GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 5 (350) Май 2024

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 3 (348) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 5 (350) 2024

METFORMIN MODULATED ADIPOKINES BIOCHEMICAL MARKERS IN TYPE-2 DIABETES PATIENTS

Hind R. Toaama[1], Entedhar R. Sarhat[2]*, Husamuldeen S Mohammed[2].

College of medicine, University of Tikrit, Tikrit, Iraq.

Abstract.

Background: Type 2 diabetes mellitus is the most widespread type of diabetes, mainly affecting adults. Long-term complications are related to the progression of type 2 diabetes mellitus. Metformin is a key treatment option for type 2 diabetes. Objectives: To evaluate serum irisin, visfatin, and RBP4 levels and to determine the effects of metformin treatment on irisin, visfatin, and RBP4 levels in patients with type 2 diabetes mellitus (Type 2 DM).

Methods: A total of 70 patients with type 2 diabetes mellitus, aged between 48 and 82 years were enrolled in the current study. Serum collected and irisin, visfatin, and RBP4 levels were measured, in Type 2 DM patients and control, using the ELISA Kit.

Results: The findings observed that there were significantly increased levels of irisin, visfatin, and RBP4 in patients with T2DM when compared with control groups. After 3 months of metformin treatment, irisin levels significantly decreased irisin, visfatin, and RBP4 in patients with T2DM when compared before treatment. Receiver operator characteristic curve investigation shows the levels of visfatin, and irisin are the best biomarkers differentiating subjects with T2DM.

Conclusion: In patients with type 2 diabetes, 3 months of treatment with metformin reduces levels of Irisin, Visfatin, and RBP4.The clinical significance of these findings remains to be investigated.

Key words. Irisin, Visfatin, RBP4, diabetes, Metformin.

Introduction.

The pancreas is a vital endocrine-exocrine organ that produces several hormones and enzymes. Its enzymes help in the digestion of carbohydrates, fats, and proteins whereas its hormones such as insulin control blood glucose levels. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia [1]. Diabetes mellitus is a chronic heterogeneous metabolic disorder with complex pathogenesis [2]. It is characterized by elevated blood glucose levels or hyperglycemia, which results from abnormalities in either insulin secretion, insulin action or both [3]. Metformin is the first-line pharmacologic treatment for type 2 diabetes and the most commonly prescribed drug for this condition worldwide, either alone or in combination with insulin or other glucose-lowering therapies [2].

Irisin, a myokine released in response to a high-fat diet and exercise, enhances glucose-stimulated insulin secretion (GSIS), irisin augments insulin biosynthesis and promotes accrual of β-cell functional mass [4,5]. The mechanism of metformin could be inducing trans-differentiation of white adipocytes into brown adipose tissue (BAT) through increased production of irisin [6]. Visfatin is a multifaceted novel adipokine, the increased expression and plasma levels of visfatin are associated with T2DM, and the hypoglycemic actions of visfatin include the inhibition of the release of glucose from hepatic cells and the activation of glucose uptake in peripheral tissues by binding insulin receptors at a site different from that of insulin [7], metformin treatment significantly reduced circulating visfatin concentrations [6]. Retinol-binding protein 4 (RBP4), a transport protein for vitamin A, is synthesized mainly by the hepatocyte and secreted into the circulation bound to vitamin A and transthyretin, RBP4 induces insulin resistance, and plasma RBP4 values are increased in type 2 diabetes mellitus, metformin decreases RBP-4 level in patients with T2DM [8]. Therefore, the present study aimed to evaluate the serum levels of irisin, visfatin and retinol-binding protein 4 in patients with type 2 diabetes after being treated with metformin therapy to determine the effect of metformin on their levels.

Materials and Methods.

Study design: This research includes 180 participants (patients and control subjects). The age range of the participants was between 35 to 70 years. The participants in this research are classified into three different groups: the first group consists of 70 patients who have already been diagnosed with type 2 diabetes and have undergone metformin therapy for more than 6 months, the second one consists of 70 patients with type 2 diabetes who do not take metformin therapy. The research also includes a control group of 40 healthy subjects with no family history of diabetes mellitus and they have a similar age range with patients. This study was conducted from the first of December 2023 to the end of March 2024 on a study population who came to Baqubah General Hospital and private clinic (Diyala City, Iraq).

Sample collection: Each individual had a vein puncture to obtain about 5 ml of blood by a sterile disposable syringe. A blood sample cleft to coagulate at room temperature for ten to fifteen minutes. To extract a serum sample, the tube was then centrifuged for 15 minutes at 3000 rounds per minute (rpm). The sample was immediately separated, placed into 3 clear, dry Eppendorf tubes and given a numerical label before being kept at -20 °C until needed for examination. The serum sample was used for the determination of irisin, visfatin and retinol-binding protein 4.

