GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GEORGIAN MEDICAL NEWS


GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.


جمالاً، هناك عدد من المجلات الجورجية والأمريكية المشاركة في هذا التجمع العلمي، تشمل SCOPUS، PubMed، وVINITI Russian Academy of Sciences. المحتوى الكامل متاح عبر دatabases EBSCO.
К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра в три сантиметра. Используемый компьютерный шрифт для текста на русском и английском языках - Times New Roman (Кириллица), для текста на грузинском языке следует использовать AcadNusx. Размер шрифта - 12. К рукописи, напечатанный на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста в tiff формате.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.


9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.
REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

   Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author’s name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **.tiff format**.

   Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html

   In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title “References”. All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author’s original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.**
1. სტატიის შექმნაში შეიძლება დაქორწინებით შეყვანა შექმნილი ტექსტი:

1.1. დეტალური შეხვდა სტატიის შექმნის პირველი ფაზის შესახებ.

1.2. სტატიის შექმნაში შეიძლება 10 გვერდის ნახევრად და 20 გვერდიან მექანიკური საშუალო ფაზი.

1.3. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

2. სტატიის შექმნაში შეიძლება დაქორწინებით შეყვანა შექმნილი ტექსტი AcadmNusx-ში.

3. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

4. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

5. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

6. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

7. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

8. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

9. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

10. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

11. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

12. სტატიის შექმნაში შეიძლება ცვლილების და შემცირების მექანიკური საშუალო ფაზი.

აღნიშნული ტექსტის დაქორწინებით შეყვანა შექმნილი ტექსტი.
APPLICATIONS OF VISCOELASTIC TESTING IN MICROSURGERY: A SYSTEMIC REVIEW AND META-ANALYSIS

LONG-TERM USE OF GLUCOCORTICOID MODULATED PARATHYROID HORMONE LEVELS IN OSTEOPOROSIS

PERSISTENT USE OF GLUCOCORTICOID MODULATED PARATHYROID HORMONE LEVELS IN OSTEOPOROSIS

ISTENT INJECT W AND KAHOOK DUAL BLADE FOR TREATING MILD-TO-MODERATE GLAUCOMA

PREVALENCE OF CHLAMYDIA AMONG WOMEN IN PLACES OF DEPRIVATION OF LIBERTY

EFFECT OF HEAT TREATMENT DURATION AND COOLING CONDITIONS ON TENSILE PROPERTIES AND HARDNESS OF SELECTIVE-LASER-MELTED COBALT-CHROMIUM ALLOY

CONGRESS REPORT OF THE 5TH NATIONAL CONGRESS OF THE BULGARIAN SOCIETY FOR DERMATOLOGIC SURGERY,

SIGNIFICANCE OF TWO-DIMENSIONAL SHEAR WAVE ELASTOGRAPHY IN PREDICTING ESOPHAGEAL VARICOSE VEINS DURING CHRONIC LIVER DISEASE

STUDY OF THE HEMOMICROCIRCULATORY CHANNEL IN PATIENTS WITH DIABETES AND THREATENING ISCHEMIA OF THE LOWER LIMB

STUDY OF LIVER AND KIDNEY FUNCTION WITHIN COVID-19 PATIENTS

THE STUDY OF VDR FOKL RS2228570 SNP IN AUTOIMMUNE THYROIDITIS

JUSTIFICATION OF THE COMPREHENSIVE PROGRAM OF PREVENTION OF HYPERTENSION DISEASE IN MEDICAL WORKERS
Rurua Magda, Ratiani L, Sanikidze T, Machvariani K, Pachkoria E, Ormocadze G, Mikadze I, Didbaridze T.
IMPACT OF THE ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ON THE COURSE OF THE SEPTIC SHOCK DEVELOPED DURING COVID-19 AND OTHER SEVERE RESPIRATORY INFECTIONS IN PRESENCE OF HYPERFERRITINEMIA.................................................................110-117

Dubivska SS, Omelchenko-Seliukova AV, Lazierykyi VO, Viedienieva RY.
STUDY OF THE PROCESSES OF LIPID PEROXIDATION, THE STATE OF THE ANTIOXIDANT SYSTEM IN PATIENTS WITH POLYTRAUMA AND ALCOHOL ANAMNESES........................................................................................................118-124

