Clarification of Neudesin and Neuregulin-4 in Insulin Resistance Among Polycystic Ovary Syndrome Phenotypes

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ABSTRACT

PCOS is a syndrome of ovarian dysfunction that is characterized by the presence of cardinal features of hyperandrogenism and polycystic ovary morphology. Clinical or biochemical hyperandrogenism (HA), ovulatory dysfunction (OD), and/or polycystic ovarian morphology (PCOM) are the three criteria that have been used to characterize PCOS since the creation of the Rotterdam Consensus in 2003, PCOS presence of at least two out of three criteria. This definition results in several PCOS phenotypes, such as phenotype A (ha, od, PCOM), phenotype B (HA, OD), phenotype C (HA, PCOM), and phenotype D (OD, PCOM). Research on adipokines that play roles in metabolic regulation has recently gained interest. This review is a part of the masterwork which would focus on neudesin, and neuregulin_4 and investigate their role as biomarkers for insulin resistance in females affected by PCOS phenotypes

Keywords: Neudesin, Neuregulin, Insulin resistance, PCOS phenotypes

Introduction: Polycystic ovary syndrome (PCOS) is the most endocrine Disorder among premenopausal women **(Louwers et al., 2020)**. In 2019, there were 6,647,566 prevalent cases of PCOS in the Middle East and North Africa (MENA) region, with an age-standardized point prevalence of 2079.7 per 100,000 women, This number reflects an increase of 37.9% since 1990 **(Motlagh et al., 2022).** The prevalence of polycystic ovary syndrome (PCOS) in Iraqi women was estimated to be 33% **(Mousa, 2019)**, which is higher than the percentage over the world representing about 20% of women of reproductive age **(Deswal et al., 2020).** The diagnosis of PCOS has different criteria. To create an extensive and descriptive definition for the diagnosis of PCOS, the National Institutes of Health (NIH) criteria came into existence in 1990 **(Franks, 2006)** the American Society of Reproductive Medicine has designed the Rotterdam criteria in 2003 **(Azziz et al., 2006)**. This criterion requires the presence of two conditions out of the three; (A) oligomenorrhea/anovulation, (B) clinical/biochemical hyperandrogenism, and (C) polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm). In 2006 the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) designed the Androgen Excess Society (AES) criteria. The AES requires the specific presence of clinical/biochemical hyperandrogenism in combination with either oligo anovulation or polycystic ovaries **(Azziz et al., 2006)**.

The Rotterdam criteriais the most common diagnostic tool used to maintain the compatibility of PCOS research which was globally introduced by the National Health and Medical Research Council (NHMRC), Evidence-based Methodology Workshop Panel on Polycystic Ovary Syndrome in 2012 **(Teede et al., 2018)**. The widely used Rotterdam criteria were mostly upheld by the NHMRC PCOS-2018 recommendations **(Moran et al., 2020).** It has four phenotypes; A, B, C, and D. The three current criteria for PCOS S: clinical and/or biochemical hyperandrogenism (HA), ovulatorydysfunction (oligo/amenorrhea) (OD), and Polycystic ovarian morphology (PCOM), phenotype A (HA +OD + PCOM), phenotype B (HA + OD), phenotype C (HA + PCOM), phenotype D (OD + PCOM) (**Polak et al., 2020**).

The prevalence of PCOS phenotypes in the study by **Sachdeva et al (2019)** the phenotypes A, B, C, and D were 67.7%, 11%, 17.7%, and 3.6%, respectively. In a study by **Maffazioli** (**2020**), the phenotypes 54.2% of women were phenotype A, 33.3% were phenotype B, 5.4% were phenotype C and 7.1% were phenotype D**.**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women **(Lizneva et al., 2016)** characterized by metabolic abnormalities like abdominal obesity or insulin resistance, which form the risk factors for metabolic syndrome **(Diamanti-Kandarakis et al., 2012).** The women with PCOS (50%-70%) are insulin-resistant **(Abdalla et al., 2020).** Although the mechanism of insulin resistance in PCOS remains incompletely understood, the underlying defect is reported to occur within the post-receptor phosphatidylinositol 3-kinase (PI3-K) insulin pathway that mediates the metabolic effects of insulin **(Barber et al., 2006)**. Thus, **Azziz** (**2018**) noted that the severity of menstrual irregularities correlates directly with the IR level**.**

