GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 4 (337) Апрель 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

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.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

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**. 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, напечатанной 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.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

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 compu-ter-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
http://www.icmje.org/urm_full.pdf
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.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 4 (337) 2023

Содержание:

GEORGIAN MEDICAL NEWS
No 4 (337) 2023

METFORMIN EFFECTS ON BLOOD LEVELS OF GREMLIN-1 IN POLYCYSTIC OVARIAN WOMEN

Shaymaa Mohammed Allow[1], Entedhar R. Sarhat[2]*.

[1]*College of Medicine, Tikrit University, Tikrit, Iraq.*

[2]*College of Dentistry, Tikrit University, Tikrit, Iraq.*

Abstract.

Background: Polycystic ovary syndrome (PCOS), a hormonal disorder affecting millions of women worldwide, characterized by symptoms such as irregular menstrual cycles, weight gain, acne, and excess hair growth. PCOS is linked to higher levels of gremlin-1, a protein involved in ovarian follicle development, which may cause insulin resistance and metabolic abnormalities.

The objective is to evaluate the effects of metformin treatment on gremlin-1 levels in patients with PCOS.

Patients and methods: Sixty patients diagnosed with PCOs based on the Rotterdam criteria were selected as the PCOS group, while 30 healthy women matched for age were selected as the control group. The patients took metformin 850 mg twice daily and provided fasting blood samples before and after treatment. Data was collected through a questionnaire, direct interviewing, ultrasound examination, and laboratory examination, and analyzed using SPSS for Windows 7.

Results: The study found that PCOS patients had increased levels of gremlin compared to the control group. Additionally, PCOS patients had increased levels of blood glucose, insulin, and HOMA-IR. After taking metformin, patients showed a significant decrease in gremlin concentration. Treatment with metformin also resulted in a decrease in body mass index, blood glucose, insulin, and HOMA-IR.

Conclusion: Metformin decrease gremlin and insulin resistance in patients with polycystic ovary syndrome.

Key words. Metformin, polycystic ovarian syndrome, blood glucose, insulin, HOMA-IR, Gremlin-1.

Introduction.

Polycystic ovary syndrome (PCOS) is a complex endocrine-gynecology disorder that affects many women of reproductive age worldwide. It is characterized by a range of signs and symptoms that include androgen excess, ovulatory dysfunction, and disruptions to the hypothalamic–pituitary–ovarian (HPO) axis function. These symptoms can manifest differently in different patients, depending on their age, phenotype, and lifestyle. The most common symptoms of PCOS are hyperandrogenism, oligo- or anovulation, and hirsutism. However, diagnosis can be challenging, as patients present with varying combinations of these symptoms, and other conditions can mimic PCOS. Proper diagnosis requires a thorough assessment of the patient's medical history, physical examination, and laboratory tests. Once diagnosed, treatment options can vary depending on the severity of the symptoms and the patient's goals. Lifestyle modifications, such as weight loss and exercise, can be effective in managing some symptoms. Medications, such as oral contraceptives and anti-androgens, can also be used to regulate menstrual cycles and reduce androgen levels. In some cases, fertility treatments may be necessary to achieve pregnancy. Management of PCOS requires a holistic approach that addresses the complex interplay of hormonal, metabolic, and psychological factors that contribute to the disorder [1-3].

Gremlin-1 is a crucial protein that plays a significant role in the regulation of the bone morphogenetic protein (BMP) signaling pathway. BMP is a family of proteins that are involved in various cellular processes, including embryonic development and tissue regeneration. Gremlin-1 acts as an antagonist to the BMP family members by binding to BMP2 and inhibiting its function. This regulatory mechanism is important for maintaining the balance between BMP signaling and cellular differentiation. The function and structure of Gremlin-1 makes it a crucial protein in the BMP signaling pathway. Its ability to inhibit BMP2 and regulate cellular differentiation is essential for various cellular processes, including embryonic development and tissue regeneration. The conserved sequence of Gremlin-1 throughout evolution indicates its significance in maintaining the balance between BMP signaling and cellular differentiation [4,5].

