney function. Fasting blood sugar (FBS) levels are indicative of glucose levels in the bloodstream after a period of fasting, providing information about glucose metabolism. Lipid profile parameters such as total cholesterol (TCh), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) offer insights into the patient's lipid metabolism and cardiovascular health. Additionally, tests for creatinine (Cr), uric acid (UA), and blood urea nitrogen (BUN) provide information about kidney function.

The use of specialized tubes for molecular analysis, particularly EDTA tubes, indicates a focus on genetic or molecular investigations, suggesting a comprehensive approach to understanding the link between genetic variations, biochemical parameters, and conditions such as Familial Combined Hyperlipidemia (FCHL) and Type 2 Diabetes Mellitus (DM2) in the studied population.

2.3 Genetic Analysis:

Blood samples were collected from the veins of 50 patients diagnosed with Familial Combined Hyperlipidemia (FCHL) and 50 individuals representing a healthy control group. DNA extraction was carried out using a DNA extraction kit, specifically the Geneaid extraction kit from Korea. This kit facilitates the isolation of DNA from collected blood samples, providing a purified genetic material for subsequent analysis. The analysis of the TCF7L2 gene involved a multi-step process. Primers, which are short DNA sequences, were designed for the amplification of a specific segment of the TCF7L2 gene. Polymerase Chain Reaction (PCR) was then performed, a molecular biology technique that exponentially replicates the targeted DNA segment, resulting in an amplified product. The amplified DNA, specifically a 196-base pair segment of the TCF7L2 gene, was subjected to electrophoresis. This process involved placing the DNA samples in a gel matrix, typically made of agarose, and applying an electric field. The DNA fragments then migrated through the gel based on their size, creating distinct bands. A gel concentration of 1.5% agarose was used in this study. Subsequent to electrophoresis, the gel was examined under ultraviolet (UV) light. UV light causes DNA to fluoresce, allowing the visualization of the separated DNA fragments as distinct bands. By analyzing the pattern of bands, researchers could determine the genotypes of the TCF7L2 gene in the studied samples. This genetic analysis provided valuable information on the variations in the TCF7L2 gene, contributing to the understanding of its association with Familial Combined Hyperlipidemia.

2.4 Statistical Analysis

The statistical analysis in this study employed the Statistical Package for the Social Sciences (SPSS 22.0), a widely used software for statistical analyses. For continuous variables, such as biochemical parameters, the study utilized measures of central tendency, specifically mean values, to represent the average, and standard deviation to assess the variability around the mean. To compare means between different groups, the t-test, a statistical method for assessing the significance of differences between two means, was applied. This allowed for a quantitative evaluation of variations in continuous variables, providing insights into the distinctions observed in biochemical parameters among different groups of participants. For categorical data, particularly genotype frequencies in the context of genetic analysis, the chi-square test was employed. This statistical test is designed to assess the independence of categorical variables and was utilized in this study to analyze the distribution of genotypes and identify any significant associations or differences between the Familial Combined

Hyperlipidemia (FHCL) group and the control group. To further understand the effects of significant risk factors and establish associations, logistic regression analysis was performed. Logistic regression is a statistical method used to model the probability of a binary outcome, and in this study, it helped assess the relationship between TCF7L2 genotypes and the risk of FHCL, considering various biochemical parameters. The criterion for statistical significance was set at $p < 0.05$, indicating that results with a probability of occurrence less than 5% were considered statistically significant. This rigorous statistical approach enhances the reliability and validity of the study's findings, providing a robust foundation for drawing meaningful conclusions.

3. Results

The study conducted a comprehensive analysis of biochemical parameters in female Iraqi patients with Familial Combined Hyperlipidemia (FHCL) and compared them with control samples. The results revealed noteworthy differences in serum concentrations between the FHCL cases and the control group, emphasizing the significance of these biochemical markers in understanding the condition. Genetic testing focused on the TCF7L2 gene, uncovering variations that exhibited a substantial difference in genotype frequencies when comparing individuals with FHCL to the control group. This genetic insight suggests a potential association between TCF7L2 gene variations and the susceptibility to FHCL, laying the groundwork for further exploration into the genetic determinants of this complex disorder. To strengthen the observed associations, logistic regression analysis was employed. The analysis not only confirmed the link between TCF7L2 genotypes and the risk of FHCL but also took into account various biochemical parameters. This comprehensive approach underscores the multifaceted nature of FHCL, where both genetic factors, represented by TCF7L2 variations, and biochemical markers play integral roles in shaping the risk profile of affected individuals. The findings contribute to the understanding of the intricate interplay between genetic and biochemical factors in the context of FHCL. By establishing associations between TCF7L2 genotypes and FHCL risk, considering the broader biochemical context, the study provides a more nuanced perspective on the complexity of this familial lipid disorder. These insights are crucial for advancing both diagnostic and therapeutic strategies tailored to the unique genetic and biochemical characteristics of FHCL patients.

4. Discussion

The study discerned variations in the TCF7L2 gene that are correlated with Familial Combined Hyperlipidemia (FHCL) and Type 2 Diabetes (DM2) in Iraqi females. TCF7L2 genotypes, which were previously identified in association with DM2, were observed to exert an influence on the characteristics of FHCL. Notably, the findings indicated a notable link between TCF7L2 gene variants and heightened levels of triglycerides (TG) in FHCL cases, underscoring the gene's pivotal role in lipid metabolism. These results contribute to the growing body of evidence supporting the intricate interconnection between genetic factors, particularly TCF7L2 gene variations, and the manifestation of metabolic disorders such as FHCL. The observed association with elevated TG levels suggests that TCF7L2 may play a significant role in regulating lipid metabolism pathways, implicating it as a potential contributor to the pathogenesis of FHCL. However, despite these valuable insights, further investigations are warranted to delve into the molecular mechanisms that underlie the association between TCF7L2 polymorphisms and FHCL. Elucidating these mechanisms would provide a deeper understanding of how specific genetic variations in TCF7L2 contribute to the development and progression of FHCL, further informing potential therapeutic targets and interventions. In essence, the study highlights the importance of TCF7L2 in the context of lipid metabolism and its potential impact on the development of FHCL in Iraqi females. The call for additional research underscores the complexity of these genetic associations and the need for a comprehensive exploration of the molecular pathways involved, offering a promising avenue for future investigations in the field of metabolic disorders.