INFLUENCE OF LONG-TERM VIBRATION ON THE ACTIVITY OF THE SUPERIOR VESTIBULAR NUCLEUS NEURONS UNDER THE CONDITIONS OF STIMULATION OF THE HYPOTHALAMUS NUCLEI..................................................125-131

Ahmad Mohammed SMADI, Salam Bani Hani, Abedalmajeed SHAJRAWI, Marwa Alhalabi.
COMPLIANCE AND CHALLENGES OF TRANSMISSION BASED PRECAUTION PRACTICES AMONG NURSES IN JORDANIAN HOSPITALS DURING THE NOVEL COVID-19: A DESCRIPTIVE STUDY.................................................................132-137

Georgi Tchernev.
THE NITROSAMINE CONTAMINATION IN BETA BLOCKERS (BISOPROLOL/ METOPROLOL), ACE INHIBITORS (LISINOPRIL/ PERINDOPRIL), THIAZIDES DIURETICS (HCT), CALCIUM CHANNEL BLOCKERS (AMLODIPINE/ FELODIPINE), SARTANS (CANDESARTAN) AND THE SUBSEQUENT SKIN CANCER DEVELOPMENT AND PROGRESSION: APOCALYPSE NOW.....138-145

MOLECULAR EFFECTS OF RESVERATROL IN THE TREATMENT OF AUTOIMMUNE DISEASES.........................................................146-147
METFORMIN EFFECTS ON NEUREGULIN-1 IN POLYCYSTIC OVARIAN WOMEN

Maryam Taher Tawfeq¹, Entedhar Rifaat Sarhat².

¹College of Medicine, Tikrit University, Tikrit, Iraq.
²College of Dentistry, Tikrit University, Tikrit, Iraq.

Abstract.

**Background and Objectives:** The study aims to assess the levels of Neuregulin 1 (NRG1) in patients with Polycystic Ovary Syndrome (PCOS) and to determine the impact of metformin treatment on their serum NRG1 levels. PCOS is a common endocrine disorder in women of reproductive age, while NRG1 is linked to regulating inflammation and ovulation.

**Methods:** The study was conducted on sixty women with PCOS and thirty healthy women as the control group. Thirty patients completed the follow-up study and continued on metformin treatment for three months. The study was a cross-sectional study done in Salah Al-Deen general hospital/gynaecology and obstetrics department in Tikrit City from November 2022 to January 2023. The participants were diagnosed with PCOS based on the Rotterdam criteria, and their BMI and insulin resistance were measured before and after therapy. Fasting serum NRG1 was also measured.

**Results:** The study found that women with PCOS had increased levels of fasting blood glucose, insulin, and insulin resistance, as well as increased levels of NRG1. However, treatment with metformin for three months resulted in a significant decrease in body mass index, blood glucose, insulin, and insulin resistance.

**Conclusion:** NRG1 level decreased significantly after 3 months of treatment with 850 mg per day with metformin in women with PCOS.

**Key words.** Metformin, PCOS, blood glucose, insulin, HOMA-IR, Neuregulin-1.

**Introduction.**

Polycystic Ovary Syndrome (PCOS) is a common female gynaecological endocrinopathy disorder that affects women between the ages of 18 to 45 years. It is estimated that the prevalence of this condition ranges from 5% to 15%, depending on the diagnostic criteria applied. The root cause of PCOS is not yet fully understood, but it is believed that hormonal imbalances play a significant role. PCOS is characterized by either hyperandrogenism or abnormal gonadotropin secretion and is sometimes associated with insulin resistance. Hyperandrogenism refers to the presence of excessive levels of male hormones such as testosterone in the female body. This can cause symptoms such as acne, hair loss, and hirsutism (excessive hair growth in unwanted areas). Abnormal gonadotropin secretion refers to the disruption of the normal hormonal cycle that regulates the menstrual cycle [1-3].

