INVESTIGATION OF THE CORRELATION BETWEEN THE LEPTIN GENE AND TYPE II DIABETES MELLITUS - RELATED BIOCHEMICAL PARAMETERS IN THE IRAQI POPULATION

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DEDICATION

I dedicate my humble effort (My Thesis) to my country, my family, and to the unknown soldier in my life, to everyone who supported me even with a kind word

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ABSTRACT

Diabetes is a frequently occurring disease all over the world. However, in Iraq, the prevalence of type II diabetes mellitus (T2DM) is particularly due to many different factors, one of which is genetics. Thus, the recognition of genetic conditions and associated contributing factors pertaining to the onset of diabetes are essential to resolve the issues related to this disease. The current study was performed in order to evaluate the possible link between polymorphisms in the leptin (*LEP*) gene and T2DM in individuals from Iraq. Serum specimens were acquired from 220 participants, 100 of which were used as control subjects with no ailments, while the remaining 120 subjects had T2DM. Gene analyses were conducted on extracted genomic DNA. A range of biochemical investigations were carried out including fasting blood glucose (FBG), haemoglobin A1c (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), insulin, thyroid stimulating hormones (T3 and T4), low-density lipoproteins (LDL), high-density lipoproteins (HDL), total cholesterol, triglycerides (TG), vitamins C and K, chromium, selenium and cobalt. Three dedicated Polymerase Chain Reaction (PCR) primers were designed to identify three prevalent single nucleotide polymorphisms (SNPs) within *LEP*, i.e. rs11761556, rs12706832 and rs2167270. Genotyping of the amplified loci was performed using polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP). Sanger sequencing was then carried out to identify representative genotypes. The relationship between targeted genetic variants and T2DM was established using logistic regression analysis. All three targeted SNPs demonstrated banding patterns following PCR-SSCP genotyping. Compared to the remaining genotypes, subjects with the AA genotype for the SNPs, rs11761556 and rs12706832, exhibited elevated parameters of body mass index, waist circumference, FBG, HbA1c, HOMA-IR, insulin, LDL and TG ($p < 0.05$). Association analysis determined that subjects with the A allele displayed a higher likelihood of developing T2DM. The results of this study suggest that the SNPs, rs11761556 and rs12706832, have a significant link to T2DM. The current study has verified the existence of an association between *LEP* gene polymorphism and T2DM, which could act as a potential marker for the appraisal of a number of variables linked with T2DM in the Iraqi community. Furthermore, the link between the *LEP* gene and traits of T2DM suggest that this could be a potential marker for T2DM in the Iraqi population.

