



Original Article

The Role of Neuregulin 4 Status in Female's Primary Infertility Patients

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ABSTRACT

Background: Female's primary infertility (FPI) is females who have not pregnant after one year of sexual intercourse without using methods of birth control. Neuregulin 4 (NRG4) is the inflammatory adipokine hormone produced by brown adipose tissues; it has activator function for Epidermal Growth Factor Receptor (EGFR).

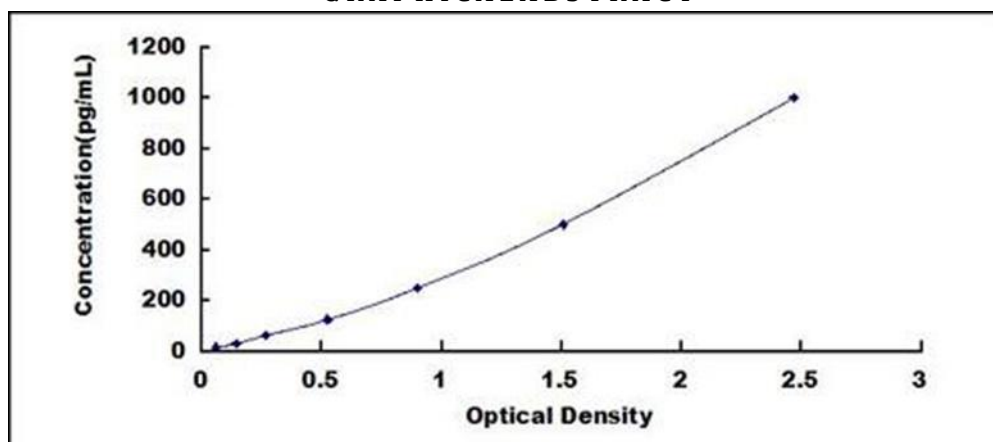
Objective of the Study: To know the NRG4 role and function in FPI patients.

Materials and Methods: The present research study was relied on selecting 80 females classified into 40 with Females having primary infertility and 40 fertile females. All female individuals were in the age range of 20-35 years old. For all female individuals measured NRG4 concentration level in serum sample and body mass index (BMI).

Results: The present research study showed increased of the serum NRG4 level and BMI in FPI group compared with fertile females group. Statistic value of NRG4 for FPI group was 422.3 ± 18.7 and for control group 240.1 ± 17.8 , while the statistic value of BMI for FPI group was 30.9 ± 1.7 and for control group 22.2 ± 2.5 .

Conclusion: The present study explained the NRG4 role that has function as mechanism of compensate in FPI patients with high BMI.

GRAPHICAL ABSTRACT



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Introduction

Female's primary infertility (FPI) is females who are not pregnant after one year of sexual intercourse without using methods of birth control. There are many causes of FPI such as menstrual cycle disorder, ovulation impair, and endometriosis, but the commonly FPI cause is Polycystic Ovary Syndrome (PCOS). The most important PCOS cause is obesity. Therefore, obesity is considered as a risk factor for FPI [1]. The features of FPI patients are significant because PCOS are hirsutism, hyperandrogenism, menstrual abnormalities, and others. FPI diagnose was done according to the American College of Obstetricians and Gynecologists that was depended on clinical and laboratory investigations [2].

Body Mass Index (BMI) is physiological indicator refers to the body weight and height with related together, also give an indication for body fat content. BMI is considered as an assessment method including the following equation: [3, 4] $BMI = \text{Weight by Kg} / \text{Height square by m}^2$:- Depended on BMI results, the human body is classified into the following:

- 1- Underweight when BMI < 18.5,
- 2- Normal when BMI 18.5 - 24.9,
- 3- Overweight when BMI 25 - 29.9, and
- 4- Obesity when BMI > 30.