Gremlin expression is a significant marker of adipose tissue dysfunction and insulin resistance. Recent studies have shown that gremlin expression is high in both subcutaneous and visceral adipose tissues, with a greater extent in the latter. This increased expression of gremlin-1 has been linked to the antagonization of insulin signaling and the subsequent reduction of its glucose-mediated response. The transcription of gremlin mRNA has been shown to increase in individuals with type 2 diabetes, glucose intolerance, non-alcoholic steatohepatitis (NASH), and non-alcoholic fatty liver disease (NAFLD). The presence of gremlin in adipose tissue could also play a role in the development of metabolic disorders. Furthermore, gremlin expression in adipose tissue has been shown to be regulated by various factors, including cytokines, growth factors, and hormones. These findings suggest that gremlin could be a potential therapeutic target for the treatment of metabolic disorders associated with adipose tissue dysfunction and insulin resistance. In conclusion, the high expression of gremlin in adipose tissue, particularly in the visceral adipose tissue, may play a significant role in the development of metabolic disorders, and further research into the regulation of gremlin expression could lead to new avenues for the treatment of these conditions [6-9]. Aim of this Study to identify the impact of metformin therapy on serum level of gremlin-1 and myonectin levels in women with polycystic ovarian syndrome.

Materials and methods.

Study Design: The study design that was carried out in the Department of Obstetrics and Gynecology at Salahdeen General

Hospital in Tikrit City from November 1st, 2022, to January 30th, 2023, aimed to investigate the efficacy of metformin treatment in patients with Polycystic Ovary Syndrome (PCOS). The study enrolled 90 subjects, 60 of whom were patients with PCOS, and the remaining 30 were controls. Out of the 60 patients with PCOS, only 30 completed the follow-up study and agreed to continue the metformin treatment for three months. The duration of the follow-up was three months, and during this time, patients who were unable to complete the study were tracked. Eight of these patients became pregnant, nine could not tolerate the drug due to its side effects, while the other patients did not communicate. The diagnosis of PCOS was made based on the Rotterdam criteria, which included anovulation and clinical and/or biochemical hyperandrogenism. This study's design has several strengths and limitations. One of the strengths is that the researchers strictly followed the Rotterdam criteria to diagnose PCOS, which is considered the gold standard for PCOS diagnosis. Moreover, the study's duration was long enough to evaluate the efficacy of metformin treatment in patients with PCOS. However, the study's sample size was relatively small, which could limit the generalization of the study's findings to the broader population. Additionally, the fact that only 30 patients completed the follow-up study and agreed to continue the metformin treatment for three months is a limitation because it reduces the statistical power of the study. Furthermore, the study's exclusion criteria were not specified, which could affect the study's internal validity.

Treatment: All subjects received metformin (Glucophage, Merck), the dosage given was 850 mg twice daily, and the study also included standard clinical evaluations and laboratory analyses to assess the safety of the medication. These evaluations and analyses were conducted at the beginning of the study, or the baseline, and again after the three-month treatment period. The purpose of these safety measures was to ensure that the medication was not causing any adverse effects to the subjects. After the three-month treatment period, the evaluations and analyses were repeated to compare the results with those obtained at baseline. This allowed the researchers to determine if the medication was effective in treating type 2 diabetes and if it was safe for use over an extended period of time. The results of this study could provide valuable information for healthcare professionals in the treatment of type 2 diabetes, as well as for patients who may be considering metformin as a treatment option.

Blood Sampling: The collection of venous blood samples is a crucial procedure in medical diagnosis and treatment. In this study, the blood samples were collected from each patient after overnight fasting, ensuring that the samples were not affected by recent food intake. The collection was done using a disposable syringe, which is a safe and effective method for obtaining blood samples. The samples were collected at a specific time interval, between 8:30 to 11 am, to ensure consistency and accuracy in the study. After collection, the samples were divided into two portions. The first 5 ml of fresh venous blood were preserved in an anticoagulant-containing tube to prevent clotting. The anticoagulant prevents the blood from clotting and ensures that the sample remains stable for analysis. The second portion of the blood samples were allowed to clot in a plain tube at room temperature. Clotting is a natural process that occurs when blood is exposed to air, and it is necessary for the separation of serum from blood. After the serum was separated from the blood by centrifugation at 3000 rpm for 10 minutes, the serum was kept frozen at -20 °C for later analysis. The freezing of serum at -20 °C is an essential step in the blood collection process as it helps to preserve the serum's integrity. Freezing the serum prevents any further biochemical reactions or degradation that may occur in the serum over time. This ensures that the serum remains stable and suitable for analysis even after an extended period. The serum can be analyzed later to determine various parameters such as glucose levels, lipid profiles, and electrolytes.

