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The Role of Melatonin and Leptin with gene expiration of *ADCY3* in Obese people

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ABSTRACT

Background: obesity is linked to early death and poses a severe danger to public health. Non-communicable diseases, including type 2 diabetes, cardiovascular conditions, high blood pressure, and various cancers, significantly contribute to the global health burden. Studying the genes, hormones, and proteins that has correlation with obesity will help explain why some people, even in identical situations, are more likely to become obese than others.

Aim: Identify relationships between Melatonin and Leptin with gene expiration of *ADCY3* gene and differences between obese and healthy individuals in obesity people.

Method: This study was carried out in laboratories of College of Science, Wasit University in Iraq form November 2023 to July 2024.This study were include 80 peoples the ages (18-50) they were measuring the BMI of them . Fifty obese people (25 male and 25 female) they are diagnosed clinically. The control group consists of 30 apparently healthy individuals (15 male and 15 female). The current study was in agreement with hospital ethics and approvals from all participants. Measuring melatonin, leptin and Gene (*ADCY3*) expiration in obese and control groups by EIESA assay.

Results: The Results was evaluated at ($P \leq 0.05$) value, significantly higher (P= 0.034) mean levels of melatonin hormone in obese person (167.12±12.11) but in healthy control group (124.76±5.84).also, Significantly higher (P= 0.002) mean levels of leptin hormone in obese person (1.47± 0.061) but in healthy control group (2.35 ± 0.411).Mean level of *ADCY3* were (1.29 ± 0.19) in obesity people and (2.01 ± 0.29) in healthy control group, data showed highly significantly (P= 0.001) decreasing of mean level of *ADCY3* in obesity people when compared with healthy control group. Moreover results showed highly significant(r=0.360, p= 0.025) Positive correlation Leptin and Melatonin .Furthermore, highly negative correlation between ADCY3 and Melatonin (r=-0.503, p= 0.001), and *ADCY3* and Leptin (r=-0.391, p= 0.004).

Conclusions: It is concluded from the present study that the gene expression of *ADCY3* and Leptin hormone, Melatonin hormone important roles in the development and severity of obesity.

Keywords: *Obesity, Melatonin, Leptin, ADCY3*

1. INTRODUCTION

A typical definition of obesity is the accumulation of excessive body fat that poses a health concern. Body Mass Index (BMI), which assesses an individual's weight in relation to height, is the most effective and widely used method for identifying obesity (1).Numerous physiological functions, including as metabolism, proliferation, and cellular homeostasis, are impacted by obesity (2).

Several hormones, including leptin and melatonin, regulate hunger, satiety, and energy metabolism .Leptin, primarily produced by adipose tissue, acts as a satiety factor and regulates food intake and energy expenditure (3) (4). Similarly, Melatonin on the other hand, is an endogenous hormone involved in various physiological functions, including the regulation of energy metabolism and circadian rhythms (5) (6).

Estimates of obesity's heritability range from 40% to 75%, highlighting the significant hereditary component. Genome-wide association studies (GWAS) have identified a variety of genes that influence energy regulation and appetite, contributing to both monogenic and polygenic forms of obesity (7). Adenylate cyclase 3 (*ADCY3*) is a crucial genetic element in the onset

of obesity. As the third member of the adenylyl cyclase family, *ADCY3* facilitates the transformation of ATP into cAMP, which is a vital process for numerous metabolic functions. Research employing both candidate genes and genome-wide association methodologies has associated genetic variations in *ADCY3* with obesity (8).

2. METHODS

2.1 Two main subjects were included in the study:

2.1.1 subjects were included in the study:

This study has included (80) person with the ages rang (18-50). Fifty people as obesity people they have more than 25 BMI and thirty healthy people as control group have BMI (19.5-24.5).

2.2. EIESA Kit Assay

2.2.1 Human Melatonin ELISA Kit.

The procedure of this kit down according to company China (BT LAB) the catalog number (E1013Hu).

Reagent Preparation

Before use, all the reagents were maintained at 25°C. To prepare a 640 ng/L standard stock solution, 120 µl of the standard (1280 ng/L) was mixed with 120 µl of standard diluent. The standard was allowed to sit for 15 min with gentle stirring before dilution. Duplicate standard points were created by diluting the 640 ng/L standard stock solution in a 1:2 ratio with the standard diluent, resulting in 320, 160, 80, and 40 ng/L solutions. The standard diluent was used as the zero standard (0 ng/ml). Any leftover solution should be stored at -20°C and used within a month.