Biochemical test: The ELISA kit uses the Sandwich-ELISA principle namely Elabscience® Human Irisin ELISA Kit for irisin and Cloud-Clone Corp for visfatin and retinol binding protein. The micro-ELISA plate provided in this kit has been pre-coated with an antibody specific to Human Irisin, Visfatin and Retinol Binding Protein. Samples or Standards are added to the micro-ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human Irisin, visfatin and RBP4 and AvidinHorseradish Peroxidase (HRP) conjugate are added successively to each microplate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those

wells that contain Human Irisin, Visfatin, Retinol binding protein, biotinylated detection antibody and Avidin-HRP conjugate will appear blue which will become yellow upon stop solution injection. The optical density is measured at 450 nm using spectrophotometry. Irisin, Visfatin, and RBP4 concentrations directly affect optical density.

Statistical analysis Data expressed as mean±SD, analysis conducted using t-test with significance considered at p-value 0.05.

Results.

The findings observed that there was a significant increase in the levels of irisin in patients with T2DM (591.53±158.06) when compared with control groups (164.20±40.30). After 3 months of metformin treatment, irisin levels significantly decreased in patients with T2DM (329.01±83.93) when compared to before treatment (591.53±158.06). The findings also observed that there was a significant increase in Visfatin levels in patients with T2DM (53.65±11.68) as compared to control (13.67±2.18). After 3 months of metformin treatment, visfatin levels significantly decreased in patients with T2DM (28.41±6.12) when compared to before treatment (53.65±11.68). The present study revealed a significant increase in the serum RBP4 levels in T2DM patients (94.89±29.64) as compared to the control (10.64±5.21). After 3 months of metformin treatment, RBP4 levels significantly decreased in patients with T2DM (46.83±19.16) when compared to before treatment (94.89±29.64) (Table 1).

Table 1. *Comparison of measured parameters in the studied group.*

Parameter	Control	-Metformin	+Metformin
Irisin(pg/ml)	164.20±40.30	591.53±158.06*^	329.01±83.93#
Visfatin(ng\ml)	13.67±2.18	53.65±11.68*^	28.41±6.12#
RBP4(ng\ml)	10.64±5.21	94.89±29.64*^	46.83±19.16#
Data Expressed as mean±SD, *^# indicate significant difference at p <0.05 *# as compared to the control group ^as compared to +Metformin group			

Discussion.

Irisin is a multifunctional myokine secreted by adipocytes, cardiac myocytes, and skeletal muscle, possibly mediating a wide range of metabolic processes including insulin resistance, muscle endurance, endothelial function, inflammatory and immune reactions and bone osteoblast activity [9]. Irisin can also stimulate in skeletal muscle cells the membrane translocation of GLUT4 (glucose transporter type 4) and induce glucose uptake via stimulating AMP-activated protein kinase phosphorylation [10,11], and thereby the role of irisin in T2DM remains unclear.

The present study showed that serum irisin levels were increased in patients with T2DM than in controls. These results disagree with those who reported decreased circulating irisin levels in T2DM patients, compared to healthy individuals [11,12]. The elevation of circulating irisin may represent a compensatory response to decreased energy expenditure, as well as to counterbalance the increasing need for irisin and prevent the development of insulin resistance. It is also plausible that excessive adipose tissue in these patients could provide an extra source of irisin [13]. Li et al. (2015), indicated that metformin therapy is a confounding factor in T2DM and obesity-related metabolic disease about the regulation of circulating irisin levels [14].

Visfatin is an adipocytokine of visceral fat that appears to be increased in patients with type 2 diabetes compared with the healthy control group as shown in this study, this result agrees with most recent studies [15]. In this study, the circulating Visfatin level in T2DM patients was compared with the control group. These increased levels of serum visfatin could be due to the effects of hyperglycaemia, as one study found that an infusion of glucose caused an increase in circulating visfatin levels [16].

Another study suggests that increased levels of visfatin are considered a compensatory mechanism for progressive β-cell deterioration aimed at ameliorating the functional consequences of endogenous insulin deficiency in patients with longer-standing type II DM [17]. This study shows elevated levels of RBP4 in patients with type 2 diabetes in both G1 (metformin+ve) and G2 (metformin–ve) when compared to the healthy control group, this finding was consistent with several other studies [18,19]. Higher blood levels of retinol-binding protein are linked to lower expression of glucose transporter 4 in adipocytes, an early pathophysiological indication of insulin resistance. Retinol-binding protein is involved in the development of type 2 diabetes and insulin resistance [20]. Antidiabetics might restore these abnormalities [21-25].

Conclusion.

In patients with type 2 diabetes, the administration of metformin over three months has been observed to significantly reduce the levels of specific adipokines, namely Irisin, Visfatin, and RBP4. These biomarkers are closely linked to metabolic processes and insulin sensitivity. The reduction in their levels suggests that metformin exerts a multifaceted effect on metabolic regulation beyond its primary role in improving insulin sensitivity and lowering blood glucose levels. While these biochemical alterations provide insight into how metformin may improve metabolic health at the molecular level, their precise clinical significance remains unclear. Further studies are needed to investigate whether these changes translate into improved clinical outcomes such as enhanced glycemic control, reduced cardiovascular risk, or other beneficial effects for patients with type 2 diabetes. Comprehensive research linking these biomarker modifications with long-term health outcomes will be critical in understanding the broader implications of metformin therapy for diabetes management.