Measurement of Insulin Resistance: Insulin resistance is a condition where cells in the body do not respond properly to insulin, which is a hormone that regulates blood sugar levels. It is a common condition that is often associated with type 2 diabetes and other metabolic disorders. The measurement of insulin resistance is an important diagnostic tool that helps healthcare professionals determine the severity of the condition and develop an appropriate treatment plan. One of the most commonly used methods for measuring insulin resistance is the homeostatic model assessment (HOMA)-IR. This index is calculated by multiplying the fasting insulin level in micro international units per milliliter (μIU/ml) by the fasting glucose level in milligrams per deciliter (mg/dl) and then dividing the result by 405. PCOS subjects with HOMA-IR $\geq$ 2.5 and QUICKI $\leq$ 0.333 are identified as the IR group. The QUICKI index is calculated as 1/ [log (insulin) + log (glucose)] and is used to measure insulin sensitivity. By using these formulas, healthcare professionals can accurately identify individuals with insulin resistance and develop a personalized treatment plan that addresses their unique needs. It is important to note that insulin resistance is a complex condition that requires a multifaceted approach to treatment, including lifestyle changes, medication, and close monitoring of blood sugar levels [10].

Results.

The age of participants enrolled in the present study has shown a non-significant ($p>0.05$) differences between patients' group (30±1.6) and control group (29.7±3)

The study's results have shown that there were highly significant differences ($P=0.00003$) in the mean levels of glucose (mg/dl) between cases and control. The mean levels of glucose in cases were found to be 97.49± 20.42 mg/dl while in control, it was 92.137±8.61 mg/dl. This indicates that the cases had higher levels of glucose as compared to the control group. The results showed a significant reduction ($P<0.05$) in blood glucose levels after treatment. The mean blood glucose level before treatment was 97.49±20.42mg/dl, whereas after treatment, it reduced to 90.122±18.601mg/dl. This reduction is significant and suggests that the treatment was effective in improving the insulin resistance of PCOS women (Figure 1A).

The study conducted observed the levels of insulin in the three studied groups (control healthy group, non-metformin-users PCOS patients, and metformin-users PCOS patients). The study revealed that non-metformin-users PCOS patients had the highest mean of insulin levels with a value of 13.9±3.2 μIU/ml, which was significantly higher than control healthy

group, which had a mean value of 11.1±2.3 µIU/ml. The difference in insulin levels between these two groups was found to be statistically significant with a p-value of less than 0.05. However, when comparing the insulin levels between non-metformin-users PCOS patients and metformin-users PCOS patients, the study found that there was no significant difference (P>0.05) between these two groups. Both non-metformin-users PCOS patients, and metformin-users PCOS patients had similar insulin levels with values of 13.9±3.2 µIU/ml and 13.7±3 µIU/ml, respectively (Figure 1B).

Based on the data of the present study, it has been found that there is a significant difference in HOMA-IR levels between different groups, and this difference is higher in the studied patient groups as compared to the control group. The values of HOMA-IR were found to be 3.5±1.1 and 2.5±0.5 in the patient and control groups, respectively, with a P-value of less than 0.05. This indicates that there is a significant difference between the two groups, with the patient groups having higher HOMA-IR levels. However, after undergoing metformin therapy, there was a significant decrease in the values of HOMA-IR, with the values decreasing to 3.2±0.8 as compared to the values before therapy (3.5±1.1) at P< 0.05. This clearly indicates that metformin therapy has a positive effect on lowering HOMA-IR levels, which is beneficial for patients. The study provides important insights into the significance of HOMA-IR levels and the effectiveness of metformin therapy in managing it (Figure 1C).