2.2.2 Human Leptin ELISA Kit.

The procedure of this kit down According to the company China (BT LAB) the catalog number (E1559Hu).

Reagent Preparation:

Before use, all reagents were maintained at room temperature. To prepare a 6ng/ml standard stock solution, mix 120ul of the standard (12.8ng/ml) with 120ul of the standard diluent. Let the standard sit for 15 minutes with gentle stirring before proceeding with dilutions. Duplicate standard points were created by serially diluting the 6ng/ml standard stock solution 1:2 with a standard diluent to achieve concentrations of 3ng/ml, 1.5ng/ml, 0.75ng/ml, and 0.375ng/ml. Any leftover solution should be stored at -20°C and used within a month.

2.2.3 Human Adenylate Cyclase Type3 ELISA Kit.

The procedure of this kit down according to the company China (BT LAB) the catalog number E2265Hu.

Reagent Preparation

All the reagents were brought to a temperature of 25°C before use. To prepare the standard, 120 µL of standard solution (12.8 ng/ml) was mixed with 120 µL of standard diluent, resulting in a 6 ng/ml standard stock solution. The standard was left to sit for 15 min with gentle stirring before dilution. Standard points were created by performing 1:2 serial dilution of the 6 ng/ml standard stock solution with the standard diluent, yielding solutions of 3, 1.5 ng/ml, 0.75 ng/ml, and 0.375 ng/ml. Any leftover solution was stored at -20°C and used within a month.

2.2.4 Statistical analysis:

Data were gathered, condensed, examined, and displayed using Statistical Package for Social Sciences (SPSS) version 26 and Microsoft Office Excel 2010. Numerical data are shown as mean and standard deviation following the Kolmogorov-Smirnov normality test, which determined whether variables were normally or non-normally distributed. An independent samples t-test was employed to examine the mean difference between the two groups, assuming that the variable followed a normal distribution. To compare means across more than two groups, a one-way ANOVA test was used, provided the variable was normally distributed. The chi-squared test was used to explore the association between the two categorical variables. Pearson's correlation was used to assess the relationship between two numeric variables, with results expressed as the correlation coefficient (r) and significance level (P). A P-value of less than 0.05 was considered significant, while a value of 0.01 or less was deemed highly significant (Daniel, 2018) (9).

3. RESULTS

3.1 Melatonin hormone parameters

The results of Melatonin hormone in obesity and healthy control person showed in table (3-1). Mean level of Melatonin hormone were (167.12± 12.11 and 124.76± 5.84), in obese person and healthy control group respectively, the mean level was higher significantly (P= 0.034) than in obese person when compared with healthy control.

Table (3-1): Melatonin hormone level in obesity person and healthy controls.

Hormone parameters	Obesity *n* = 50	Healthy control *n* = 20	*P value*
Melatonin hormone level			
Mean± SD	**167.12 ± 12.11**	**124.76 ± 5.84**	**0.034** †**S**
Range	34.26 – 433.84	67.52- 170.01	

n: number of cases; **SE**: standard deviation; †: independent samples t-test; S: significant at P ≤ 0.05.

3.2 Leptin hormone parameters

Results in The table (3-2) showed mean of leptin hormone (1.47± 0.061 and 2.35 ± 0.411) in obesity people and healthy control group respectively. The mean level was significantly lower than in obesity people in comparison with healthy control (P= 0.002).

Table (3-2): Leptin hormone level in obesity and healthy controls.

Hormone parameters	Obesity people *n* = 50	Healthy control *n* = 20	*P value*
Leptin hormone level			
Mean± SD	**1.47 ± 0.061**	**2.35 ± 0.411**	**0.002** †**S**
Range	0.10 – 2.98	0.15- 6.72	

n: number of cases; **SD**: standard deviation;; †: independent samples t-test; S: significant at P ≤ 0.05.

3.3. Adenylate Cyclase 3 (*ADCY3*).

The values of Adenylate Cyclase3 (*ADCY3*) highly significant (P= 0.001) lower (1.29 ± 0.19) in obesity people but in healthy control are (2.01 ± 0.29) as demonstrated in table (3-3).

