The Important Effect of NRG-4 Level on the Iraqi Obese Infertility Women's

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Abstract

Infertility Women's (IW) this term refers to unable of female for pregnant after at least 1 year of the frequent sexual encounter without any contraceptive agent used. NRG-4 (Neuregulin 4) is a protein hormone classified within adipokine or neuregulin family encode by special gene called NRG-4 (Neuregulin 4) gene, this gene mostly exists in brown adipose tissues. NRG-4 has an important biological role in endocrine and paracrine signaling, it is as erb-b2 receptor tyrosine kinase 4 (ERBB4) activator. To explain the NRG- 4 important function in obese IW women's patients. This study was designed on select females' individuals were divided into 30 individuals having obese IW and 30 fertile women's (as healthy control) individuals. The age of all individuals was 19-34 years old. For all female individuals were assessment of serum NRG-4 level with body mass index (BMI) measurement. The current results of study appeared to increase at the serum NRG- 4 level and BMI in obese IW group compared with fertile women's group. The statistic value for NRG-4 biomarker at obese IW group was 432.2 ± 17.8 and for fertile women's 241.0 ± 19.7, while the statistic value of BMI for obese IW group was 31.7 ± 1.5 and for fertile women's group 23.4 ± 2.3. The current study shows the NRG- 4 role that has function as compensate factor in compensate mechanism for obese IW patients.

Keywords: Infertility Women's (IW) , NRG-4 (Neuregulin- 4) , Polycystic Ovary Syndrome (PCOS) and Body mass index (BMI)

1. Introduction

Infertility Women's (IW) this term refers to unable of female for pregnant after at least 1 year of the frequent sexual encounter without any contraceptive agent used. The IW have various pathologic factor to cause it for example endometriosis, menstrual cycle un-regular and others, but the Polycystic Ovary Syndrome (PCOS) is most frequency causes for IW in populations [1]. On the other hand, obesity disorder is considered commonly cause for PCOS, so the obesity condition can lead to IW and classify as risk factor to it [2]. The IW caused by PCOS can identify via many manifestations (signs and symptoms) like hyperandrogenism, acne, ovaries largest, hirsutism, un-regular periods. Diagnosis of IW depend on tow type of examinations are the laboratory and clinically, this depending on the American College of Obstetricians and Gynecologists guideline [3]. Obesity is a metabolic disorder characterized by increase at body weight and can cause many healthy complications. Obesity can be measured by body mass index (BMI), that is considered as best indicator to obesity. BMI measured via weight and height.

With apply specific equation, according to BMI value the body can classify it into underweight (BMI less than $18.5 Kg/m^2$), Normal (BMI 18.5 to 24.9Kg/m2), Overweight (BMI 25 to 29.9Kg/m2) and Obesity (BMI more than $30 Kg/m^2$) [4-5]. NRG-4 (Neuregulin 4) is a protein hormone classified within adipokine or neuregulin family encode by special gene called NRG-4 (Neuregulin 4) gene, this gene mostly exists in brown adipose tissues. NRG-4 has an important biological role in endocrine and paracrine signaling, it is as erb-b2 receptor tyrosine kinase 4 (ERBB4) activator [6]. ERBB4 after activated by NRG-4, it acts to phosphorylation of tyrosine in cytoplasm to generate cell signal can transfer between cells. The NRG4 has other functions in human body for example apoptotic regulation factor, inflammation inhibiter and others [7]. This study aims to explain the NRG4 role at IW that suffer of obesity PCOS disorder.

2. Materials and Methods

2.1. Study design

Present study designed according to case and control study that included two groups of females: - The first group was IW with obesity of 30 individuals .The second group was healthy control of 30 individuals. The all-individuals age of the two groups were between 19 -34 years. According to American College of Obstetricians and Gynecologists guideline that depend on two examinations (clinically and laboratory), all groups were diagnosed with IW or healthy individuals [8]. Also, for all individuals were applied BMI equation (via weight and height) to classify them obese or normal. The collection of blood was through withdraw 5 ml of whole blood for all individuals then transferred into gel tube, after 5 min all samples separated via centrifuge to obtain pure serum samples. These serum samples were used to measure NRG-4 status for all individuals via immunoassay Technique that called Sandwich ELISA (The Catalog No. CSB -EL016080HU - CUSABIO Co. – US) [9], see figure 1.

2.2. Ethics

The all of studies' individuals were collected in January 2024 from the Karkh hospital for child and birth / Iraq. This study was conducted after the 2013 Helsinki Declaration 2013 on ethics in scientific research and patients' agreement to include them in this study.