The present study focused on the gremlin levels in women with Polycystic Ovary Syndrome (PCOS) and compared it with the control group. The findings revealed that the mean gremlin level was significantly higher in women with PCOS (2.0718 ± 0.0162 ng/mL) compared to the control group (1.3200 ± 0.2676 ng/mL). This difference was statistically significant at p ≤ 0.00006. These results suggest that gremlin may play a role in the development of PCOS in women. Furthermore, the study also investigated the impact of metformin treatment on gremlin levels. The researchers found that the overall group of patients experienced a significant decrease in gremlin levels after metformin treatment. Specifically, the gremlin levels in metformin-users PCOS patients decreased significantly when compared with non-metformin-users PCOS patients (8.000 ± 0.559 vs 6.100 ± 0.376 ng/mL: P ≤ 0.00009). This finding suggests that treatment may be effective in reducing gremlin levels in women with PCOS. Overall, this study sheds light on the potential role of gremlin in the development of PCOS in women. The findings suggest that gremlin levels may be a useful marker for diagnosing PCOS and monitoring the effectiveness of treatment. Further research is needed to fully understand the role of gremlin in PCOS and to explore potential treatment options that target this pathway (Figure 1D).

The results of the study revealed a positive correlation between gremlin and insulin in PCOS patients, with a correlation coefficient of 0.195 and a highly significant result of p<0.05. This suggests that as gremlin levels increase, so does insulin resistance (Figure 2A). Additionally, a positive correlation was found between gremlin and IR in PCOS patients, with a correlation coefficient of 0.358 and a significant result of p < 0.05. This indicates that as gremlin levels increase, so does the severity of IR in PCOS patients (Figure 2B). These findings highlight the potential of gremlin as a therapeutic target for the treatment of IR in PCOS patients, as reducing gremlin levels may help improve insulin sensitivity and prevent the development of metabolic disorders.

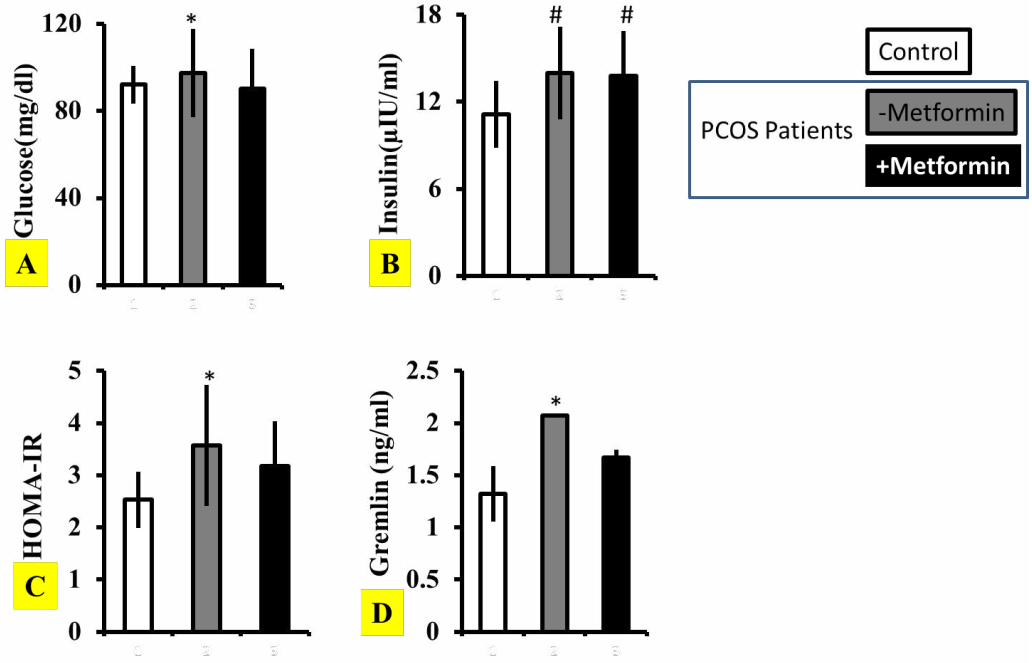

Figure 1. *Metformin modulated measured parameters compared to studied groups. Data expressed as mean±SD, *#p<0.05. *significant differences in non-metformine-users PCOS patients compared to control and non-metformine-users PCOS patients. #significant differences in non-metformine-users PCOS patients and non-metformine-users PCOS patients compared to control. PCOS=polycystic ovarian syndrome, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance.*