Table (3-3): Adenylate Cyclase 3 level in obesity people and healthy controls.

Protein parameters	Obesity people *n* = 50	Healthy control *n* = 20	*P value*
Adenylate Cyclase 3 (*ADCY3*) level			
Mean± SD	**1.29 ± 0.19**	**2.01 ± 0.29**	**0.001** †**S**
Range	0.72 – 1.89	0.52- 5.07	

n: number of cases; **SD**: standard deviation; †: independent samples t-test; S: significant at P > 0.05.

3.4. Correlation between parameters studied in obesity people.

The present results show significant positive correlation between leptin and melatonine (r=0.360, p= 0.025). Furthermore, and significant negative correlation between *ADCY3* and Melatonin (r=-0.503, p= 0.001), and *ADCY3* and Leptin (r=-0.391, p= 0.004).

3.4.1. Logistic regression correlations between different parameters.

In obesity people the Logistic regression model illustrated the correlation of the leptin and melatonin in figure (3-1). But indirectly correlation was appeared between *ADCY3* and melatonin as in figure (3-2). And *ADCY3* and Leptin as in figure (3-3).

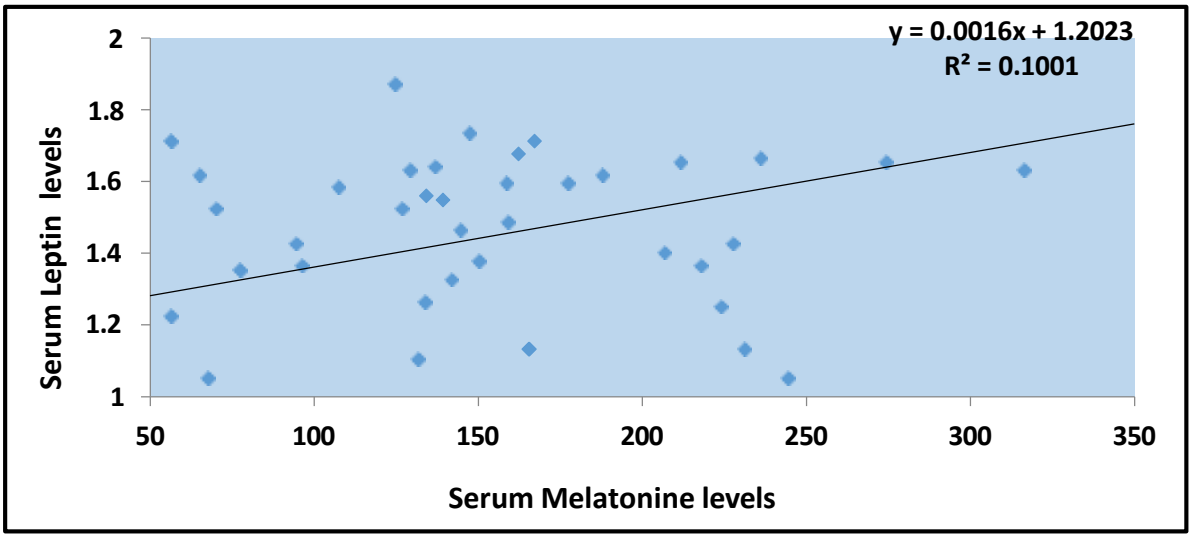

Figure (3-1): The Logistic scatter correlation between serum leptin and serum melatonin level