Neuregulin 1 (NRG1) type I, also known as neuregulin, Neu differentiation factor (NDF), or acetylcholine receptor inducing activity (ARIA), is a protein that plays an important role in the development and maintenance of the nervous system. NRG1 was first identified as a 44-kD glycoprotein, and since then, research has revealed that it is a paracrine, autocrine, and juxtacrine signalling peptide that belongs to a family of proteins structurally related to epidermal growth factor (EGF). NRG1 is involved in a variety of cellular processes, including cell proliferation, differentiation, migration, and survival. It plays a critical role in the development and maintenance of the nervous system, including the formation and maintenance of myelin, which is essential for the proper functioning of nerve cells. Studies have also shown that NRG1 is involved in the development of several neuropsychiatric disorders, including schizophrenia and bipolar disorder. It has been suggested that NRG1 may be a key factor in the pathophysiology of these disorders [4-8].

NRG1 is a protein that is known to be involved in various cellular processes such as the growth and differentiation of cells, as well as the development of the nervous system. Recent studies have suggested that NRG1 may also play a role in the regulation of inflammation and immune system response. This is particularly relevant in the context of Polycystic Ovary Syndrome (PCOS), a common endocrine disorder that affects women of reproductive age. Both glucose intolerance and hyperinsulinemia have been reported to be the main metabolic features of PCOS, and it is believed that the interaction between NRG1 and its receptors (ErbBs) may be impaired in insulin-resistant diseases. Interestingly, insulin and NRG1 have been found to have competitive, non-synergistic effects on the liver. It has been shown that insulin can decrease NRG1 expression and impair its binding to receptors through a PI3K-dependent pathway. Additionally, hyperinsulinemia has been found to down-regulate ErbB3 receptors, which are specific targets of NRG1. These findings suggest that Erb receptors may be a possible key factor in insulin hemostasis in PCOS [9-14].

**Materials and methods.**

Study Design: The study investigated the effects of metformin treatment on biochemical markers in patients with PCOS. 90 subjects were recruited, including 60 patients with PCOS and 30 controls. Only 30 patients completed the three-month follow-up study on metformin treatment, with some unable to complete it due to pregnancy, side effects, or lack of communication. The diagnosis of PCOS was made based on the Rotterdam criteria, which requires the presence of anovulation and clinical and/or biochemical hyperandrogenism in patients, following a visit to the gynecologist for diagnosis of symptoms related to ovarian disease. This includes measuring weight and height, as well as gathering information such as age, duration of infertility, and number of children.
Patients with newly diagnosed PCOS were treated with metformin pills orally for three months. The diagnosis of PCOS was based on the presence of hyperandrogenism and either oligo/anovulation or polycystic ovaries as determined by a specialist gynaecologist using ultrasound and hormonal tests.

The study protocol was approved by the Scientific Committee at Tikrit University- College of Medicine. The agreement to collect samples from patients at Salah al-Din General was approved by the Directorate of Salah al-Din Health. Patients were informed about the study's purpose, filled out a questionnaire, and signed a consent form to participate.

Blood samples were taken from each subject via vein puncture and transferred to a sterilized plain tube. The tube was left to clot for 10-15 minutes at room temperature and then centrifuged at 3000 rpm for 10 minutes to obtain serum samples. The serum samples were then placed into 3 clear dry Eppendorf tubes, labelled, and stored at -20°C until analysis. Body Mass Index (BMI) is a diagnostic method for measuring obesity in a population. The study involves measuring the weight and height of each patient and calculating their BMI using a specific formula.

BMI = the weight (kilogram or kg) / the height (square meter or m²).

Chemicals and reagents: specific chemicals and reagents used in a study, including insulin and NRG1 ELISA kit from Cusabio Biotech Co., an insulin ELISA kit and C-peptide ELISA kit from Demeditec Diagnostics GmbH, and a spectrophotometric kit for measuring blood glucose.

The method of measuring insulin resistance using IR indices such as HOMA-IR. Subjects with HOMA-IR ≥ 2.5 and QUICKI ≤ 0.333 were identified as the insulin-resistant group. The calculation of HOMA-IR was based on the provided formula [14].

HOMA-IR = (Fasting insulin (μIU/ml) × Fasting glucose (mg/dl))/405.

Results.

In the present study, the patient's profile of PCOS was analyzed, and the results were presented in Table 1. The study included 30 patients, out of which 27 (90%) were married, and 3 (10%) were unmarried. It was found that 60% of the patients were from rural areas, while 40% were from urban areas. Furthermore, the study revealed that 33 patients (41.25%) had a baby, while 47 patients (58.75%) did not have any children. Additionally, the study examined the presence of hirsutism, which is a common symptom of PCOS characterized by excessive hair growth on the face, chest, and back. The results showed that 16 patients (53.33%) had hirsutism, while 14 patients (55%) did not have any excessive hair growth.