2.3. Statistical analysis

At the current study, the statistical analysis method used is T-test analysis method. This method is used to compare between two groups by mean $\pm$ standard deviation (SD) and to show the clinically significant value between the comparison groups used p-value, p-value consider significant when become less than 0.05, [10] SPSS Vers.18 2022. This study used a T-test analysis method to compare between first group (IW with obesity) and second group (healthy control).

3. Results and discussion

After making a comparison between the first and second groups using the T- test statistical method that depends on the mean, SD and P- values. It became clear from the results of the current study that there was a noticeable increase in the levels of NRG-4 status and BMI biomarkers in the first group compared to the second group, because the P- values were less than 5. See Table 1 and Figures 1 and 2. IW is a female's condition that unable to pregnancy after one year of marriage due to various causes for example obesity. The elevation of BMI for women to arrive obesity state can cause ovarian cyst generation (that know PCOS), this situation characterized by disorder of period cycle and hormones secretion [11]. The obesity that causes PCOS consider the most frequency cause for IW. This study results shown increase of BMI at first group (females suffered of IW with obesity) compared with second group (healthy control females). Current results of study explain and focus on the important role of obesity for metabolic syndrome and PCOS that lead to the change in the function of the hypothalamic pituitary ovarian axis [12]. The BMI elevation to become obesity can cause increase of ovarian androgen and insulin secretions. In addition, obesity led to adipose tissues accumulation and increase it, these tissues able to the aromatization of androgen hormones for estrogen production. Estrogen hormone acts to disturb the negative feedback mechanism for hypothalamic pituitary ovarian axis that cause the gonadotropin secretion alteration [13]. On the other hand, the adipose tissues accumulation can cause insulin secretion elevation (hyperinsulinemia) with situation of insulin resistance cells. All these conditions of pathological factors can cause dys-regulation of period cycle and ovulation that result the IW [14]. This study revealed the BMI increased at females suffered of IW with obesity as an indicator for the accumulation of brown adipose tissues, the brown adipose tissues can act as the gland for several adipokines secretion. Also, this study confirms elevation of NRG-4 level at females suffered of IW with obesity, that consider one of adipokines family members. The brown adipose tissues accumulation is the important cause to increase NRG-4 level because NRG-4 secret from it in human body [15]. The results of this study agree with Ghalib MM, et al .2023 that also confirmed increase of NRG-4 level in obese infertility women's [16].
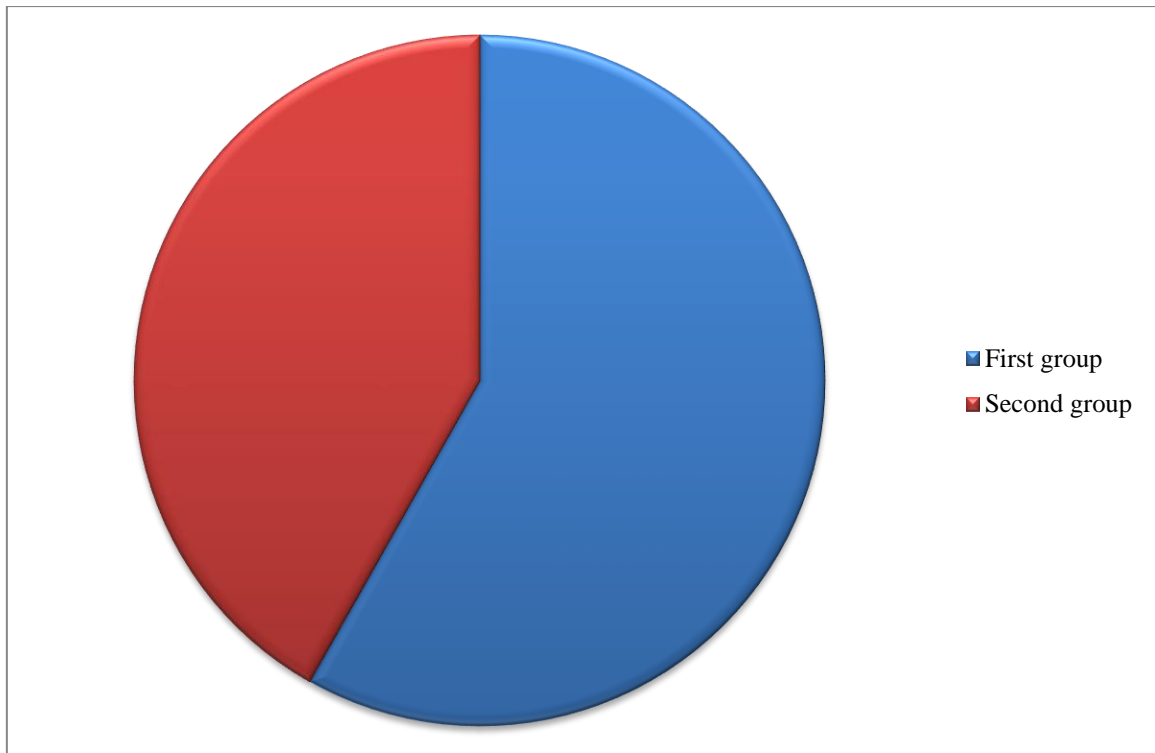
Table 1. The first (IW with obesity) and second (healthy control) groups comparison via the serum NRG-4 status and BMI biomarkers by t- test method