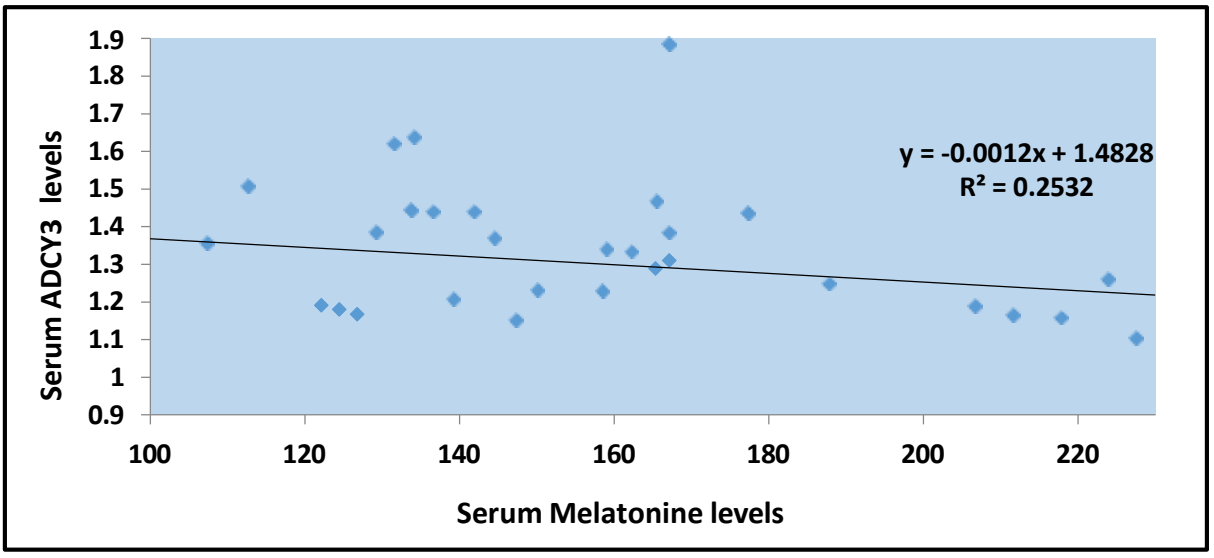

Figure (3-2): The Logistic scatter correlation between *ADCY3* and melatonin levels.

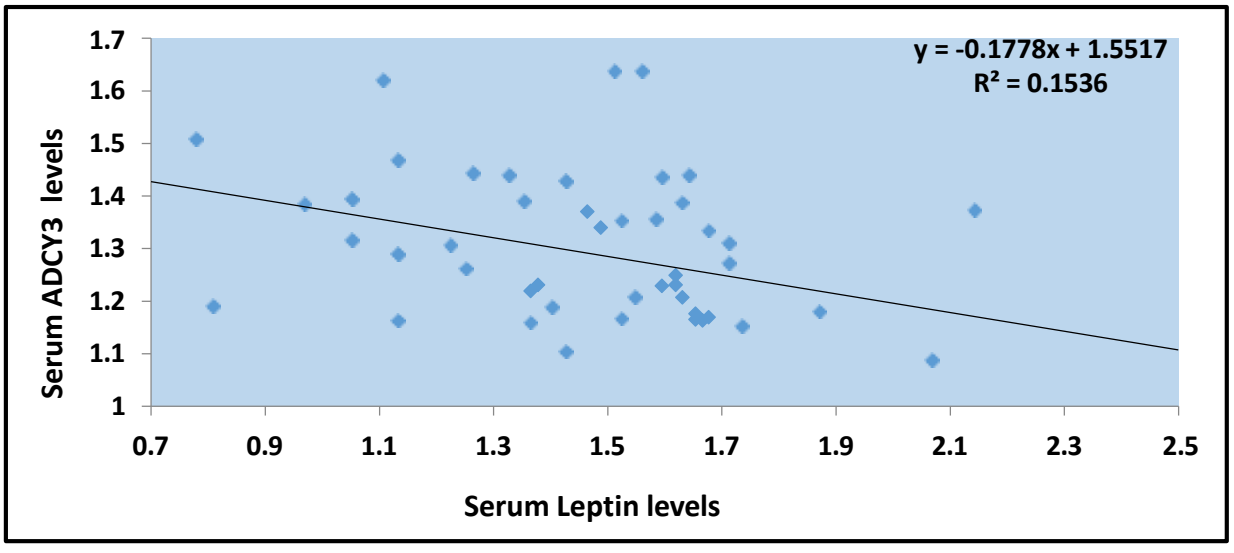

Figure (3-3): The Logistic scatter correlation between *ADCY3* and Leptin levels .

4. DISCUSSION

The study find that Melatonin exerts several effects on obesity. It influences the expression of genes related to appetite by stimulating and inhibiting anorexigenic and orexigenic signals, respectively. Disruption of sleep can disrupt this balance, thereby increasing the risk of weight gain.there is evidence to support the use of melatonin in the management of obesity, showing its impact on weight reduction, BMI, and waist circumference (10).

