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Studying the Role of Irisin, Chemerin and Some Other Hormonal Levels in Obese, Diabetic (type II) and Sub-Fertile Men

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Abstract

Role of two polypeptides hormones Irisin and chemerin and other hormones (follicular stimulating hormone FSH, luteinizing hormone LH, testosterone T and prolactin PRL) in obese, diabetic and sub-fertile men was investigated. This investigation
has 80 men aged 35-45 years, they were divided into four groups (20 men / group) as **control**, **obesity**, **diabetic** and **sub-fertility** groups. The results revealed that irisin increased significantly ($p \leq 0.01$) in obesity group and decreased significantly in diabetic and sub-fertility groups in compression with the control.

Chemerin increased significantly in different groups in compression with the control ($p \leq 0.01$), while FSH, LH and T decreased significantly (except T in diabetic group) in different groups in comparison with the control ($p \leq 0.01$). PRL increased significantly in different groups in comparison with the control ($p \leq 0.01$). The physiological impact of these results were be discussed according to the influence of the fat mass (indicated by body mass index BMI), insulin resistance (IR) and the high level of prolactin hormone on all the studied parameters in obesity, diabetic and sub-fertility groups.

In conclusion, the irisin and chemerin levels and their relations with the others hormones indicated a metabolic dysfunction and / or a low fertility in these different groups.

Keywords: Irisin, Chemerin, Obesity, Diabetic, Sub-fertility.

1. Introduction

Irisin is a polypeptide hormone with 112 amino acid residues that is primarily generated in muscle tissue after proteolytic cleavage of its precursor, fibronectin domain-containing protein 5 (*FNDC5*) , it has a molecular weight of about 12 kDa [1, 2]. It belongs to the adipomyokine class since it operates in both adipose and muscle tissue (adipokine and myokine) and is a thermogenic protein that stimulates energy expenditure via white adipose tissue (WAT) browning [3]. Boström et al. [4] report that exercise training induces the expression of the *FNDC5* gene in human muscle, producing irisin, which can convert white fat into brown fat [5].

Obesity is associated with a significant imbalance in cytokine secretion, which is a strong predictor of insulin resistances and type 2 diabetes (T2D) development.[6] Furthermore, increased *FNDC5* / irisin levels were associated to an improved metabolic profile and a lower risk of T2D in middle-aged males with grade 1 obesity [7]. Irisin level improved the obesity and glucose homeostasis [8]and it could be used as a therapeutic protein for human metabolic disorder and other diseases that improve with exercises, a number of researches have suggested that circulating irisin levels in plasma or serum are related to overweight / obesity in various groups of people [9]. Irisin improves insulin resistance and type 2 diabetes by increasing insulin receptor sensitivity in skeletal muscle and the heart, improving hepatic glucose and lipid metabolism, promoting pancreatic cell activities and converting white to brown adipose tissue [10,11]. Some researchers found a positive correlation between irisin levels and body mass index (BMI) [12, 13], while others found a null [14] or even a negative correlation [15].

On the other hand, chemerin is an immunomodulating factor [16], as it is a protein encoded by the Retinoic Acid Receptor Responder 2 (RARRES2) gene in humans, first discovered as a retinoid responsive gene found in psoriatic skin

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lesions [17, 18, 19]. Chemerin was first identified as an adipokine in 2007, It is also highly expressed in the liver [20, 21]. Chemerin receptors (G-protein coupled receptor chemokine like receptor 1 *CMKLR1*, G protein-coupled receptor 1 *GRP1* and the CC chemokine receptor-like 2 *CCRL2*) are present in human and rodent testes, and are located specifically on leydig cells and partially on germ cells [22] [23].

Furthermore, chemerin expression increase in obesity, insulin resistance, metabolic syndrome and type 2 diabetes.[24] Obese individuals had significantly higher plasma chemerin levels than individuals who were healthy weight, Chemerin levels are lower in obese patients who have lost weight by diet or bariatric surgery [25, 26]. Also, it has been discovered that serum chemerin levels were higher in patients with type 2 diabetes than in healthy, and concluded that chemerin plays an important role in obesity and related disorders like diabetes. [27]

Besides, chemerin levels are lower in sub-fertile males than in control, and they are negatively associated with plasma luteinizing hormone (LH) and sex hormone binding globulin (SHBG) concentrations in humans.[28] Thus, understanding the chemerin's role in male fertility is crucial, its concentration in seminal fluid was found to be negatively correlated with spermatic motility and positively correlated with sperm concentration [29].