One of the main symptoms of PCOS is insulin resistance, which can lead to an increase in the levels of fasting blood glucose. In the present study, women with PCOS and healthy women showed a significant difference in the serum levels of fasting blood glucose. The PCOS group had a higher level of fasting blood glucose (100.8±20.7 mg/dl) compared to the healthy group (90.2±18 mg/dl). However, the study also found that after three months of metformin treatment, the PCOS group showed a significant reduction in serum blood glucose levels (93±17.9 mg/dl) compared to pre-treatment levels (98.8±20.6 mg/dl) (Table 2, Figure 1A).

### Table 1. PCOS Patient's demographic profile.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCOS Cases</th>
<th>Metformin Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>30.57±6.3</td>
<td>30.4±4.7</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>No %</td>
<td>No %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 90</td>
<td>3 11.11</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>3 10</td>
<td>1 33.33</td>
</tr>
<tr>
<td>Residence</td>
<td>Rural</td>
<td>18 60</td>
<td>3 16.66</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>12 40</td>
<td>3 25</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Absent</td>
<td>14 46.66</td>
<td>0 0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>16 53.33</td>
<td>1 3.33</td>
</tr>
</tbody>
</table>

### Table 2. Demographic characteristics and biochemical results of the two groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PCOS Mean±SD</th>
<th>Control Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>30.4±5</td>
<td>29.6±5.5 NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.4±1.9</td>
<td>28.5±0.4 *</td>
</tr>
<tr>
<td>Insulin (mIU/mL)</td>
<td>14.6±3.4</td>
<td>11.1±2.4 *</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.6±1.2</td>
<td>2.5±0.54 *</td>
</tr>
<tr>
<td>NGR1 (ng/mL)</td>
<td>6.6±2.7</td>
<td>4.7±1.9</td>
</tr>
<tr>
<td>FSG (mg/dl)</td>
<td>100.8±20</td>
<td>90.2±18</td>
</tr>
</tbody>
</table>

* P<0.05, NS: non-significance

Figure 1. Metformin modulated measured parameters compared. Data expressed as mean±SD, *p<0.05. *significant differences in non-metformin-users PCOS patients compared to metformin-users PCOS patients. PCOS=polycystic ovarian syndrome, FSG=Fasting serum glucose, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance, NGR1= Neuregulin-1.

The present study aimed to compare serum insulin levels and HOMA-IR (Homeostatic Model Assessment-Insulin Resistance)
in PCOS patients and healthy controls, as well as to investigate the effect of metformin treatment on insulin resistance. The results of the study show that PCOS patients have significantly higher serum insulin levels compared to healthy controls. The mean serum insulin level in PCOS groups was 14.66±3.3798, while it was 11.14±2.3132 in healthy control groups. This finding supports the notion of insulin resistance as a hallmark feature of PCOS. However, after three months of metformin treatment, serum insulin levels significantly decreased in PCOS groups. The mean serum insulin level in PCOS groups after treatment was 13.200±3.0778, which was significantly lower than the pre-treatment level of 16.123±3.0571 (p < 0.05). This suggests that metformin treatment can effectively reduce insulin resistance in PCOS patients (Table 2, Figure 1B). The study also compared HOMA-IR between PCOS patients and healthy controls. HOMA-IR is a widely used index for assessing insulin resistance. The results of the study show that the mean HOMA-IR was significantly higher in the PCOS group (3.5710±1.15889) compared to the control group (2.5283±0.53879). This finding further supports the notion of insulin resistance as a hallmark feature of PCOS. However, after three months of metformin treatment, the values of HOMA-IR were significantly reduced in PCOS groups. The mean HOMA-IR after treatment was 3.1710±0.87079, which was significantly lower than the pre-treatment value of 3.9727±1.28194 (p<0.05). This suggests that metformin treatment can be effective in reducing insulin resistance in PCOS patients, as evidenced by the significant reduction in HOMA-IR values (Table 2, Figure 1C).