ABSTRAK

Diabetes merupakan penyakit yang kerap berlaku di seluruh dunia. Walau bagaimanapun, di Iraq, kelaziman diabetes melitus jenis II (T2DM) berlaku kerana banyak faktor yang berbeza, salah satunya ialah genetik. Oleh itu, pengenalpastian keadaan genetik dan faktor-faktor penyumbang yang berkaitan dengan bermulanya diabetes adalah penting untuk menyelesaikan isu-isu berkaitan penyakit ini. Kajian ini dijalankan untuk menilai hubungan yang mungkin antara polimorfisme dalam gen leptin (*LEP*) dan T2DM dalam individu-individu dari Iraq. Spesimen serum telah diperolehi daripada 220 peserta, 100 peserta sebagai kawalan yang tiada penyakit, manakala 120 yang lain menghidapi T2DM. Analisis gen telah dijalankan pada DNA genomik yang diekstrak. Pelbagai ujian biokimia yang telah dijalankan termasuk glukosa darah puasa (FBG), hemoglobin A1c (HbA1c), penilaian model homeostatik untuk rintangan insulin (HOMA-IR), insulin, hormon merangsang tiroid (T3 dan T4), lipoprotein ketumpatan rendah (LDL), lipoprotein ketumpatan tinggi (HDL), jumlah kolesterol, trigliserida (TG), vitamin C dan K, kromium, selenium dan kobalt. Tiga primer tindak balas berantai polimerase (PCR) khusus telah direka bentuk untuk mengenalpasti tiga polimorfisme nukleotida tunggal lazim (SNP) yang berlaku dalam *LEP*, iaitu rs11761556, rs12706832 dan rs2167270. Penjenisan gen lokus teramplifikasi dilakukan menggunakan tindak balas berantai polimerase-polimorfisme konformasi bebenang tunggal (PCR-SSCP). Kemudian penjujukan Sanger dijalankan untuk mengenal pasti genotip wakil. Hubungan antara varian genetik yang disasarkan dan T2DM telah diwujudkan dengan menggunakan analisis regresi logistik. Kesemua tiga SNP yang disasarkan menunjukkan pola kejaluran berikutan daripada penjenisan gen PCR-SSCP. Berbanding dengan genotip yang lain, subjek dengan genotip AA bagi SNP, rs11761556 dan rs12706832, menunjukkan kenaikan parameter indeks jisim badan, lilitan pinggang, FBG, HbA1c, HOMA-IR, insulin, LDL dan TG ($p < 0.05$). Analisis perkaitan menentukan bahawa subjek dengan alel A menunjukkan kemungkinan mendapat T2DM yang lebih tinggi. Keputusan kajian ini menunjukkan bahawa SNP, rs11761556 dan rs12706832, mempunyai hubungan yang ketara dengan T2DM. Kajian ini telah mengesahkan kewujudan hubungan di antara gen polimorfisme *LEP* dan T2DM, yang mungkin bertindak sebagai penunjuk berpotensi bagi penilaian bilangan pemboleh ubah yang berkait dengan T2DM dalam komuniti di Iraq. Selain itu, kaitan antara gen *LEP* dan ciri-ciri T2DM mencadangkan bahawa ini boleh menjadi penunjuk berpotensi bagi T2DM dalam masyarakat Iraq.

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A	-	Adenine
AAS	-	Atomic absorption spectroscopy
BMI	-	Body mass index
C	-	Cytosine
Co	-	Cobalt
Cr	-	Chromium
DI		Diabetes Insipidus
DM	-	Diabetes mellitus
DNA	-	Deoxyribonucleic acid
F	-	Female
FBG	-	Fasting blood glucose
G	-	Guanine
HbA1c	-	Haemoglobin A1c
HDL	-	High-Density Lipoproteins
HOMA-IR	-	Homeostatic model assessment for insulin resistance
HPLC	-	High-performance liquid chromatography
HWE	-	Hardy-Weinberg equilibrium
IGF-I	-	Insulin-like growth factor 1
IGT	-	Impaired glucose tolerance
IR	-	Insulin resistance
LADA	-	Latent autoimmune diabetes in adults
LDL	-	Low-Density Lipoproteins
LEP	-	Leptin
M	-	Male
MENA	-	Middle East and North Africa
MODY	-	Maturity Onset Diabetes of the Young
NCBI	-	National Centre for Biotechnology Information
PCR	-	Polymerase chain reaction
PPI	-	Proton Pump Inhibitors

P-value	-	Probability *v*alue
Se	-	Selenium
SNP	-	Single nucleotide polymorphism
SSCP	-	Single strand conformation polymorphism
T	-	Thymine
T1DM	-	Type I diabetes mellitus
T2DM	-	Type 2 diabetes mellitus
T3	-	Triiodothyronine
T4	-	Thyroxin
TC	-	Total cholesterol
TG	-	Triglycerides
TSH	-	Thyroid stimulating hormone
U.A	-	Uric acid
UTR	-	Untranslated region
VLDL	-	Very low density lipoprotein
WC	-	Waist circumference

CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes is a metabolic syndrome characterised by insulin release and activity which is not under optimal physiological control. The consequent ongoing raised serum glucose concentrations are associated with chronic morbidities, e.g. functional impairment of a number of viscera, and affect ophthalmic, renal, nervous, cardiac and circulatory systems, amongst others. Several underlying disease processes contribute to the aetiology of diabetes, e.g. autoimmune damage to pancreatic cells, thus leading to insufficient insulin levels. Irregularities in carbohydrate, lipid and protein metabolism occur as a consequence of the development of insulin resistance (IR) in target cells. The combination of inapposite insulin release and diminished tissue sensitivity to insulin effectively result in a lack of insulin at several potential sites in multiple hormonal pathways. Issues with both insulin liberation and tissue resistance frequently arise concurrently within one individual, thus compounding the recognition of the specific elements which could potentially be the cause of raised serum glucose levels (American Diabetes Association, 2014).

Symptoms of elevated glucose concentrations include the classic triad of polyuria, polydipsia and weight loss. They are frequently accompanied by polyphagia and visual disturbances. Ongoing derangement of glucose levels may additionally impact growth and heighten vulnerability to infection. Two potentially critical metabolic emergencies that may arise in uncontrolled diabetes are hyperglycaemia associated with ketoacidosis and non-ketotic hyperosmolar syndrome.

Visceral complications include retinopathy, renal disease and peripheral neuropathy. Associated morbidities encompass blindness, kidney impairment, and foot ulceration, amputation and Charcot’s arthropathy, respectively. Concomitant

that progressively hinder serum glucose homeostasis and which are involved in the onset of both micro- and macrovascular pathologies associated with T2DM include cellular functional impairment, resistance to insulin and chronic activation of inflammatory pathways (DeFronzo, 2009; 2010).

The link between genetic variants and diabetes mellitus does not immediately give rise to the pathology, but instead relates to intermediary molecular phenotypes that can lead to transformations in higher order pathology characteristics. Recognition of the molecular phenotypes that are altered as a result of DNA fluctuations and which additionally correspond to varying pathological traits provides an opportunity to acquire the functional information necessary to not just identify and to verify the susceptibility genes that are immediately impacted by alterations in DNA, but additionally to understand the mechanisms underlying the function of such genes and the way in which they influence pathological processes at a molecular level (Schadt et al., 2008).

T2DM acts as a major promoter for numerous single nucleotide polymorphisms (SNPs), which have a possible crucial function in the governance of the disease processes underlying the condition (Sun et al., 2018). There is a void of data pertaining to T2DM and obesity within Arabic communities and in particular, with respect to the criteria for ethnic-specific diagnosis and management of diabetes. Additional genome-wide association studies in obese or diabetic individuals from these regions could therefore enhance both the comprehension of the disease processes underlying these conditions within these communities, and the development of prophylactic and potential reversal measures. Such work could assist in restricting the extensive prevalence of T2DM which affects the Arabic territories (Bisher et al., 2016).

A protein comprised of 167 amino acids, leptin is situated on chromosome 7q31.3 and synthesised by the *LEP* gene (Comuzzie et al., 1997). Acting as an adipocyte hormone, it forms the afferent component of a negative feedback circuit that is essential for the homeostatic regulation of adipose tissue (Dallner et al., 2019). Numerous researchers have proposed a link between gene polymorphisms of leptin,

GDM and the presentation of diabetes-associated complications, e.g. cardiovascular disease (Pawlik et al., 2017; Issa, 2011).

Numerous incidences of T2DM can be circumvented by optimising body mass index (BMI), healthy eating habits, frequent 30 minute exercise sessions, avoiding tobacco and only consuming alcohol on occasion (Schellenberg et al., 2013; Hu et al., 2001). This is especially relevant if an individual is cognizant that he/she has a genetic tendency to develop T2DM. It is therefore essential to identify the components of genetic SNPs that are linked with the leptin (*LEP*) gene, and which contribute to obesity and the development of T2DM.

1.2 Problem statement

T2DM is one of the principal diseases states that impacts the Iraqi community and additional global regions. It is a long-term condition that has a significant effect on all families and their routine daily activities.