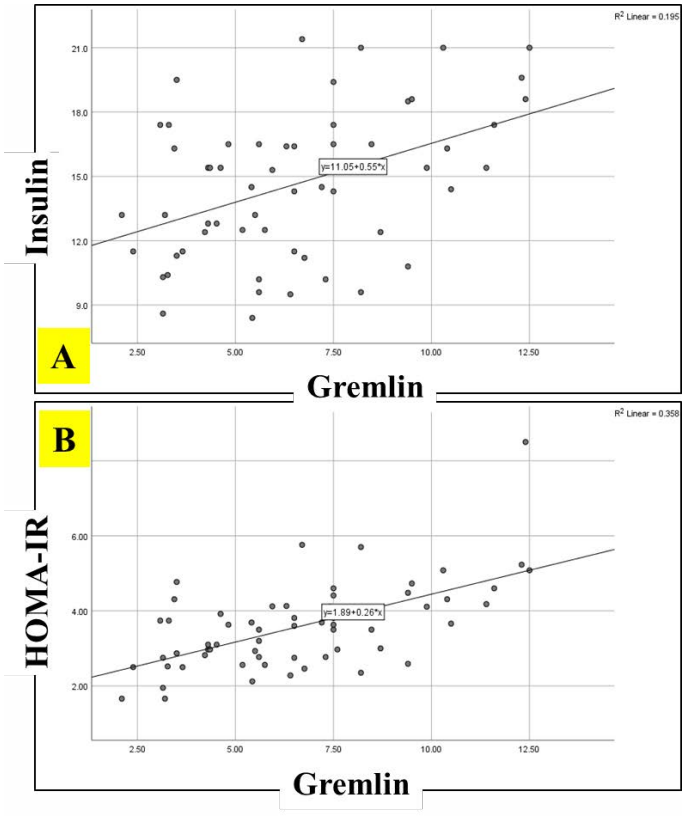

Figure 2. *Correlation between measured parameters, (A) Correlation of gremlin with inslin in PCOS patients. (B)Correlation of gremlin with inslin resistance in PCOS patients.*

Discussion.

The article explains that insulin resistance in PCOS is caused by impaired insulin action in various target tissues, resulting in a reduced insulin response to glucose overload. PCOS affects many organ systems and tissues, and insulin plays different roles in balancing the supply and demand of nutrients [11]. HOMAIR is a method to evaluate insulin resistance and β-cell function by analyzing basal glucose and insulin levels. A normal HOMA-IR value is one, indicating a balance between hepatic glucose output and insulin secretion [12,13]. Insulin resistance is identified when fasting insulin levels are above 10Mu/ml and HOMA-IR is greater than 2. PCOS can be classified into metabolic and reproductive groups based on HOMA-IR values, with a cut-off value of 2. Metabolic PCOS patients are typically more obese than reproductive PCOS patients [14-17].

The study confirmed that metformin treatment significantly decreases glucose levels by suppressing hepatic glucose production, increasing glucose uptake, fatty acid oxidation, and insulin sensitivity. Metformin also has direct effects on the ovary [18-20]. However, a study in Iran showed no significant changes in fasting glucose, fasting insulin, and HOMA-IR after 6 months of metformin administration for 45 PCOS patients [21].

Metformin response varies between studies due to genetic, environmental, lifestyle and physiological factors [22-24]. A study by Jayagopal et al. [25], showed no significant reduction in glucose, insulin, and HOMA-IR in PCOS patients with a specific diet and metformin dosage, but attributed the results to the diversity of HOMA-IR in PCOS and suggested increasing sample size.