Based on the findings, Leptin functions as the principal regulator of the brain-gut axis, conveying a satiety signal through its interaction with the central nervous system receptors located in the hypothalamus. Activation of hypothalamic leptin receptors results in the suppression of food intake and promotion of energy expenditure pathways. Notably, leptin levels decreased in response to weight reduction. Despite the capacity of leptin to suppress appetite, the majority of obese individuals exhibit hyperleptinemia and leptin resistance, which impedes the effectiveness of exogenous leptin therapy (11); (12). This paradoxical condition, wherein elevated circulating leptin levels fail to suppress appetite or induce weight loss, is a defining characteristic of obesity and is termed leptin resistance. Leptin resistance significantly contributes to obesity, thereby complicating efforts by most individuals to achieve and maintain weight loss (13).

Research indicates that elevated levels of DNA methylation in *ADCY3* are implicated in the pathogenesis of obesity. Dysfunction of *ADCY3* is associated with increased body weight and fat mass, whereas its activation may result in a reduction in body weight. This gene plays a crucial role in energy homeostasis by influencing appetite regulation, metabolism, and adipose tissue functions. Additionally, it is involved in cAMP signaling pathways that regulate lipolysis and thermogenesis in adipocytes. Mutations in *ADCY3* or its reduced expression have been linked to impaired satiety signaling, leading to increased food intake and subsequent weight gain. Wu *et al*,. (2016) demonstrated through animal model studies that *ADCY3* plays a significant role in obesity. ADCY3 dysfunction promotes body weight and fat accumulation, whereas its activation decreases body weight (14). Several genetic variants of *ADCY3* associated with obesity have been found in humans, and studies utilizing rodent knockout models have validated the gene's involvement in the control of energy homeostasis (15).

The positive correlation between leptin and melatonin indicates a possible connection between circadian rhythms and energy homeostasis. The research discovered that the melatonin and leptin hormones display a positive genetic correlation, as proven by their correlated functions in the regulation of body mass and energy equilibrium. Both hormones exhibit circadian rhythms, with a rise at the period of the nocturnal phase (16). Melatonin receptors have also been identified in adipocytes, the primary location of leptin production, hence a direct cellular interaction between leptin and melatonin. Research indicates that melatonin enhances insulin-stimulated leptin expression in rat adipocytes isolated, which is indicative of a synergistic action (16).

But this result show that a negative correlation between melatonin levels and ADCY3 gene expression, which may influence metabolic processes and sleep patterns. This inverse relationship could have significant implications for understanding sleep disorders, metabolic syndromes, and the intricate interactions between genetic factors and hormonal regulation .These findings are consistent with previous research demonstrating that melatonin, primarily secreted at night, regulates metabolic processes through its interaction with melatonin receptors (MT1 and MT2). These receptors are linked to G-protein signaling pathways that inhibit cAMP production, a process in which *ADCY3* is critically involved. This inhibition results in a reduction of *ADCY3* activity during nighttime (17).

While Studies suggest that a negative genetic correlation between leptin and *ADCY3* suggests that elevated leptin concentrations may lead to a reduction in *ADCY3* activity, potentially influencing metabolic processes. This correlation has significant implications for understanding obesity, metabolic disorders, and energy regulation. Empirical evidence has indicated that increased leptin levels may downregulate *ADCY3* expression, thereby impairing its role in energy regulation and contributing to weight gain.This finding is consistent with that of the study by Saeed *et al.*, (2018), which demonstrated that loss-of-function mutations in *ADCY3* are associated with severe obesity.These mutations compromise the enzyme's capacity to produce cAMP, a molecule essential for mediating signals from hormones such as leptin, which regulate appetite and energy expenditure(18). Furthermore, genetic variants of *ADCY3* have been linked to alterations in body composition and fat mass, suggesting that certain alleles may modify responses to dietary intake, thereby exacerbating obesity. This negative correlation implies that as *ADCY3* activity diminishes, leptin levels increase, thereby contributing to obesity (19); (20).

5. CONCLUSIONS

The gene expression of *ADCY3* and Leptin hormone, Melatonin hormone important roles in the development and severity of obesity.

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