Numerous genetic markers have been linked with the development and advancement of T2DM, including the *LEP* gene. It has been postulated that the *LEP* gene is involved in the onset of the condition and contributes to the diminished release of insulin.

This study has therefore focused on *LEP* variants in order to evaluate their potential connection with the complications of T2DM. Thus, screening was performed for 3 SNPs that arise with significant frequency, i.e. rs11761556, rs12706832 and rs2167270, and that are sited in 3 varied loci on the *LEP* gene in order to evaluate their prospective relationship with the appraised characteristics of T2DM. Despite the fact that the SNPs screened during this work have been linked to a number of metabolic conditions, their part in the development of T2DM requires further elucidation, both in individuals from Iraq and from other nations.

1.3 Research objectives

The study objectives are:

(i) To explore the association between IR, thyroid function, antioxidants, lipid profile and trace elements, and to utilise a statistical paradigm in order to comprehend their influence and involvement in the onset of T2DM;

(ii) To recognise SNPs relating to the *LEP* gene in individuals with T2DM and healthy controls, and to generate their genotypic characteristics; and

(iii) To recommend an innovative detection technique founded on a combination of geno and pheno studies together for the link between the SNPs from the *LEP* gene and T2DM.

1.4 Scope of research

This research encompasses the association between physical variables of well-being and factors that will assist in optimising metabolic pathways in order to surmount anomalies observed in T2DM. It will include a case-control study of individuals with T2DM (n = 120) and a healthy control cohort (n = 100) with participants' ages ranging between 35 to 50 years. Serum specimens will be acquired from medical institutions in Iraq and analysed using Mindray and Maglomy chemical analysers, respectively. Parameters, including low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), total Cholesterol (TC), uric acid, T3, T4, and TSH will be assayed. Quantities of the trace elements cobalt (Co), selenium (Se) and chromium (Cr) will be determined by atomic absorption spectroscopy.

In order to determine the association between the assessed variables and T2DM, a genetic design for *LEP* gene primers will be constructed utilising the National Centre for Biotechnology Information (NCBI) primer BLAST server.

Polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) will be used to perform genotyping studies. The sequencing analysis mode of the SnapGene Viewer, version 4.0.4, will be employed to interpret the electropherogram series and gene sequence files. PCR-SSCP pattern sequences will be oriented together with their matching reference sequences from the *LEP* gene; this will be achieved with the use of BioEdit software, version 7.1 (DNASTAR; Madison, USA). Given that this research evaluated subjects of a particular age, i.e. between 35 and 50 years, it can be considered to be autonomous of gender. This is uncommon within the cohort of individuals living with diabetes in Iraq and made the sample collection procedure more complex.

1.5 Significance of study

The aim of the study is to determine whether any relationship is present between the 3 high-frequency *LEP* gene SNPs and T2DM in adults from Iraq. A population-based control study was performed in order to investigate any potential links and to establish whether any determined connections, i.e., SNPs-T2DM, were of clinical relevance for the timely identification of T2DM within the Iraqi people.

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LIST OF PUBLICATIONS

1. Musafer, K. N. J., Huyop, fahrul Z., Ewadh, M. J., Supriyanto, E., & Rava, M. (2020). A Systematic Mapping Study on the Risk Factors Leading to Type II Diabetes Mellitus. Karbala International Journal of Modern Science, 6(3), 275–283. https://doi.org/10.33640/2405-609X.1677.

2. Musafer, K. N. J., Huyop, F. Z., Ewadh, M. J., Supriyanto, E., Al-Thuwaini, T. M., & Al-Shuhaib, M. B. S. (2021). The single nucleotide polymorphisms rs11761556 and rs12706832 of the leptin gene are associated with type 2 diabetes mellitus in the Iraqi population. Archives of Biological Sciences, 73(1), 93–101. https://doi.org/10.2298/ABS210129005M.