The protein Gremlin 1 is secreted and increases in subcutaneous adipose tissue with expanded adipose cells, which is associated with insulin resistance and other obesity-related complications [26]. Gremlin 1 also antagonizes BMP2- and BMP4-induced suppression of androgen secretion but does not affect responses to BMP6 and BMP7 [27]. The functions of inhibitors of bone morphogenic proteins, including gremlin, noggin, chordin, and follistatin, are less well-established [28].

The study found that individuals affected by insulin resistance have significantly increased levels of serum gremlin. Gremlin 1 protein can directly antagonize insulin signaling, attenuating both insulin signaling and insulin-stimulated glucose transport. Anti-Gremlin 1 treatment is more effective in insulin-resistant cells, indicating a direct inhibitory effect on insulin sensitivity. The insulin-sensitizing effect of anti-Gremlin 1 is related to the degree of cellular insulin responsiveness [29-32].

Conclusion.

Metformin is a medication commonly used to treat PCOS. It works by reducing glucose production in the liver and improving insulin sensitivity in the body. Recent studies have shown that Metformin can also decrease gremlin, a protein that is known to contribute to insulin resistance in patients with PCOS. Gremlin is secreted by the ovaries and can inhibit insulin signaling in the body. By reducing gremlin levels, Metformin can improve insulin sensitivity and reduce the risk of developing diabetes and other metabolic disorders. In addition to its effect on gremlin, Metformin can also regulate menstrual cycles and improve fertility in women with PCOS. Although this medication is generally safe and effective, it may cause side effects such as nausea, diarrhea, and abdominal discomfort. Therefore, it is important to consult with a healthcare provider before starting this medication. In summary, Metformin is a valuable treatment option for women with PCOS, and its ability to decrease gremlin levels and improve insulin sensitivity makes it an effective tool in managing this condition.

REFERENCES

1. Sarhat ER, Abid IM, Kamel NA, et al. Changes of serum Interleukin and Chemerin levels in patients with Polycystic Ovary syndrome. J Adv Pharm Educ Res. 2021;11:11-14.
2. Sadeghi HM, Adeli I, Calina D, et al. Polycystic Ovary Syndrome: A Comprehensive Review of Pathogenesis, Management, and Drug Repurposing. Int J Mol Sci. 2022;23:583.
3. Zbaar SA, Sarhat ER, Khalaf SJ. Association of C-Reactive Protein with Risk of Complications of diabetic nephropathy. Egyptian Journal of Chemistry. 2022;65:3-4.
4. Sarhat ER, Wadi SA, Mahmood AR. Effect of ethanolic extraction of moringa oleifera on paraoxonase and arylesterase enzyme activity in high fat diet-induced obesity in rats. Research Journal of Pharmacy and Technology. 2018;11:4601-4604.
5. Sarhat ER, Rmaid ZJ, Jabir TH. Changes of salivary interleukine17, Apelin, Omentin and Vaspin levels in normal subjects and diabetic patients with chronic periodontitis. Ann Trop Med & Pub Health. 2020;23:S404.