5. Conclusion

In conclusion, this study offers crucial insights into the correlation between variations in the TCF7L2 gene and familial combined hyperlipidemia (FHCL) and type 2 diabetes (DM2) in Iraqi females. The established genetic associations highlight the significance of TCF7L2 in lipid metabolism, shedding light on its potential role in predicting hereditary susceptibility to FHCL. By identifying specific genetic links, the study contributes to a deeper understanding of the molecular underpinnings of these metabolic disorders, particularly in the context of the Iraqi female population. The implications of these findings extend beyond the immediate scope of the study, emphasizing the relevance of TCF7L2 in the intricate network of lipid regulation. The identification of TCF7L2 gene variants associated with FHCL and DM2 underscores the genetic complexity involved in these conditions. Understanding such genetic predispositions is crucial for advancing personalized medicine approaches, allowing for tailored interventions and preventive strategies based on an individual's genetic profile. However, to enhance the robustness and generalizability of these findings, it is imperative to conduct further research with larger sample sizes. A broader and more diverse participant pool would enable researchers to validate and expand upon the

observed associations. Additionally, exploring the molecular mechanisms that link TCF7L2 polymorphisms to FHCL would provide a more comprehensive understanding of the gene's role in lipid metabolism and metabolic disorders. In summary, this study serves as a stepping stone in unraveling the intricate interplay between genetic factors, specifically TCF7L2 gene variations, and the manifestation of FHCL and DM2 in Iraqi females. The knowledge gained from this research sets the stage for future investigations aimed at refining diagnostic and therapeutic strategies tailored to the genetic makeup of individuals at risk of these metabolic conditions.

References

[1] R. A. DeFronzo, R. C. Bonadonna, and E. Ferrannini, "Pathogenesis of NIDDM: A balanced overview," Diabetes Care, vol. 15, pp. 318-368, 1992.
[2] C. J. Nolan, P. Damm, and M. Prentki, "Type 2 diabetes across generations: from pathophysiology to prevention and management," Lancet, vol. 378, pp. 169-181, 2011.
[3] F. M. Ashcroft and P. Rorsman, "Diabetes mellitus and the beta cell: The last ten years," Cell, vol. 148, pp. 1160-1171, 2012.
[4] S. F. Grant et al., "Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes," Nat. Genet., vol. 38, pp. 320-323, 2006.
[5] A. Helgason et al., "Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution," Nat. Genet., vol. 39, pp. 218-225, 2007.
[6] P. C. Lin et al., "Transcription factor 7-like 2 (TCF7L2) rs7903146 polymorphism as a risk factor for gestational diabetes mellitus: a meta-analysis," PLoS One, vol. 11, p. e0153044, 2016.
[7] J. C. Florez et al., "TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program," N. Engl. J Med., vol. 355, pp. 241-250, 2006.
[8] J. Wang et al., "Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish diabetes prevention study and are associated with impaired glucose regulation and impaired insulin secretion," Diabetologia, vol. 50, pp. 1192-1200, 2007.
[9] A. C. Alibegovic et al., "The T-allele of TCF7L2 rs7903146 associates with a reduced compensation of insulin secretion for insulin resistance induced by 9 days of bed rest," Diabetes, vol. 59, pp. 836-843, 2010.
[10] C. Giannini et al., "Co-occurrence of risk alleles in or near genes modulating insulin secretion predisposes obese youth to prediabetes," Diabetes Care, vol. 37, pp. 475-482, 2014.
[11] M. Heni et al., "Glycemia determines the effect of type 2 diabetes risk genes on insulin secretion," Diabetes, vol. 59, pp. 3247-3252, 2010.
[12] K. Faerch et al., "Incretin and pancreatic hormone secretion in Caucasian non-diabetic carriers of the TCF7L2 rs7903146 risk T allele," Diabetes Obes. Metab., vol. 15, pp. 91-95, 2013.
[13] S. A. Schafer et al., "Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms," Diabetologia, vol. 50, pp. 2443-2450, 2007.
[14] L. Shu et al., "Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP-1 receptors and impaired beta-cell function," Hum. Mol. Genet., vol. 18, pp. 2388-2399, 2009.
[15] S. F. Wang et al., "TCF7L2 is a master regulator of insulin production and processing," Hum. Mol. Genet., vol. 23, pp. 6419-6431, 2014.
[16] O. Le Bacquer et al., "TCF7L2 rs7903146 impairs islet function and morphology in non-diabetic individuals," Diabetologia, vol. 55, pp. 2677-2681, 2012.
[17] R. K. Mitchell et al., "Selective disruption of Tcf7l2 in the pancreatic beta cell impairs secretory function and lowers beta cell mass," Hum. Mol. Genet., vol. 24, pp. 1390-1399, 2015.
[18] S. Cauchi et al., "Transcription Factor TCF7L2 Genetic Study in the French Population Expression in Human β-Cells and Adipose Tissue and Strong Association With Type 2 Diabetes," Diabetes, vol. 55, pp. 2903-2908, 2006.