In view of this survey, the aim of our study is to investigate the role of irisin and chemerin hormones and their relation with some other reproductive hormones (FSH, LH, T and PRL) in obese, diabetic and sub-fertility men to introduce a new study for researchers in their future research.

2. Materials and methods

2.1. Subjects

The current study was included eighty men aged 35-45 years that divided into four groups were classified into: control, obesity, diabetic (type 2) and sub-fertile. Each one has twenty men. The sample was conducted in some health centres in Misan province / Iraq, during December 2020 to July 2021. Each sample has been checked medically by physicians and has been diagnosed with obesity, diabetic (type 2) and sub-fertile (hyperprolactinemia) according to (body mass index BMI, glycated hemoglobinA1c HbA1c and prolactin levels respectively) and the healthy men as a control group. Men with chronic diseases, tumours and those whom treatment with hormonal drug has been excluded.

2.2. Sample collection

Eight to ten millilitres of venous blood samples were drawn at 9-11 am, using a disposable syringe for each man. The blood was left at room temperature for 15 min for coagulation, centrifuged at 3000 rpm for 5 min, then serum and plasma separated and transferred for storage.

2.3. Data collection and laboratory tests

Serum irisin and chemerin levels were accurately measured using a highly quantitative enzyme-linked immunosorbent assay (ELISA) kit from Sunlong biotech/China. The range from 0.5-30 ng/ml and 32-2000 pg/ml respectively. FSH, LH, testosterone and prolactin were accurately measured using a vidas/Italy (BioMeriux/France). The range from 1.7-12 mlU/ ml, 1.7-7 mlU/ ml, 2.80-8 mlU/ ml and 4.6-21.4 mlU/ ml, respectively. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared [30].

2.4. Statistical Analysis

Statistical analysis was performed by IBM SPSS statistics, version 23 (IBM Co., Armonk, NY, USA). The statistical analysis was performed by one-way Analysis Of Variance (ANOVA) , followed by *Duncan's* new multiple range *test* (DMRT) at a $(p \leq 0.05)$, $(p \leq 0.01)$ significant level[31].

3. Results and Discussion

Irisin level in sub-fertility group (19.62 ± 2.88 ng/ml) decreased significantly $(p \leq 0.01)$ in comparison with other groups; control (22.91 ± 2.92 ng/ml), obesity group (26.33 ± 1.73 ng/ml) and not significantly with diabetic group (20.70 ± 1.56 ng/ml). Also, Irisin decreased significantly $(p \leq 0.01)$ in diabetic group and it increased significantly in obesity group $(p \leq 0.01)$ in comparison with the control (Figure 1).

The high level of irisin in obesity group might be attributed to lipoprotein irisin's secretion mainly by adipose tissue and by the adipocytes cells in obese individuals whom have a high BMI. Obese individuals had a higher circulating irisin level than controls, according to a clinical trial comprising 94 obese patients who participated in a weight management program [10]. In diabetic group, irisin level decreased according to influence of insulin resistance, which has a negative association with insulin resistance, and in sub-fertility group irisin level decreased significantly due to the less amount of testosterone production via the inhibition of gonadotropin (FSH and LH) by the high levels of prolactin in sub-fertile men. (Figure 1). These results are agreed with many studies that indicating that

irisin level was higher in obese than in healthy people.[32,33].