Biomarkers	First Group(IW with obesity) (No. 30 individuals)	Second Group (healthy control) (No. 30 individuals)	P-Value
NRG-4 Concentration (pg/ml)	432.2 ± 17.8	241.0 ± 19.7	0.007*
BMI (Kg/m2)	31.7 ± 1.5	23.4 ± 2.3	0.01*

*/Clinical significant value
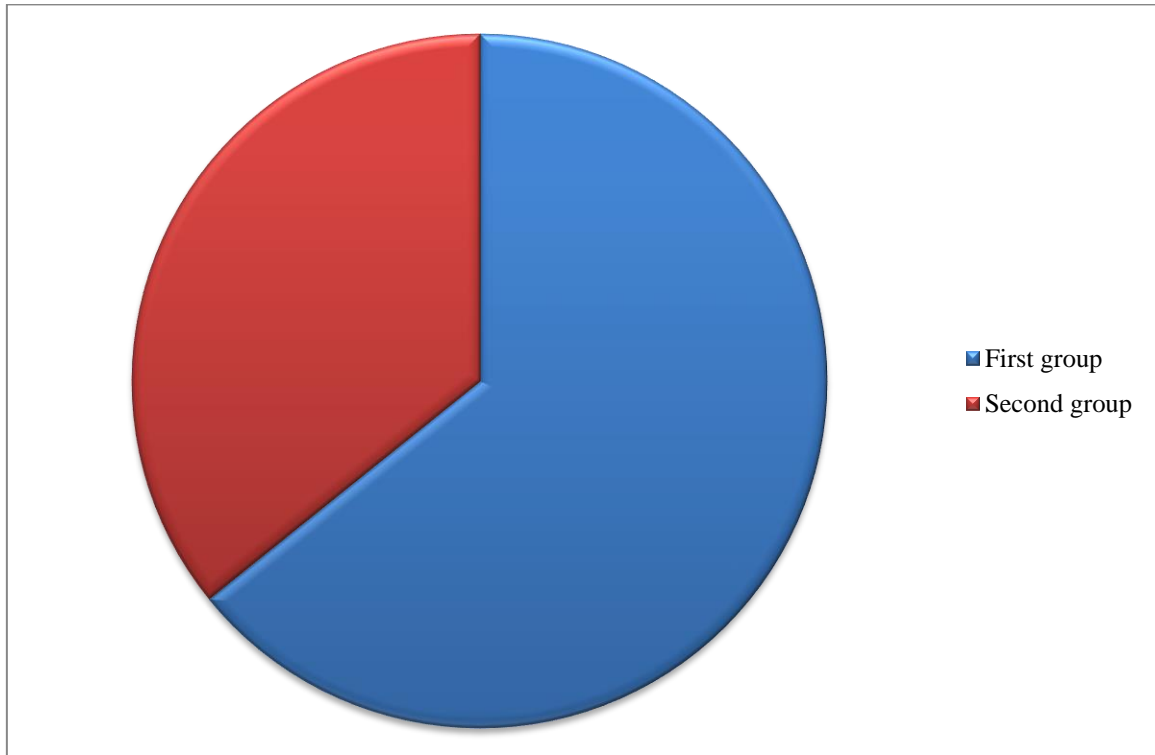
Figure 1. The first (IW with obesity) and second (healthy control) groups comparison via the serum NRG-4 status biomarker

Figure 2. The first (IW with obesity) and second (healthy control) groups comparison via the BMI biomarker

4. Conclusions

This study concluded to show the function and role of NRG-4 concentration that plays as compensation factor in compensation mechanism for obese IW women's. When, the BMI level become obese state this mean elevation of the brown adipose tissues accumulation in body, that consider source of NRG-4 in body . By depend on this study results, we recommend all females must be within acceptable weight and attend to special clinic if have not pregnant after 1 year of marriage.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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