6. Sulaiman EA, Dhiaa S, Merkhan MM. Overview of vitamin D role in polycystic ovarian syndrome. MMSL. 2022;91:37-43.
7. Aoshima Y, Enomoto Y, Muto S, et al. Gremlin-1 for the differential diagnosis of idiopathic pulmonary fibrosis versus other interstitial lung diseases: a clinical and pathophysiological analysis. Lung. 2021;199:289-298.
8. Ibrahim S, Sarhat E. Evaluation of serum levels of interleukin-6, fetuin-A, lipocalin-2, and c-reactive protein in rheumatoid arthritis patients. Georgian Medical News. 2022;1:42-45.
9. Hedjazifar S, Khatib Shahidi R, Hammarstedt A, et al. The novel adipokine Gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH. Diabetes. 2020;69:331-341.
10. Abolghasemi M, Mahjoub S, Esmaeilzadeh S. Serum dipeptidyl peptidase-4 activity and progranulin level in polycystic ovary syndrome patients. Caspian J Intern Med. 2022;13:70-75.
11. Mohammed SA, Allwsh TA. Asprosin and its relationship to insulin resistance in metabolic syndrome. MMSL.
12. Dhiaa S, Thanoon IA, Fadhil NN. Vitamin E versus propolis as an add-on therapy to sitagliptin/metformin on oxidant/antioxidant status and lipid profile in type 2 diabetic patients. Age (years). 2022;54:6-16.
13. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-419.
14. Wongwananuruk T, Rattanachaiyanont M, Leerasiri P, et al. The usefulness of homeostatic measurement assessment-insulin resistance (HOMA-IR) for detection of glucose intolerance in Thai women of reproductive age with polycystic ovary syndrome. International journal of endocrinology. 2012;2012.
15. Yahya AZ, Taqa GA, Alkataan MA. Evaluation of the effects of n-acetylcysteine on serum glucose, lipid profile, and body weight in rats with fructose-induced metabolic syndrome. MMSL.
16. Jasim AH, Al-Naddawi AM, FIBoG CA. Association between serum fructose level and insulin resistance in women with polycystic ovary syndrome: The effect of obesity. Journal of the Faculty of Medicine. 2022;64.
17. Ożga K, Krzyczkowska-Sendrakowska M, Hubalewska-Dydejczyk A, et al. The value of the free androgen index depends on the phenotype of polycystic ovary syndrome—A single-centre experience. Endokrynologia Polska. 2019;70:330-335.
18. Miller RA, Chu Q, Xie J, et al. Biguanides suppress hepatic glucagon signaling by decreasing production of cyclic AMP. Nature. 2013;494:256-260.
19. Tokubuchi I, Tajiri Y, Iwata S, et al. Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats. PloS one. 2017;12:e0171293.
20. Alzamily AA, Obaid KM, Al-Azzawi B. Metformin may ameliorate inflammatory events of IL-18 in some inflammatory conditions. MMSL. 2022;91:170-181.
21. Behradmanesh S, Ranjbar Omrani GH, Ghazanfarpour F, et al. Effect of metformin on serum ferritin level in women with polycystic ovary syndrome. Iran Red Crescent Med J. 2011;13:487-492.
22. Akhondzadeh S. Personalized medicine: a tailor-made medicine. Avicenna J Med Biotechnol. 2014;6:191.
23. Meyer UA, Zanger UM, Schwab M. Omics and drug response. Annu Rev Pharmacol Toxicol. 2013;53:475-502.
24. Wu KC, Lu YH, Peng YH, et al. Decreased expression of organic cation transporters, Oct1 and Oct2, in brain micro vessels and its implication to MPTP-induced dopaminergic toxicity in aged mice. Journal of Cerebral Blood Flow & Metabolism. 2015;35:37.
25. Jayagopal V, Kilpatrick ES, Holding S, et al. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab. 2005;90:729-733.
26. Hoffmann JM, Grünberg JR, Church C, et al. BMP4 gene therapy in mature mice reduces BAT activation but protects from obesity by browning subcutaneous adipose tissue. Cell reports. 2017;20:1038-1049.
27. Kruszewska J, Laudy-Wiaderny H, Kunicki M. Review of Novel Potential Insulin Resistance Biomarkers in PCOS Patients—The Debate Is Still Open. International journal of environmental research and public health. 2022;19:2099.
28. Glister C, Regan SL, Samir M, et al. Gremlin, Noggin, Chordin and follistatin differentially modulate BMP induced suppression of androgen secretion by bovine ovarian theca cells. Journal of Molecular Endocrinology. 2019;62:15-25.
29. Koroglu N, Aydogan Mathyk B, Tola EN, et al. Gremlin-1 and gremlin-2 levels in polycystic ovary syndrome and their clinical correlations. Gynecol Endocrinol. 2019;35:604-607.
30. Hedjazifar S, Khatib Shahidi R, Hammarstedt A, et al. The novel adipokine Gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH. Diabetes. 2020;69:331-341.
31. Hedjazifar S, Khatib Shahidi R, Hammarstedt A, et al. The novel adipokine Gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH. Diabetes. 2020;69:331-341.
32. Sarhat ER, Sulaiman YA, Abass KS. Evalution of liver function tests in patients with psoriasis. Revista Latinoamericana de Hipertension. 2022;17:396-403.