Also, it has been reported that irisin level decreased in diabetic group that be attributed to irisin receptor (PGC-1α) expression and activity are low in type 2 diabetes patients, that PGC-1α is important for mitochondrial homeostasis for it regulates mitochondrial biogenesis and oxidative metabolism, and mitochondrial function also plays a role in insulin resistance.[34]

Besides, in sub-fertility (hyperprolactinemia) group, it has been found that high prolactin inhibits the pulsatile release of FSH and LH, reducing gonadal testosterone synthesis and possibly leading to hypogonadotropic hypogonadism.[35] Treatment with irisin in obese male rats enhanced the FSH , LH and testosterone hormone levels in blood resulting in promotion spermatogenesis and sperm properties such as sperm count and motility.[36]

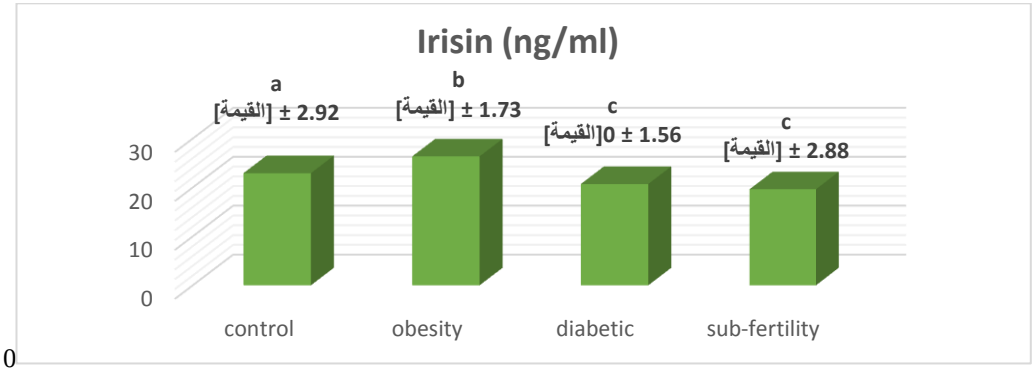

Figure 1: Irisin Levels in four groups of investigation.

*The values represent mean ± SD .

*Different small letters represent significant difference in ($p \leq 0.01$) between groups.

*Similar small letters represent no significant difference .

Chemerin level increased significantly ($p \leq 0.01$) in sub-fertility group (769.85 ± 2.20 pg/ml), in obesity group (680.01 ± 2.80 pg/ml) and in diabetic group (532.25 ± 4.19 pg/ml) in comparison with the control (472.90 ± 3.61 pg/ml) (Figure 2).

The reasons of high level of chemerin might be attributed to lipoprotein chemerin's secretion mainly by adipose tissue and by the adipocyte's cells according to a high BMI and / or a high insulin resistance and / or the inhibition of prolactin hormone on gonadotropin (FSH, LH) thereby testosterone production, leading to an increase in chemerin secretion in obesity, diabetic and sub-fertility groups. In addition, these three groups classified as a low-grade inflammation therefore, chemerin as a pro-inflammatory cytokine attracts and activates immune cells and might be played a physiological role in these different groups and increased in these groups (Figure 2).[37]

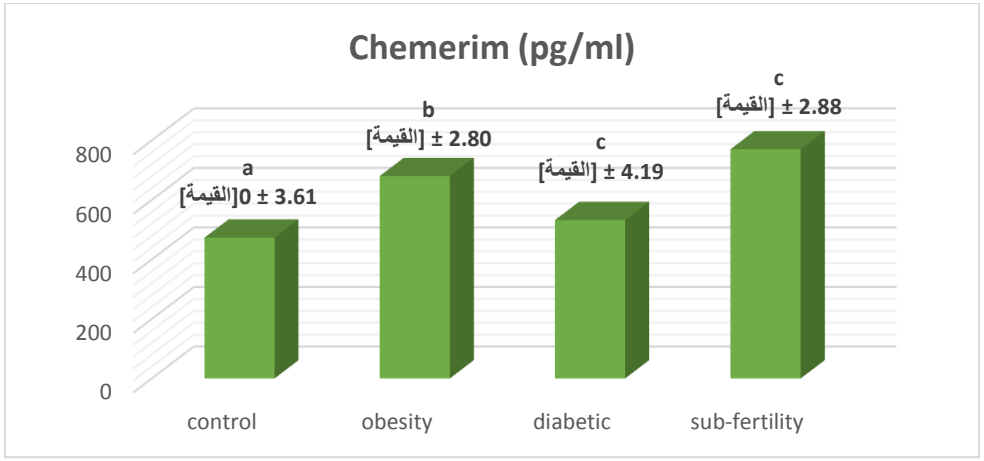

Figure 2: Levels of Chemerin hormone in different groups.

