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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

**GEORGIAN MEDICAL NEWS**

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**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.

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# COMPARATIVE EFFECT OF INSULIN, GLIMEPIRIDE, AND METFORMIN ON INFLAMMATORY MARKERS IN TYPE 2 DIABETES MELLITUS

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## Abstract.

**Background:** Insulin, glimepiride, and metformin prescribe as monotherapy or in combination to control glycemic state. The present study aimed to identify the anti-inflammatory activity of commonly used antidiabetic medications insulin, glimepiride, and metformin if any.

**Methods:** A follow-up study of added metformin alone or with glimepiride to newly diagnosed diabetic patients and add metformin to patients treated with insulin or glimepiride monotherapy to establish the effect on the glycemic and inflammatory state.

**Results:** There are highly significant differences in glycemic and inflammatory markers when adding metformin to newly diagnosed diabetic patients and when combined with insulin or glimepiride monotherapy.

**Conclusion:** Metformin is associated with high anti-inflammatory action in addition to improving glycemic and lipidomics states.

**Key words.** Type 2 diabetes mellitus, insulin, glimepiride, metformin, CRP, IL-1B, IL-6.

## Introduction.

Type 2 diabetes mellitus (T2DM) is a complex chronic disorder with multiple metabolic and endocrine disturbances, a rapidly growing health problem that affects 9% of all individuals worldwide, some reports exhibited that near the year 2050, almost a third of the total population of the world have diabetes. So demanding risk-drop policies, and endless medical maintenance besides glycemic control [1].

The physiological inflammatory response is arranged to permit leukocytes migration from the circulation to the word inflammatory injured restore homeostasis or healing within a short time as acute inflammation. Nevertheless, the inflammation might convert to chronic or even progressive inflammation that developed into serious inflammatory diseases. Another type that originated from metabolic cells (liver, adipose tissue, and muscles) responding to excess nutrients with the influence sedentary lifestyle, termed met-inflammatory low-grade chronic inflammation, which aggravates peripheral tissue's resistance to insulin or impairs secretion of insulin [2,3].

Inflammation is the main pathophysiological event linked to impaired insulin secretion and insulin resistance. Unresolved inflammation, together with oxidative stress and glucolipotoxicity of the cells of the pancreatic islets and boosted resistance to insulin and immune cells infiltration as macrophages to the site of islets, fatty tissues, and liver that cause dysfunction of □-cells, worsen resistance and impaired insulin secretion, insulin receptor signaling and decreasing tissues responsiveness to insulin with developing insulin resistance that aggravates stress and inflammation with metabolic dysregulation with low-grade met inflammation that evokes responses of inflammation through the release of oxidative and pro-inflammatory mediators, such as IL-1β, and IL-6, that switch point of metabolic homeostasis leading to T2DM [4-6].

Chronic low-grade inflammation is accompanied by high production of inflammatory markers which can be detected in the inflammatory state [7], the most important inflammatory markers are Erythrocyte sedimentation rate [8], C-reactive protein (CRP) [9], and the functional cytokines as interleukin family, as IL1Beta and IL-6 [7]. Cells intrinsically secrete a plethora of bioactive agents including cytokines [10], which might be anti-inflammatory or pro-inflammatory cytokines and the concentration of which might change based on the surrounding environment including drugs [4-6], oxygen [11] or cell behavioural architectures [12]. Anti-diabetic has induced changes in diabetes profile based on the type of oral hypoglycemia agents changing the selection of the proper antidiabetic medication for serious illnesses, such as COVID-19 [13]. The present study aimed to identify the inflammation-modulation effects of antidiabetics which are in current use, including metformin, glimepiride, and insulin.

## Materials and Methods.

The present study was designed as a prospective interventional follows up study that involved eighty patients who were selected according to strict individual selection criteria which has excluded patients with acute or chronic illness rather than T2DM, diabetic patients treated with another antidiabetic agent rather than monotherapy of insulin, and glimepiride or history of drug intake that affects the pancreatic function or interacts with the result or having anti-inflammatory action, pregnant, lactating mothers, alcoholic, smokers. obese or central obesity.

The patients were divided into four groups of 20 patients.

Group A newly diagnosed diabetic patients: treated for 4 months with metformin alone daily dose beginning of 500 mg and increased to 1850 mg.