The study by **Afjal Hossain et al. (2021)** comprised insulin resistance in a different phenotype that relieved the highest frequency of IR was found in phenotype B 83.33% followed by phenotype A 72.73%, and phenotype C 33.33%, least in phenotype D 27.28%. According to the traditional World Health Organization (WHO) definition of body mass index (BMI), around 50% of patients diagnosed with PCOS are obese **(Abusailik et al., 2021).** The majority of women with PCOS (38%-88%) are either overweight or obese **(Barber et al., 2006)**. The frequency of obesity reaches 86.0% in patients with phenotype A, 27.9% with phenotype B, 46.6% with phenotype C, and 38.8% with phenotype D PCOS **(Kim et al., 2013)**.

Obesity, especially visceral adiposity is common in obese and non-obese women with PCOS. Total body fat (TBF) includes visceral adipose tissue (VAT), which is responsible for high metabolic activity because it releases many bioactive hormones and molecules **(Marinou et al., 2014)**. There are a number of metabolic and hormonal abnormalities associated with PCOS that are conducive to higher VAT deposition **(lffers et al., 2017).** Hypertension, abnormal lipid profiles, insulin resistance (IR), and elevated blood sugar levels have all been linked to elevated VAT levels **(Silveira et al., 2020)**.

Adipokines are cytokines secreted by adipose tissue and play crucial roles in regulating metabolic homeostasis and developing various diseases **(Xu et al., 2022)**. Many adipokines influence insulin sensitivity and overall cardiometabolic risk **(Barber et al., 2021).**

One such adipokine, white adipose tissue (WAT) such as Neudesin known as a GIG47 oncogene or the neuron-derived neurotrophic factor (NENF), **(Al-Hetty et al., 2023)**, is a 172-amino acids protein with a neurotrophic activity that belongs to the membrane-associated progesterone receptor (MAPR) family **(Mifsud et al., 2002).** So far, research has mostly focused on its synthesis within the neural tissue **(Kimura et al., 2006)**; however, neudesin is also expressed in the adipose tissue **(Kimura et al., 2009),** in the internal organs (e.g., lungs, heart, and kidneys) and the numerous neoplasms **(Ohta et al., 2015).**

Fig (1) shows a proposed link by authors between the Neuregulin_4 and Neudesin levels in different PCOS phenotypes based on the UpToDate literature review.

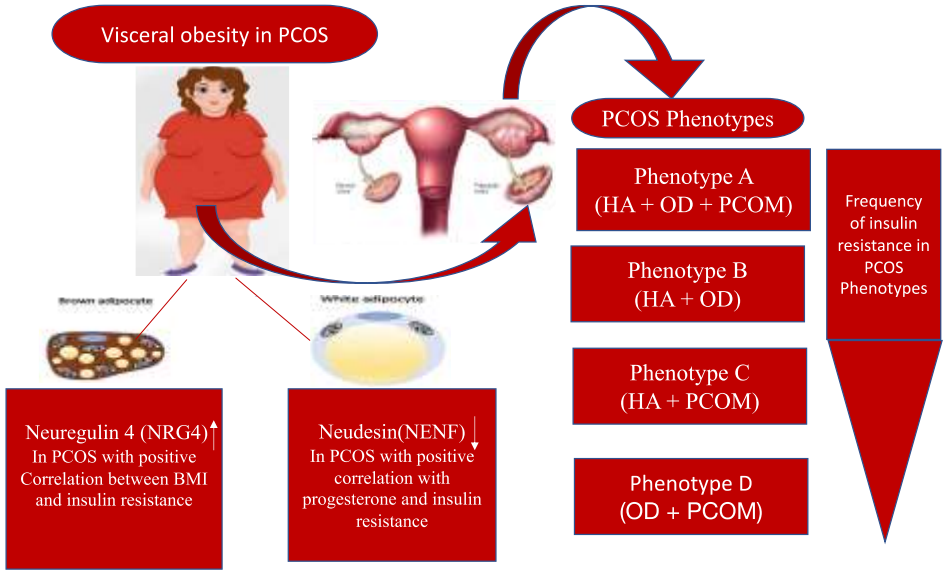

Figure (1): Proposed link between the Neuregulin_4 and Neudesin levels in different PCOS phenotypes based on UpToDate literature

The study by **Bozkaya et al. (2020)** comprised the first attempt to investigate a putative link between PCOS diagnosis and serum neudesin concentration, in this study, its level did not significantly differ between the study and control group and a positive correlation between neudesin and progesterone was noted in the affected individuals. However, compared PCOS patients with and without insulin resistance, there was no significant variation in neudesin concentration. In a study by Yasar et al. in 2021, the neudesin level were shown to be lower in the PCOS group and to havepositively correlated with progesterone and insulin levels **(Yasar et al., 2021)**. The newest study by **Kruszewska et al. (2022)** confirms the lower neudesin level in PCOS patients that have insulin resistance.