*The values represent mean ± SD.

*Different small letters represent significant difference in ($p \geq 0.01$) between groups.

*Similar small letters represent no significant difference

On the other hand, FSH level decreased significantly ($p \leq 0.05$)in sub-fertility group (2.34 ± 0.65 mlU/ml), obesity group (3.00 ± 0.85 mlU/ml) and diabetic group (3.15 ± 0.72 mlU/ml) in comparison with the control (3.71 ± 0.82 mlU/ml) (Figure 3).

Also, LH level decreased significantly ($p \leq 0.05$) in sub-fertility group (1.93 ± 0.47 mlU/ml), obesity group (2.75 ± 0.78 mlU/ml) and diabetic group (2.80 ± 0.38 mlU/ml) in comparison with the control (3.46 ± 0.34 mlU/ml) (Figure 4).

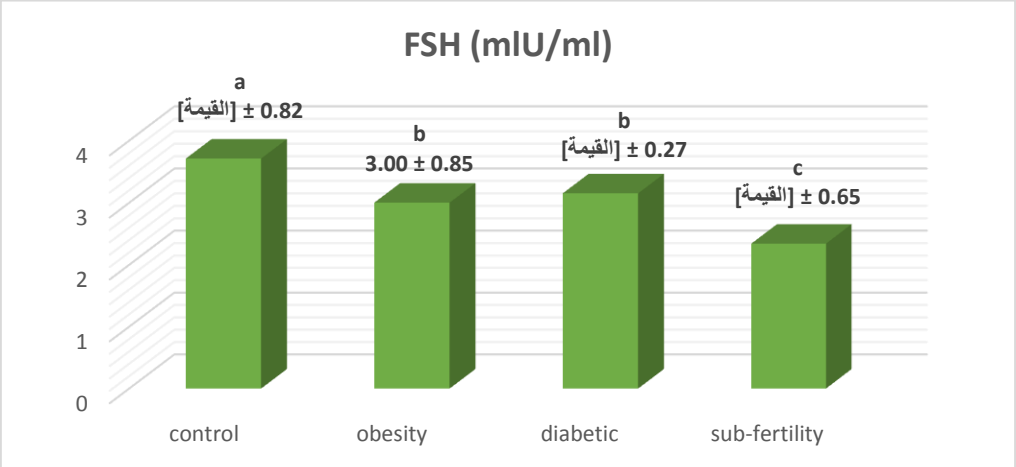

Figure 3: Levels of FSH in different groups.

*The values represent mean ± SD.

*Different small letters represent significant difference in (p ≤ 0.05) between groups.

*Similar small letters represent no significant difference .

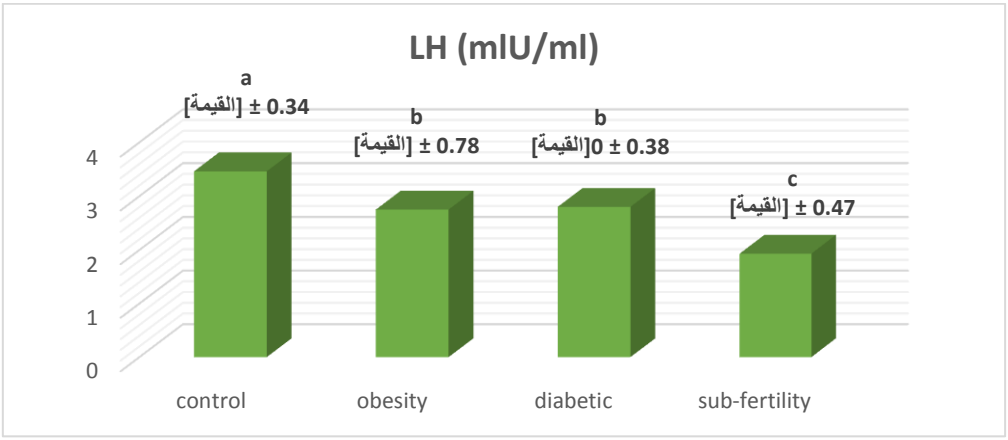

Figure 4: Levels of LH in different groups.

*The values represent mean ± SD.

*Different small letters represent significant difference in (p ≤ 0.05) between groups.