Group B newly diagnosed diabetic patients: s treated for 4 months with metformin plus glimepiride daily dose beginning of 500 mg and increased to 1850 mg, glimepiride at the beginning in a dose of 2 mg increased to 4mg.

Group C diabetic patients on insulin monotherapy (40 to 60 unit per day )add metformin for 4 months dose beginning of 500 mg and increased to 1850 mg.

Group D diabetic patients on glimepiride monotherapy (4 mg daily ) add metformin for 4 months in a dose beginning of 500 mg and increased to 1850 mg. classified patients groups according to treatment strategies.

About 6 millilitres (ml) of venous blood was withdrawn at two-time intervals from an antecubital vein. In the first interval

draw 3 ml in the morning after an overnight. From the first, about 1 ml was put in an EDTA tube with a shake used as 0.8 ml to the Westergren tube for assay of ESR Using the Sediplast Westergren system . a little amount of whole blood was retained for rapid examination of glycated haemoglobin utilizing an A1C EZ 2.0 analyzer system. The remaining blood was centrifuged, and aspirated supernatant for immediate fasting plasma glucose (FPG) estimation by colorimetric enzymatic spectrometric methods using the Randox glucose kit. CRP was determined quantitatively by photometric immunoturbidity methods (15). CRPLX kit cobas c111. and others for deep freeze until time of measurement of Interleukin 1β (IL-1β), IL6 by Enzyme-linked immunoassay (ELISA) sunlong biotech –china kit used sandwich-ELISA method depend on spectrophotometric determination to obtain optical density. The second interval draws 3 after 13 hours for lipid profile via the enzymatic colourimetric method, Using -the Biolabo kit (France).

Statistical analysis of data was conducted using Minitab (Version 21) software. Differences between values of the parameters are considered significant at P≤ 0.05. Standard statistical methods were applied to determine the mean, standard deviation. Paired t-test was applied among data of pre- and post-value of the parameter.

## Results.

Tables (1 and 2) show the result of groups A, and B in the newly diagnosed patient treated with metformin alone, metformin and glimepiride There are highly significant differences in FPG, HbA1c, ESR, CRP, IL1β, IL6, TC, TG, HDL-c, and VLDL-c at (P-value* 0.001). while LDL-c shows a significant difference.

***Table 1.*** *Parameters of group A new diagnosis treated with metformin.*

| Parameters | **PreM ± SD** | **Post M ± SD** | **P-value** |
|---|---|---|---|
| FPG (mmol/l) | 11.1 ± 0.81 | 9.79 ± 0.49 | 0.001 |
| HbA1c (%) | 8.5 ± 0.45 | 8.2 ± 0.48 | 0.001 |
| ESR (mm/h) | 32.2 ± 3.87 | 28.95 ± 4.22 | 0.001 |
| CRP (mg/l) | 11.84 ± 2.36 | 10.38± 1.75 | 0.001 |
| IL-1β (pg/ml) | 20.77 ± 3.78 | 17.24 ± 3.042 | 0.001 |
| IL-6β (ng/l) | 17.75 ± 3.175 | 16.46 ± 3.26 | 0.001 |
| TC (mmol\l) | 5.7 ± 0.39 | 5.3 ± 0.26 | 0.001 |
| TG (mmol\l) | 1.9 ± 0.28 | 1.7 ± 0.22 | 0.001 |
| HDL(mmol\l) | 1.0 ± 0.08 | 1.1 ± 0.07 | 0.007 |
| LDL(mmol\l) | 3.8 ± 0.39 | 3.2 ± 1.06 | 0.015 |
| VLDL(mmol\l) | 0.85 ± 0.128 | 0.69 ± 0.241 | 0.009 |