Neuregulin 4 (NRG4) is protein adipokine hormone encoded and synthesized by NRG4 gene that is commonly presented in adipose tissue (especially brown tissue) [5]. The NRG4 belongs to a family called neuregulin family as one of the

family members. The important function of NRG4 is activator for the erb-b2 receptor tyrosine kinase 4 (ERBB4) that begins tyrosine phosphorylation at cytoplasm to produce cell signaling, especially for gland system (paracrine with endocrine) signals. On other hand, there are secondary NRG4 functions in human body like apoptosis, inflammation inhibition, and regulation factor [6]. The current research study aims to show the important NRG4 function to make FPI that result from obese with PCOS.

Materials and Methods

This research study was depended on selecting 80 female individuals that were classified into 2 groups. 40 female individuals with FPI as the first group (patients group) and 40 female individuals healthy as the second group (control group). The age of all study individuals was between 20 to 35 years old. All individuals were diagnosed as FPI patients or healthy via applying the American College of Obstetricians and Gynecologists criteria's that was depended on laboratory and clinical investigations [7]. The blood sample (5 ml) obtained from the all study individuals and separated via centrifuge method to obtain serum, and then measured NRG4 concentration level using immunoassay method [8]. Also, for all study individuals measured BMI using height and weight of individuals. The present study done at Al-Yarmouk Technical Hospital, Baghdad, Iraq, through August 2022 to October 2022 after the agreement of the Research Ethical Committee. See Figure 1.

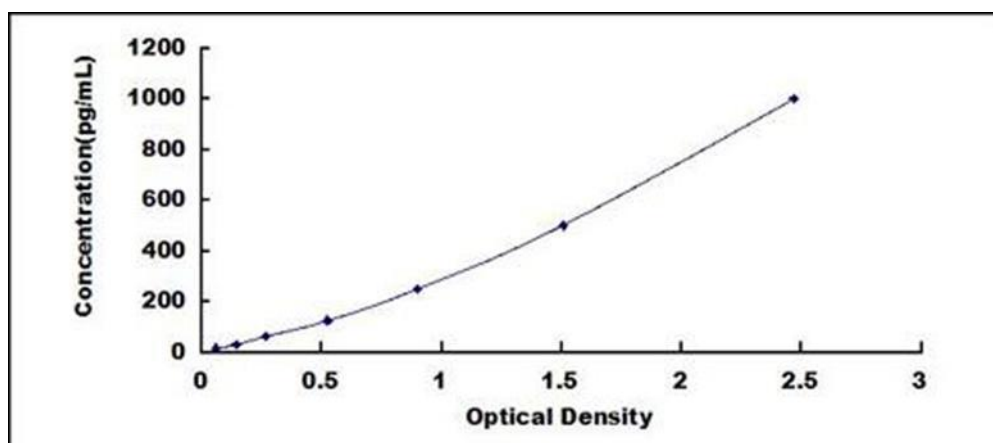


Figure 1: NRG4 standard curve

Technique called Sandwich ELISA Catalog Number. CSB -EL016080HU - CUSABIO company - USA. *

Statistical analysis

The present comparative study enrolled the FPI comparison with control groups using the NRG4 concentration level and BMI by mean + standard deviation (SD) and p-value that is called T-test method (p-value <0.05 is significant) [9].

The present study included the comparison between FPI group and control group via t-test method (mean + SD). The results of this study showed and confirmed the significant different values at NRG 4 level and BMI between FPI and control groups. According to the NRG4 level in serum sample, a significant elevation of NRG4 level in FPI group compared with control group. Likewise, according to the BMI level, the significant elevation of the BMI level in FPI group was observed compared with control group, as presented in Table 1 and Figures 2 and 3.

Results and Discussion

Table 1: Comparison according to the serum NRG4 level and BMI by statistical method called t- test between FPI and control groups

P-value	Control group (No. 40) (mean+SD)	FPI group (No. 40) (mean+SD)	Parameter
<0.001**	240.1+17.8	422.3+18.7	Serum NRG4 level (pg/ml)
<0.001**	22.2 + 2.5	30.9 + 1.7	BMI (Kg/m ²)