*Similar small letters represent no significant difference .

Testosterone (T) decreased significantly ($p \leq 0.05$) in sub-fertility group (2.23 ± 0.84 ng/ml), diabetic group (3.62 ± 1.62 ng/ml) and not significant with obesity group (2.54 ± 0.65 ng/ml) .in comparison with control (3.94 ± 0.51 ng/ml) Figure (5).

These results of low level of FSH, LH and Testosterone (T) were caused either by the aromatase activity in the obese group or by the influence of insulin resistance and / or hyperprolactinemia or both of them. Chambers and Richard [38]found that obese individuals exhibited a decrease in testosterone levels , based on the fact that in obese subjects there is more aromatase activity that converts testosterone to estradiol, thus hypoandrogenemia and increased estrogen levels that change the negative feedback system in hypothalamic and pituitary area.[39]

Testosterone decreased significantly as a BMI increased that indicated an occurrence of

hypogonadism in patients with type 2 diabetes and overweight or obesity , due to the high conversion of testosterone into estrogen by the high activity of aromatase enzyme leading to reduction the level of testosterone.[40]

The hyperprolactinemia in the present study had the depressed levels of FSH , LH and Testosterone compared to the normal prolactin and this finding is in agreement with the report by Benjamin and his colleagues [41]who also reported the depressed levels of FSH , LH and Testosterone among Nigerian infertile males presenting with hyperprolactinemia associated with hypogonadotropic hypogonadism compared to the normal controls .

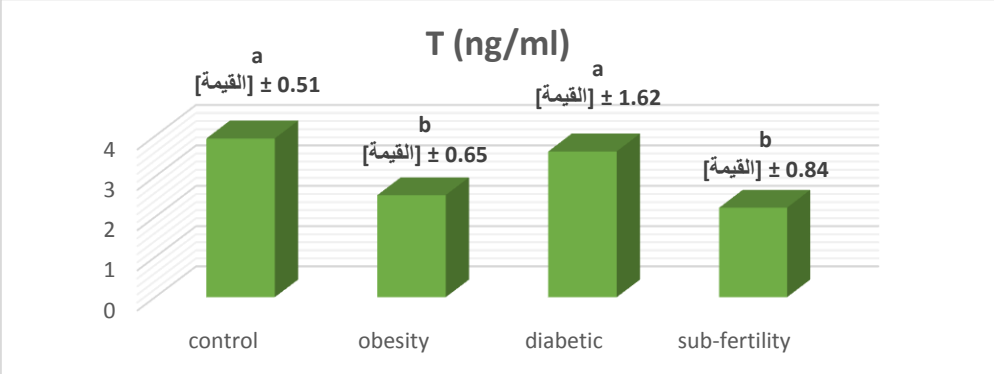

Figure 5: Levels of T in different groups.

*The values represent mean ± SD.

Different small letters represent significant difference in ($p \leq 0.01$) between groups.

*Similar small letters represent no significant difference

PRL level increased significantly ($p \leq 0.01$) in sub-fertility group (35.20 ± 2.37 ng/ml), in obesity group (14.11 ± 1.02 ng/ml) and diabetic group (13.65 ± 1.92 ng/ml) in comparison with the control (11.39 ± 0.75 ng/ml) (Figure 6).

BMI level increased significantly ($p \leq 0.05$) in sub-fertility group (28.36 ± 1.48) and not significantly with diabetic group (27.62 ± 2.74) and decreased significantly ($p \leq 0.05$) with the obesity group (33.67 ± 2.32) in comparison with the control (24.04 ±1.60). (Figure 7).