***Table 2.*** *Parameters of group B newly diagnosed patients treated with metformin and glimepiride.*

| Parameters | PreM ± SD | Post M ± SD | P-value |
|---|---|---|---|
| FPG (mmol/l) | 12.5 ± 0.72 | 9.96 ± 0.70 | 0.001 |
| HbA1c (%) | 9.4 ± 0.47 | 8.7 ± 0.68 | 0.001 |
| ESR (mm/h) | 31.8 ± 4.55 | 28.5 ± 4.43 | 0.001 |
| CRP (mg/l) | 11.7 ± 2.11 | 10.8 ± 1.54 | 0.001 |
| IL-1β (pg/ml) | 19.5 ± 3.87 | 17.3 ± 2.88 | 0.001 |
| IL-6β (ng/l) | 17.6 ± 3.78 | 16.4 ± 3.27 | 0.001 |
| TC (mmol\l) | 5.68 ± 0.26 | 5.34 ± 0.28 | 0.001 |
| TG (mmol\l) | 2.0± 0.21 | 1.79 ± 0.225 | 0.001 |
| HDL(mmol\l) | 1.01 ± 0.07 | 1.06 ± 0.06 | 0.006 |
| LDL(mmol\l) | 3.74 ± 0.285 | 3.155 ± 1.067 | 0.016 |
| VLDL(mmol\l) | 0.93 ± 0.097 | 0.74 ± 0.259 | 0.003 |

Tables (3 and 4) show the resulting group C and D the groups of monotherapy with insulin and glimepiride that follow up by adding metformin. There are highly significant differences in FPG, HbA1c, ESR, CRP, IL1β, IL6, TC, and LDL-c while TG, HDL, and LDL show a significant difference.

***Table 3.*** *Parameters of group C add metformin to insulin monotherapy.*

| Parameters | PreM ± SD | Post M ± SD | P-value |
|---|---|---|---|
| FPG (mmol/l) | 9.3 ± 0.67 | 8.9 ± 0.95 | 0.028 |
| HbA1c (%) | 7.9 ± 0.40 | 7.8 ± 0.37 | 0.022 |
| ESR (mm/h) | 24.8 ± 3.39 | 22.2 ± 3.72 | 0.002 |
| CRP (mg/l) | 7.7 ± 1.34 | 7.3 ± 1.21 | 0.001 |
| IL-1β (pg/ml) | 12.3 ± 2.07 | 11.4 ± 1.74 | 0.002 |
| IL-6β (ng/l) | 12.8 ± 2.36 | 12.0 ± 2.24 | 0.008 |
| TC (mmol\l) | 4.9 ± 0.29 | 4.8 ± 0.29 | 0.003 |
| TG (mmol\l) | 1.65 ± 0.17 | 1.56 ± 0.16 | 0.013 |
| HDL(mmol\l) | 1.06± 0.07 | 1.1 ± 0.09 | 0.015 |
| LDL(mmol\l) | 3.1 ± 0.26 | 3.0 ± 0.25 | 0.004 |
| VLDL(mmol\l) | 0.74± 0.081 | 0.71 ± 0.072 | 0.013 |

***Table 4.*** *Parameters of group D add metformin to glimepiride monotherapy.*

| Parameters | PreM ± SD | Post M ± SD | P-value |
|---|---|---|---|
| FPG (mmol/l) | 9.1 ± 0.86 | 8.83 ± 1.05 | 0.016 |
| HbA1c (%) | 7.9 ± 0.42 | 7.7 ± 0.40 | 0.034 |
| ESR (mm/h) | 28 ± 3.71 | 25.4 ± 5.78 | 0.017 |
| CRP (mg/l) | 8.9 ± 1.913 | 8.5 ± 1.65 | 0.002 |
| IL-1β (pg/ml) | 13.7 ± 2.25 | 12.8 ± 2.23 | 0.002 |
| IL-6β (ng/l) | 14.4 ± 2.44 | 13.9 ± 2.54 | 0.001 |
| TC (mmol\l) | 4.9 ± 0.19 | 4.76 ± 0.24 | 0.002 |
| TG (mmol\l) | 1.62 ± 0.12 | 1.59± 0.12 | 0.011 |
| HDL(mmol\l) | 1.04 ± 0.08 | 1.07 ± 0.08 | 0.010 |
| LDL(mmol\l) | 3.12 ± 0.19 | 2.97 ± 0.23 | 0.002 |
| VLDL(mmol\l) | 0.74 ± 0.055 | 0.72 ± 0.059 | 0.011 |

## Discussion.

The little and even lack of randomized, large, double-blind, trials on the study of the anti-inflammatory state after a combination between antidiabetic drugs insulin, glimepiride or metformin, or head-to-head studies with other antidiabetic agents, antidiabetic drugs exert their anti-inflammatory action by direct modulating inflammatory response or indirectly concerned with their hypoglycemic and hypolipidemic action, so the correction of glycemic and lipidomic stay can reflect the correction of inflammatory state [8].