**Significant value [10]

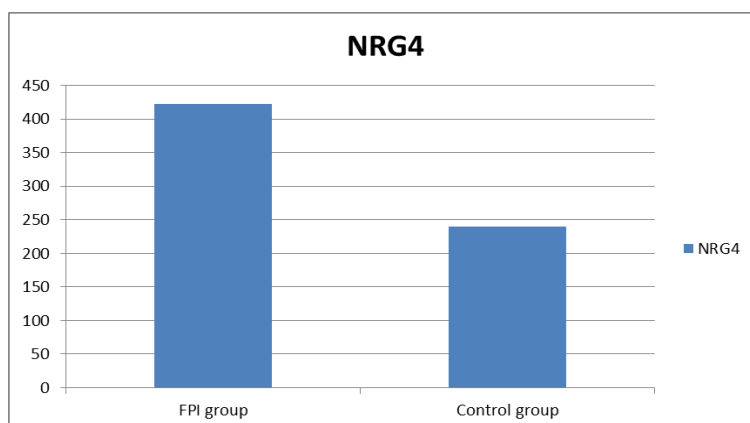


Figure 2: Comparison between FPI and control groups depended on NRG4 in serum samples by T test method

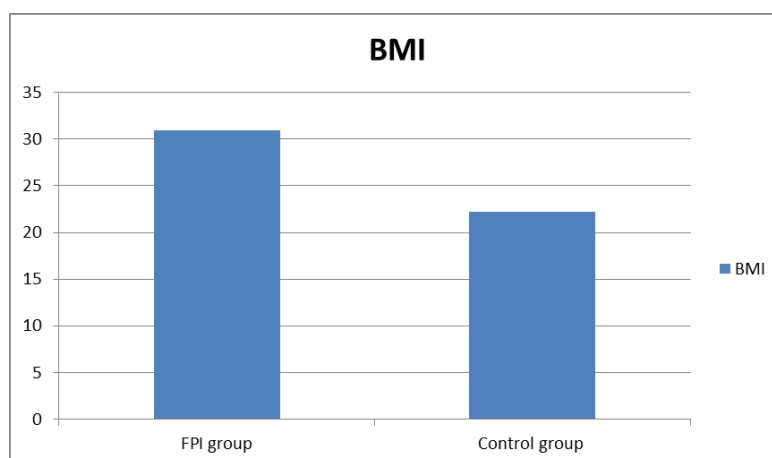


Figure 3: Comparison between FPI and control groups depended on NRG4 in serum samples by T test method

FPI is unable to pregnant females after one year of sexual intercourse because of many causes like obesity. The most common disorders of females are caused by cyst formation in ovarian that results in defect at hormones secretion and menstrual cycle [11]. The female obesity (it means the BMI increase) can cause PCOS that is considered as the common reasons for FPI. The present result study confirms a high BMI level for group with FPI compared with control group. The present results study explain the important obesity role to cause PCOS and metabolic syndrome that can cause the alteration of axis function for hypothalamic pituitary ovarian (HPO). Obesity is considered as the cause to increase of insulin with ovarian androgen secretion. On other hand the obesity occurs with increase of the adipose tissues that causes androgens aromatization to produce estrogen that effects on negative feedback mechanism for HPO axis and results in the alteration of the gonadotropin secretion [12, 13]. In addition, the high adipose tissues can cause the hyperinsulinemia coupled with insulin resistance. These all pathological condition can cause the ovulation impairment with menstrual cycle dysregulation leading to the primary infertility of females. The results of the present study revealed the high BMI at FPI patients as an indicator for the current brown adipose tissues increase, the brown adipose tissues are able to act as the gland to secretion of several adipokines [14]. One of adipokines family is NRG4 that it is produced by brown adipose tissue is able to activate the epidermal growth factor receptor (EGFR) that has an important role in the function of healthy luteinizing hormone-releasing hormone (LHRH). LHRH is responsible for female normal pubertal development due to the EGFR reduction that can cause failed LHRH production. Therefore, the NRG4 increase acts as a compensation mechanism during PFI [15]. The results of this study are in agreement with Kruszewska *et al.* (2022) that also confirmed a high NRG4 level in FPI with BMI elevation [16].

Conclusion

The results of this study explained the NRG4 role as a compensation mechanism in female patients with FPI that have a high BMI.

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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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