Also, Neuregulin 4 (NRG4) is a member of the neuregulin protein family (NRG1-NRG4) and serves as an adipokine that is synthesized in many tissues, especially in brown adipose tissue (BAT), **(Gavaldà-Navarro et al., 2021)**. Similarly to other neuregulin members, NRG4 activates epidermal growth factor receptors (EGFR), also known as ErbB receptors, and binds specifically to ErbB3 and ErbB4 receptors initiating cell-to-cell signaling via tyrosine phosphorylation **(Gumà et al., 2020)**, NRG4 has been shown to have an effect in the development of obesity and metabolic disorders including type 2 diabetes mellitusand non-alcoholic fatty liver disease in animals and humans **(Wang et al., 2019).** An inverse correlation was found between the levels of NRG4 andthe risk of metabolic syndrome with insulin resistance **(Heim et al., 2020)**.

In a study done by **Eken et al. (2019)**, the research comparing NRG4 levels in obese and non-obese PCOS patients, compared to obese and non-obese healthy controls, the highest serum NRG4 levels were noted in obese PCOS patients, the second highest in non-obese PCOS, and the lowest in the obese and non-obese control groups. In Eken et al. indicated that circulating NRG4 was significantly associated with insulin resistance, markers of obesity, and hormonal levels. The study by **KRUSZEWSKA et al. (2022)** confirms the elevation of NRG4 levels in PCOS patients that have insulin resistance. While, **Ayoob (2022)** confirmed that the elevation of NRG4 levels in PCOS patients who have higher BMI**.** Recent years have seen a rise in interest in the study of neuregulin_4 and neudesin, two proteins with potential roles in metabolic regulation and insulin resistance marker potential in medical conditions like diabetes mellitus, obesity, and

polycystic ovary syndrome (PCOS), despite the fact that their relationship to PCOS is poorly represented in the literature **(Zhang et al., 2021)**.

Knowledge gap

Many studies have implicated the importance of adipokines in PCOS; **Yasar (2021)** requested a further studythat should be carried out to elucidate the neuroendocrine functions of neudesin and novel mechanisms regulating the progesterone effect in patients with PCOS. Also, **Kruszewska et al. (2022)** requested more research to determine the functions of these markers, how they function in the etiology of PCOS, and whether or not quantifying their levels would be useful in clinical settings. While, **Eken et al. (2019)** indicated that research on PCOS is warranted to reduce obesity. **Bozkaya et al. (2020)** indicated in their study that decreased neudesin levels were related to hormonal abnormalities in PCOS. Neudesin levels were inversely associated with having PCOS risk. Neudesin may involve in the development of various pathophysiological pathways of PCOS and required further research based on the phenotypes. **Hossain (2021)** confirmed that screening of metabolic abnormalities should be done in all PCOS women specially hyperandrogenic phenotypes which have long-term impacts on health. Furthermore, a study by **Sachdeva (2019)** who identified that various phenotypes will have diagnostic implications and assist in providing appropriate treatment and prognosticating patients with PCOS-related infertility.

Therefore, this review may serve as a basis for future studies investigating Neudesin and Neuregulin-4 levels in different PCOS phenotypes can thereby contribute to the clarification of problems related to the pathophysiology of PCOS.

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List of abbreviations

AE: Androgen Excess
AES: Androgen Excess Society
BMI: Body mass index
ErbB3: Epidermal growth factor receptor 3
ErbB4: Epidermal growth factor receptor4
HA: Hyperandrogenism
IR: Insulin resistance
NHMRC: National Health and Medical Research Council
NRG4: Neuregulin 4
OD: Ovulatory dysfunction
PCOM: Polycystic ovarian morphology
PCOS: Polycystic ovary syndrome
VAT: Visceral adipose tissue

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