The result of glycemic parameters and inflammatory markers of groups A, and B in the newly diagnosed patient treated with metformin alone metformin and glimepiride are in accordance with [14] that show metformin monotherapy and when used in combination with other SUs provide good glycemic control and decrease inflammatory state via decreased inflammatory markers. Metformin therapy in newly diagnosed patients decreases CRP and IL6 [15]. Mo et al., [16] in disagreement with the obtained results showing that metformin monotherapy needs one year to a reduce level of inflammatory markers.

The result of glycemic parameters and inflammatory markers

of group C patients that add metformin to insulin therapy in accordance with [17,18] show metformin ad on insulin therapy are associated with improved glycemic and lipidomics state that consequently decreases the inflammatory state.

The result of glycemic parameters and inflammatory markers of group D patients that add metformin to glimepiride therapy. Metformin monotherapy when combined with other OADs as SUs have equally effective in proving glycemic control and decreasing inflammatory states that reduce inflammatory markers [14]. Better glycemic and lipidomic after a combination of metformin with glimepiride consequently decreases the inflammatory state [19].

The percentage of improvement rate of inflammatory markers parameters among all groups. There are high improvement rates in all parameters of all groups greatest in groups A and B followed by other groups. Metformin monotherapy is associated with more inhibition of inflammation when compared with other OADs [20]. Metformin-based therapy reduced inflammation and modify macrophage to decrease inflammatory markers release [21]. Metformin monotherapy when combined with other OADs as SUs equally effective in proving glycemic control and decreasing inflammatory state that reduced inflammatory markers [14].

The available antidiabetic agents (insulin, glimepiride, and metformin) together with glucose-lowering activity may exert immunomodulatory action that involves reduction of the inflammatory infiltration in pancreatic islets with consequent reduction synthesis of pro-inflammatory mediators. The doubt about exerting anti-inflammatory effects of OADs results from their action on hyperglycemic and dyslipidemic abilities or by direct modulation of the inflammatory response partially a statement [2,22].

Insulin in addition to its hypoglycemic action may attenuate the process of inflammation, inhibit NF-κB, increase NO synthesis, decrease the expression of pro-inflammatory cytokines such as IL-1β and IL-6, reduce serum level of CRP despite to glycemic state, other indirect process involving achievement of glycemic control [2,23-25].

Glimepiride has numerous extra pancreatic and pleiotropic benefits, which include insulin-sensitizing properties and anti-inflammatory action The possible anti-inflammatory action is associated with blocking the voltage-dependent K+ channels which have vital to stimulate insulin secretion and reducing the concentration of inflammatory mediators IL-1, IL-6, and CRP [23,26,27].

Recent studies have proposed that Metformin in adding to improves hyperglycaemic state and insulin resistance they have anti-inflammatory action by inhibiting the NF-kB activation pathway that induced cytokine pro-inflammatory cytokine release via AMPK-dependent and independent pathways, activation of this pathway suppresses pro-inflammatory response, and others proposed anti-inflammatory action through the action of metformin inhibit the formation of advanced glycation end products, inhibit the production of NO and proinflammatory cytokines IL-1β and IL-6, and reduction of CRP, above action, contributed directly to explain the anti-inflammatory action related to metformin [27-29].

Metformin's anti-inflammatory effects may be attributed to the regulation of the gastric microbiome [30]. No difference in the glycemic state between monotherapy of insulin glimepiride and metformin, while adding metformin improves glycemic and lipidemic as well as reducing BMI which may equalise the glycemic attributed action on the inflammatory state [30]. The anti-inflammatory action of metformin is indirectly obtained through decreasing glucolipotoxicity via controlling glycemic and lipidomic state, there is no definite that anti-inflammatory action is related principally to direct or indirect action [2,22].

## Conclusion.

Metformin when added as monotherapy or in combination with other antidiabetic drugs improves hyperglycaemic and hyperlipidemic state and insulin resistance, and significantly decrease inflammatory markers when added to newly diagnosed or insulin or glimepiride monotherapy indicate that metformin possesses high anti-inflammatory action in comparison with insulin and glimepiride in addition to glycemic control action.

## Conflict of interest.

Authors have no known rival monetary attention or private dealings that could affect the work of this manuscript Funding No funding available.

## Adherence to Ethical Standards.

The present study had approval from the medical research ethics committee of Nineveh health directorate) and medical research ethics committee college of medicine, Mosul University, Nineveh, Iraq. Ethical approval reference number: UOM/COM/MREC/20-21(35).

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