REFERENCES

1. Mostafa A, Gantsova EA, Serova OV, et al. Interaction between Endocrine and Exocrine Pancreas. Journal of Evolutionary Biochemistry and Physiology. 2024;60:792-801.
2. Younis HY, Thanoon IA, Fadhil NN, et al. Effect of zinc as an add-on to metformin therapy on glycemic control, serum insulin, and c-peptide levels and insulin resistance in type 2 diabetes mellitus patient. Research Journal of Pharmacy and Technology. 2022;15:1184-8.

3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2010;33:S62-9.
4. Marrano N, Biondi G, Borrelli A, et al. Irisin and incretin hormones: Similarities, differences, and implications in type 2 diabetes and obesity. Biomolecules. 2021;11:286.
5. Oliveira FR, Mamede M, Bizzi MF, et al. Effects of short term metformin treatment on brown adipose tissue activity and plasma irisin levels in women with polycystic ovary syndrome: A randomized controlled trial. Hormone and Metabolic Research. 2020;52:718-23.
6. Ozkaya M, Cakal E, Ustun Y, et al. Effect of metformin on serum visfatin levels in patients with polycystic ovary syndrome. Fertility and sterility. 2010;93:880-4.
7. Mir MM, Mir R, Alghamdi MA, et al. Differential association of selected adipocytokines, adiponectin, leptin, resistin, visfatin and chemerin, with the pathogenesis and progression of type 2 diabetes mellitus (T2DM) in the asir region of Saudi Arabia: A case control study. Journal of Personalized Medicine. 2022;12:735.
8. Christou GA, Tselepis AD, Kiortsis DN. The metabolic role of retinol binding protein 4: an update. Hormone and Metabolic Research. 2012;44:6-14.
9. Berezin AA, Fushtey IM, Pavlov SV, et al. Predictive value of serum irisin for chronic heart failure in patients with type 2 diabetes mellitus. Molecular Biomedicine. 2022;3:34.
10. Gorska-Ciebiada M, Ciebiada M. Association between Serum Irisin and Leptin Levels and Risk of Depressive Symptoms in the Diabetic Elderly Population. Journal of Clinical Medicine. 2023;12:4283.
11. Shoukry A, Shalaby SM, El-Arabi Bdeer S, et al. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. IUBMB life. 2016;68:544-56.
12. Rana KS, Pararasa C, Afzal I, et al. Plasma irisin is elevated in type 2 diabetes and is associated with increased E-selectin levels. Cardiovascular diabetology. 2017;16:1.
13. Leustean L, Preda C, Teodoriu L, et al. Role of Irisin in Endocrine and Metabolic Disorders—Possible New Therapeutic Agent?. Applied Sciences. 2021;11:5579.
14. Li M, Yang M, Zhou X, et al. Elevated circulating levels of irisin and the effect of metformin treatment in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2015;100:1485-93.
15. Gouda A. 1005 Study of visfatin and fetuin-A in type 2 diabetes mellitus in children. Archives of Disease in Childhood. 2021;106:A189-A190.
16. Harikrishnan S, Shyam S, Khoo SP. Serum visfatin in Type 2 Diabetes Mellitus-A systematic review and meta-analysis. International E-Journal of Science, Medicine & Education. 2021;15.
17. Abdel-Hassib M, Hassabo AA, Elashmawy H, et al. Serum visfatin level in prediabetics and its relation to left ventricular function. The Egyptian Journal of Internal Medicine. 2019;31:703-14.
18. Elias NG, Akram RS, Isaa MQ. Role of Retinol Binding Protein-4 (RBP-4) and some Biochemical Parameters in Type II Diabetes Mellitus Patients. Journal for Research in Applied Sciences and Biotechnology. 2023;2:210-4.
19. Tahir NT, Ahmed HS, Ahmed HS. Studies on the role of retinol binding protien-4 in type 2 diabetic Iraqi patients with metabolic syndrome. The Nucleus. 2023:1-7.
20. Rafaqat S, Hafeez R, Mairaj R, et al. Pancreatic biomarkers: role in diabetes mellitus. Journal of Pancreatology. 2023;6:169-77.
21. Merkhan MM. Effect of metformin, glibenclamide and insulin on lipid profile in type 2 diabetic patients. Tikret Journal of Pharmaceutical Sciences. 2013;9.
22. Merkhan MM. The effects of glibenclamide on thyroid function tests in type 2 diabetic patients. Iraq J Pharm Vol. 2013;13.
23. Younis HY, Imad A, Thanoon IA, et al. Effect of zinc as an add on to metformin therapy on serum lipid profile and uric acid in type 2 diabetes mellitus patients. Curr topics in Pharmacology. 2021;25.
24. Mohammad S, Fadhil N, Mahmood M. Effects of metformin and cinnamon on 1, 5 anhydroglucitol, adiponectin and ghrelin on newly diagnosed type 2 diabetes mellitus patients. Jordan Medical Journal. 2021;55.
25. Mustafa B, Shareef A, Mahmood M. Comparison of bone maturation response to treatment with short and long-term growth hormone therapy in short-stature pediatric patients. Georgian Medical News. 2022;331:27-30.