The results presented in Table 1 indicate a significant difference in the levels of serum NGR1 (ng/mL) between women with PCOS and controls. Specifically, the mean serum NGR1 level for women with PCOS was 6.5780±2.71658, whereas the mean serum NGR1 level for controls was 4.6963±1.88404. This difference was statistically significant, as indicated by the P value of less than 0.05. Furthermore, after therapy, there were no statistically significant decreases in serum NGR1 observed for the PCOS group, as the mean serum NGR1 level for this group was 6.1800±2.16634, which was not significantly different from the pre-treatment level of 6.9760±3.16123 (P=0.000) (Table 2, Figure 1D).

The question in study aimed to compare the body mass index (BMI) of women with polycystic ovary syndrome (PCOS) to that of a healthy control group. The results of the study showed that the highest mean BMI was recorded in PCOS women (33.36±1.89 Kg/m2) in comparison to those of the healthy group (28.46±0.39 Kg/m2) (Table 3).

**Table 3. Level of BMI in women before and After Treatment.**

<table>
<thead>
<tr>
<th>PCOS women</th>
<th>BMI (Kg/m²)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>33.36</td>
<td>1.89</td>
</tr>
<tr>
<td>After treatment</td>
<td>31</td>
<td>2.42</td>
</tr>
</tbody>
</table>

Discussion.

Hirsutism is the excessive growth of unwanted hair in areas typically associated with male sexual characteristics, such as the chest, chin, lower abdomen, buttocks, and thighs. This is caused by the effects of androgen on the grease unit and is often accompanied by oily skin and acne, which is due to increased androgen production from the ovaries [15].

The overproduction of androgen in females with PCOS leads to skin changes including acne, hirsutism, and androgenic alopecia. High concentrations of testosterone contribute to symptoms such as hirsutism, acne, and infertility [16]. The study found that metformin therapy resulted in a significant reduction in hirsutism among women with PCOS, which is consistent with previous research [17,18].

The study shows that metformin treatment in PCOS patients resulted in a significant decrease in mean BMI. Obesity is only associated with PCOS and is not a diagnostic criterion. Other causes of menstrual disorders and hyperandrogenism should be investigated [19].

The correlation between Polycystic Ovary Syndrome (PCOS) and higher Body Mass Index (BMI) in women. Several studies have been conducted on this subject, including Findakly et al. in 2021 [20], and Garzia et al in 2022 [21]. Both studies found that women with PCOS had significantly higher BMIs than those without the condition. Similarly, Kumar et al in 2022 [22] reported similar results, further cementing the connection between PCOS and higher BMI. Another study conducted by Kogure in 2019 [23] found that being overweight or even obese is a common feature of PCOS and that these patients were often present with perceptual distortions of self-image. This research is important because it sheds light on the potential health risks associated with PCOS and highlights the need for preventative measures and early intervention. By understanding the link between PCOS and higher BMI, healthcare professionals can better tailor treatment plans to help patients manage their weight and reduce the risk of associated health complications.

The Koiou et al. study [24] aimed to assess the effect of metformin on weight loss, as well as other metabolic parameters such as testosterone and glucose, in PCOS patients of varying weights. The study found that while metformin alone was effective in reducing BMI, testosterone, and glucose levels in normal-weight PCOS patients after six months of treatment, it was not as effective in overweight and obese patients. These patients required additional interventions such as the use of orlistate® or sibutramine, as well as a low-calorie diet, to achieve weight loss. These findings suggest that metformin alone may not be enough to achieve weight loss in overweight and obese PCOS patients. Instead, a combination of interventions may be necessary to achieve significant weight loss and improve metabolic parameters. However, it is important to note that the study only assessed the effects of these interventions over six months. Further studies are needed to determine the long-term efficacy and safety of these interventions, as well as to identify the most effective combination of treatments for PCOS patients of varying weights. Overall, the Koiou et al. study provides valuable insights into the complex nature of PCOS, and the challenges associated with managing the condition, particularly in patients who are overweight or obese.

