# Leptin Gene Polymorphism and Dyslipidemia in Obese Diabetic Patients: Pilot Study

*Thesis*

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# دراسة تأثير تعدد أشكال جين اللبتين على مستوى الدهون في الدم في مرضى السكر البدناء: دراسة استطلاعية

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**توطئة للحصول علي درجة الماجستيرفي الباثولوجيا الإكلينيكية**

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# List of Abbreviations

| | | |
|---|---|---|
| **ANOVA** | : | Analysis of variance |
| **Arg** | : | Arginine |
| **Asn** | : | Asparagine |
| **ATMs** | : | Adipose tissue macrophages |
| **BBB** | : | Blood–brain barrier |
| **BMI** | : | Body mass index |
| **CDC** | : | Centers for Disease Control and Prevention |
| **CNS** | : | Central nervous system |
| **CSF** | : | Cerebrospinal fluid |
| **dL** | : | Deciliter |
| **DM** | : | Diabetes mellitus |
| **EDTA** | : | Ethylenediaminetetraacetic acid |
| **FBG** | : | Fasting blood glucose |
| **GABA** | : | Gamma aminobutyric acid |
| **GIT** | : | Gastrointestinal tract |
| **Gln** | : | Glutamine |
| **HbA1c** | : | Hemoglobin a1c |
| **HDL** | : | High-density lipoprotein |
| **HS** | : | Highly significant |
| **IL** | : | Interleukin |
| **LDL** | : | Low-density lipoprotein |
| **LEP** | : | Leptin gene |
| **LepRs** | : | Leptin receptors |
| **Lys** | : | Lysine |
| **MHO** | : | Metabolically healthy obese |
| **mL** | : | Milliliter |
| **MUO** | : | Metabolically unhealthy obese |
| **N** | : | Number, |
| **NS** | : | Nonsignificant. |
| **NTS** | : | Nucleus tractus solitarius |
| **OGTT** | : | Oral glucose tolerance test |
| **PCR** | : | Polymerase chain reaction |
| **RBG** | : | Random blood glucose |
| **rpm** | : | Revolutions per minute |
| **rs** | : | Reference single nucleotide polymorphism |

| | | |
|---|---|---|
| **S** | : | Significant, |
| **SAT** | : | Subcutaneous adipose tissue |
| **SHBG** | : | Sex hormone-binding globulin |
| **Sig** | : | Significance, |
| **SLR** | : | Soluble leptin receptor |
| **SNP** | : | Single-nucleotide polymorphism |
| **SP1** | : | Specificity protein 1 |
| **SVF** | : | Stromal vascular fraction |
| **TC** | : | Total cholesterol |
| **TE** | : | TRIS- EDTA |
| **TG** | : | Triglycerides |
| **Th** | : | T-helper |
| **TNF** | : | Tumour necrosis factor |
| **Trp** | : | Tryptophan |
| **uL** | : | Microliter |
| **VAT** | : | Visceral adipose tissue |
| **WAT** | : | White adipose tissue |
| **WHO** | : | World health organization |

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# Abstract

The prevalence of obesity has steadily been rising over the past decades in adults and children, to become a global epidemic and represent a major public health challenge. Obesity is a multifactorial condition influenced by the combined effects of genes, environment and their interactions. Despite intense efforts, the genetic pathways underlying obesity remain elusive.

Many studies have identified the role of genetic variants related to obesity, although the results are still contradictory. This may have occurred due to the diversity of the ethnic groups involved and their respective genetic variability as well as to variations in age, gender, and sample size. Furthermore, there is divergence regarding diets and lifestyles, which modulate the phenotype of body weight.

Leptin is a key hormone in the regulation of body weight. Synthesized and secreted by the adipose tissue, it functions as an afferent satiety signal for the hypothalamus, where it triggers a cascade of neuroendocrine responses that result in the inhibition of orexigenic peptides. These events regulate appetite and metabolism, controlling the body fat mass.

About 60–90% of patients with type 2 diabetes are obese. Insulin resistance is a characteristic feature in abdominal obesity. Both diabetes and obesity have a strong genetic component, and their inheritance is polygenic. Furthermore, they may share a common genetic background, that is, the risk alleles for obesity may also be involved in the increased risk of developing type 2 DM.

## Key word:

Low-density lipoprotein, Metabolically healthy obese, Oral glucose tolerance test, Glutamine, Subcutaneous adipose tissue, Total cholesterol

# Introduction

Obesity is the most prevalent nutritional public health problem. The prevalence of obesity is increasing in most of westernized and developing countries in the world ***(Bagriacik et al., 2009).*** It has a complex pathogenesis that results from interactions between genetic and environmental factors ***(Farooqi and O'Rahilly, 2006).***

Leptin is a hormone that is transcribed by the leptin gene (LEP) and secreted primarily by adipocytes ***(Houseknecht and Portocarrero, 1998)***. It is an important signal in the regulation of adipose-tissue mass and body-weight. Leptin regulates body weight by inhibiting food intake and stimulating energy expenditure. Its expression and secretion are highly correlated with body fat and adipocyte number and size ***(Jequier, 2002).***

Obese subjects are characterized by elevated circulating levels of leptin that can be primarily explained by an increased leptin release from enlarged adipocytes ***(Lonnqvist et al., 1997).*** However, several studies have reported a wide range of plasma leptin levels at any given level of body fat content ***(Fried et al., 2000).*** This suggests that factors other than adipose tissue mass per se may control leptin expression ***(Fain and Bahouth, 2000).***

Another mechanism by which the adipocyte may influence leptin production is through genetic variance in hormone secretion ***(Strobel et al., 1998).***

Several sequence variants have been detected within the 5′ flanking region of the human leptin gene. One of these polymorphisms, a common 2548G/A leptin promoter variant, has previously been shown to be associated with either variations in serum leptin levels or the degree of obesity in obese and overweight subjects ***(Hoffstedt et al., 2002).***

Substantial data indicated that the LEP –2548 G/A polymorphism was associated with the variations in plasma leptin and body mass index (BMI) in both obese and non-obese individuals. The mechanism may be that the LEP –2548 G/A polymorphism influences leptin expression, possibly at the transcriptional level, and therefore also adipose secretion levels of the hormone. However, the direct association between the 2548 G/A polymorphism and obesity remains vague ***(Zhang et al., 2014).***

# Aim of the work

This study aims to determine LEP 2548G>A polymorphism for leptin gene in obese diabetic patients, and its correlation to obese non diabetic patients and normal-weight individuals, and to assess their influence on the lipid profile.

# Obesity

## A) Definition:

In 2010, the Center for Disease Control and Prevention (CDC) considered obesity a threat to the national health, and defined obesity as a body mass index (BMI) equal to or more than 30. BMI is calculated as the weight in kilograms divided by the height in meters squared, rounded to one decimal place ***(Ogden et al., 2010)***.

## B) Epidemiology:

Obesity is the most prevalent nutritional disorder worldwide. Its prevalence is increasing rapidly worldwide ***(De Onis et al., 2010),*** and it is increasing at a faster rate in low and middle income countries compared with high income countries. Obesity has reached particularly alarming levels in the Middle East and North Africa region ***(Musaiger, 2011)***. An estimated 2.6 million people die from non-communicable diseases each year as a result of being overweight or obese, with the majority of deaths occurring in poor countries ***(Aitsi-Selmi et al., 2012).***

## C) Risk Factors of Obesity:

Diet is the most prominent cause of obesity, in addition to the modern sedentary lifestyles. Other causes of obesity include endocrine disturbances, genetic syndromes,