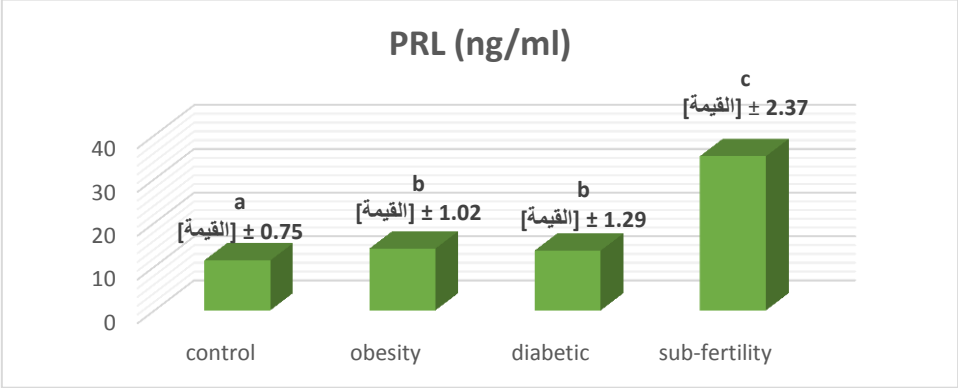

Figure 6: Levels of PRL in different groups

*The values represent mean ± SD.

Different small letters represent significant difference in ($p \leq 0.01$) between groups.

*Similar small letters represent no significant difference.

The present high secretion of prolactin may be occurred due to the high fat mass , insulin resistance and the influence of prolactin secretion in these obese , diabetic and sub-fertile groups respectively , these studied parameters may be agreed with the facts mentioned by Brandebourg and his colleagues [42] found that human adipose tissue produced PRL as well as expressed the PRL receptor (PRLR) highlighted an action of PRL as a cytokine involved in adipose tissue function, biologically active PRL secreted by all adipose tissue such breast, visceral and subcutaneous[42] . in addition to the conclusion of Liu and his colleagues mentioned that increased PRL level might be an adaptive response for protecting against metabolic disorders in obesity [43].

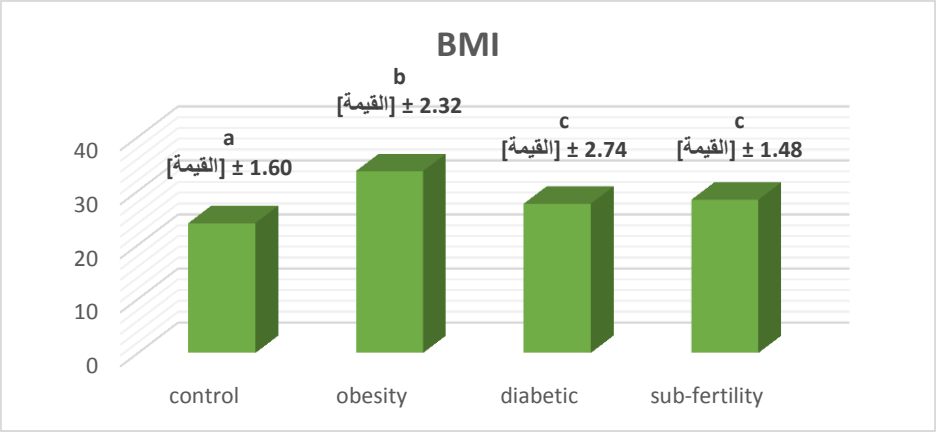

Figure 7: Levels of BMI in different groups.

*The values represent mean ± SD.

Different small letters represent significant difference in ($p \leq 0.01$) between groups.

*Similar small letters represent no significant difference .

Altered prolactin secretion in obesity appears to be a marker of hypothalamic-pituitary dysfunction that may be explained by alterations in central dopaminergic tone [44]. Park and his colleagues [45] mentioned that the effect of a physiologically high prolactin level and pathological hyperprolactinemia on glucose metabolism could be different, excessive high levels of prolactin exacerbate whole-body and hepatic insulin resistance and impair the insulin secretory capacity in diabetic mice. [45]

4. Conclusion

The results revealed that irisin, increases significantly ($p \leq 0.01$) in obesity group and decreased significantly in diabetic and sub -fertility groups in comparison with the control. Chemerin increased significantly ($p \leq 0.01$) in different groups in comparison with the control. In conclusion, these present changes might be indicated a metabolic dysfunction, a pro- inflammatory action and low fertility in obesity, diabetic and sub-fertility groups, therefore we recommended for more studies to illustrated the action mechanisms of these two hormones in different metabolic syndromes, also obese persons they should reduce their weight to avoid conversion of testosterone into estradiol in males, as well as, reducing weight will decrease insulin resistance and treat T2D.

5. Conflicts of interest

"There are no conflicts to declare".

6. Acknowledgments

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