The study conducted by Sharma et al in 2019 [25] presented results that showed metformin treatment for PCOS during
findings suggest that metformin may be an effective treatment not necessary for metformin-induced glucose lowering. These glucagon-like peptide-1 (GLP-1) release in the gastrointestinal blood glucose by altering the gut microbiome and stimulating blood glucose levels. Furthermore, metformin may also lower (ACC), AMPK improves insulin sensitivity, which helps lower phosphorylating and inhibiting acetyl-CoA carboxylase and activating AMP-activated protein kinase (AMPK). By inhibition of metformin in the liver is crucial for suppressing hepatic explanation for this discrepancy is that the accumulation of the hypothalamus, may be responsible for the weight loss observed in the study. Metformin, the medication administered to the participants, is known to reduce appetite and caloric intake in the gastrointestinal tract. Additionally, it alters the adenosine monophosphate-activated kinase in the hypothalamus, which mediates anorectic effects. As a result, metformin reduces body weight, leading to a reduction in body mass. These findings are significant because they shed light on the potential efficacy of metformin as a treatment option for women with PCOS who struggle with weight management. Further research is needed to explore the long-term effects of this medication and its potential benefits for this population.

The current study focused on the impact of treatment on women with PCOS and found that there were significant reductions in body weight and BMI after three months. This study is consistent with the findings of Patel and Shah in 2014, indicating that the results are reliable and valid. The researchers suggest that the decrease in orexigenic peptides, including neuropeptide Y and agouti-related proteins in the hypothalamus, may be responsible for the weight loss observed in the study. Metformin, the medication administered to the participants, is known to reduce appetite and caloric intake in the gastrointestinal tract. Additionally, it alters the adenosine monophosphate-activated kinase in the hypothalamus, which mediates anorectic effects. As a result, metformin reduces body weight, leading to a reduction in body mass. These findings are significant because they shed light on the potential efficacy of metformin as a treatment option for women with PCOS who struggle with weight management. Further research is needed to explore the long-term effects of this medication and its potential benefits for this population.

The statement "These data are similar to those reported by Miller (2013) [29], Diamanti-Kandarakis (2010) [30], and Tokubuchi et al. (2017) [31], implies that the findings presented in the current study are consistent with those reported in previous studies. However, the statement goes on to mention that there are conflicting data on the glucose-lowering effect, particularly in women with polycystic ovary syndrome (PCOS). One possible explanation for this discrepancy is that the accumulation of metformin in the liver is crucial for suppressing hepatic glucose production. This process involves inhibiting fructose-1,6-bisphosphatase and mitochondrial glyceraldehyde 3-phosphate and activating AMP-activated protein kinase (AMPK). By phosphorylating and inhibiting acetyl-CoA carboxylase (ACC), AMPK improves insulin sensitivity, which helps lower blood glucose levels. Furthermore, metformin may also lower blood glucose by altering the gut microbiome and stimulating glucagon-like peptide-1 (GLP-1) release in the gastrointestinal tract. However, the statement notes that increases in GLP-1 are not necessary for metformin-induced glucose lowering. These findings suggest that metformin may be an effective treatment option for PCOS-related glucose intolerance, but more research is needed to fully understand the mechanisms behind its glucose-lowering effects [32].

The topic at hand is a comparison of two studies on the effects of metformin administration on insulin resistance and fasting glucose levels in patients with polycystic ovary syndrome (PCOS). The first study, conducted by Behradmanesh et al., [33] did not confirm any decrease in fasting glucose, fasting insulin, or HOMA-IR after six months of metformin administration for 45 PCOS patients in Iran's Shiraz city. Insulin resistance is a condition in which the body's ability to respond to insulin stimulation is impaired, leading to hyperinsulinemia and a range of metabolic impacts, including hyperglycemia, elevated blood pressure, dyslipidemia, visceral adiposity, chronic inflammatory responses, endothelial layer function impairment, and dysregulation of the hemostasis balance. The second study, which is not explicitly mentioned but is presumably being contrasted with the first, may have found different results regarding the effects of metformin on PCOS patients. While the first study suggests that metformin may not be effective in reducing insulin resistance and fasting glucose levels in PCOS patients, further research is needed to confirm the findings and explore alternative treatments for this condition [34,35].

The HOMA-IR test is a fast and cost-effective way to estimate insulin resistance, with results comparable to the gold standard approach. PCOS can be classified into metabolic and reproductive groups based on HOMA-IR values, with metabolic PCOS patients being more obese. The top two mechanisms of insulin resistance increasing PCOS-free testosterone levels are triggered insulin receptors in the pituitary gland releasing luteinizing hormone and the inhibition of sex hormone-binding globulin synthesis in the liver. Metformin is effective in increasing insulin sensitivity and reducing glucose absorption, but the mechanisms of insulin resistance in PCOS and metformin's actions are still largely unknown [36-41].

One study by Sharma in 2019 [25] showed a decrease in insulin levels from 23.6-20.2 μU/mol. Similarly, another study by Agarwal et al in 2003 [42] also showed a significant reduction in insulin levels from 20.45 to 12.59 μU/mol. Additionally, Liu et al in 2019 [43] found that metformin treatment can decrease hyperinsulinemia and hyperandrogenemia by improving glycolipid metabolism even in normal insulin resistance PCOS patients. The study conducted by Santana et al in 2004 [44] also supports the fact that metformin helps in improving insulin resistance and hyperandrogenemia by acting on IGF-1 and carrier protein. These studies suggest that metformin is an effective treatment for reducing insulin levels in the human body and can help in managing various conditions such as PCOS and hyperandrogenemia. The reduction in insulin levels is crucial for maintaining the balance of glucose in the body and preventing the onset of diabetes and other related conditions. Further research is required to explore the potential of metformin in the treatment of such conditions [45].

Recent studies have suggested that the effect of metformin on HOMA-IR in PCOS patients is mainly attributed to gut microbiome modulation, as metformin is concentrated in the intestine. A study by Manal Ibrahim in 2021 [46], showed that
metformin can significantly decrease HOMA-IR only in insulin-resistant PCOS patients. Similarly, Nawrocka and Starczewski [47] reported that metformin can significantly decrease HOMA-IR only in insulin-resistant PCOS patients. Goldenberg et al. [48] divided their PCOS population into quintiles according to HOMA-IR and compared the bottom and top quintiles after one year of intervention with metformin and diet. They demonstrated an improvement in menstrual cyclicity in the bottom quintile that did not differ from that of the top quintile. The finding of elevated PCOS in women with BC in this study is consistent with several other studies, like Jie et al. 2012 [49], who reported that the NRG1 levels of PCOS subjects with high HOMA-IR or fasting insulin levels were found to be similar to the NRG1 levels of the normoinsulinemic PCOS subjects. Because the NRG1/ErbBs interaction is impaired in diseases with insulin resistance, the low levels of NRG1 that we detect in PCOS patients may be in response to hyperinsulinemia. Overall, these studies suggest that metformin can be an effective treatment option for improving HOMA-IR in insulin-resistant PCOS patients, and that gut microbiome modulation may play a significant role in this effect.

NRG1 is a growth factor that activates intracellular signalling proteins and inhibits apoptosis by binding to tyrosine kinase receptors ErbB3 and ErbB4 via the PI3K-Akt and MAPK/ERK pathways. It is believed to be a new marker for evaluating oocyte quality, and studies have shown that it regulates rupture timing in periovulatory follicles. NRG1 expression was found in LH-stimulated granulosa cells and prevents premature progression of metaphase II stage oocyte, leading to abnormal fertilization. Supplementation of the culture medium with NRG1 improves oocyte quality and developmental competence [49-53]. Surrounding cytokine milieu optimizes the effects of metformin and shapes the fate of outcome response based on localized milieu and plethora of cytokine release in the vicinity [55-57].

The study found that decreased NRG1 levels can negatively affect follicle development and reduce ovulation quality and fertility rates in PCOS. Normalization of ovulatory function increases pregnancy rates in PCOS patients with improved insulin resistance. Low NRG1 levels may explain the increased number of unruptured follicle rates and negatively affect follicle developmental potential and fertilization rates [58,59].

Conclusion.
The study suggests that NRG1 levels are significantly decreased after 3 months of treatment with 850 mg per day of metformin in women with PCOS. This finding may have important implications for the treatment of PCOS, as it suggests that metformin may have a beneficial effect on the nervous system in women with PCOS. Further research is needed to confirm these findings and to investigate the mechanisms by which metformin affects NRG1 levels in women with PCOS.

REFERENCES
17. Abd Elaak NL, Ellakwa HE, El Halaby AE, et al. Effects of metformin alone and in combination with spironolactone on


