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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

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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ASSESSMENT OF SUBCLINICAL RENAL INSULT IN SHORT - AND LONG-TERM UNCONTROLLED HYPERTENSION USING INTEGRATED MOLECULAR INDEX OF NGAL AND KIM-1

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Abstract.

Background: Uncontrolled Hypertension (UHTN) is a major cause of rapidly deteriorating kidney function. Typical clinical indicators often lack the sensitivity necessary for early detection of tubular changes preceding irreversible damage to the nephrons. **Objective:** To evaluate the diagnostic performance of a novel kidney damage index derived from the integrated values of Neutrophil gelatinase-associated lipocalin (NGAL) and Kidney injury molecule-1 (KIM-1), alongside Caspase-3 and Advanced protein oxidation products (AOPP), focusing on how disease duration of UHTN influences these molecular signatures of kidney injury. **Methods:** 90 participants were categorized into three groups (n=30): healthy controls, short-term UHTN (<5 years), and long-term UHTN (>10 years). NGAL, KIM-1, Caspase-3, and AOPP were quantified using ELISA.

Results: Significant progressive elevations in serum NGAL, KIM-1, and Caspase-3 were observed in UHTN patients compared to controls ($P<0.05$). **Conclusion:** UHTN triggers 'silent' tubular deterioration. These structural markers offer a superior diagnostic advantage by detecting subclinical damage at an early stage of UHTN. The clinical application of these sensitive biomarkers could be instrumental in preventing the rapid progression of HTN to overt chronic kidney disease and avoiding long-term complications.

Key words. Uncontrolled hypertension, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, caspase-3, advanced protein oxidation products.

Introduction.

Hypertension (HTN) is a widespread global problem resulting from genetic reasons or from an unhealthy lifestyle; it is considered a chronic medical state characterised by considerably high blood pressure that constantly flows through vessels, predominantly leading to gradual damage of multiple organs, mainly the renal and cardiovascular systems [1]. Uncontrolled hypertension (UHTN) remains a difficult global health challenge, with a high prevalence rate, mostly in the countries of the Eastern Mediterranean [2]. The constant increase in systemic blood pressure equal to or more than 140/90 mmHg subjects the microvessels in the kidney to stress, leading to barotrauma, as a sequence of accelerated nephrosclerosis and tubular atrophy [3]. This state of hemodynamic instability activates numerous sequences of molecular changes which occur long before the clinical symptoms of kidney damage appear [4].

It is well-established that the clinical assessment of kidney function relies primarily on blood creatinine and urea levels, as well as the estimated glomerular filtration rate (GFR). However, considering creatinine as an indicator of kidney injury has several limitations, including its inaccurate correlation with eGFR [5]. Furthermore, it is not considered a reliable biomarker for early detection of kidney damage, as creatinine levels remain within normal limits until a significant portion of the nephrons are damaged, leading to permanent impairment of their function. This delay in diagnosis makes treatment more difficult. [6]

Both neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are novel biomarkers reflecting renal tubular stress and injury. Therefore, they are considered promising diagnostic biomarkers [7]. NGAL serves as an essential component of the innate immune system and acts as a homeostatic regulator of low-grade inflammation responses to modulate immunity under physiological conditions. Elevated NGAL levels associate with the impairment of the kidney; therefore, it helps to monitor disease progression for patients with kidney disease [8].

Similarly, KIM-1 is a transmembrane glycoprotein; when the body is functioning normally, KIM-1 plays an important role in maintaining the balance of the immune system despite its low gene expression, but its elevation in blood is closely associated with the severity of proximal tubule damage in both acute and chronic kidney injury [9].

On the other hand, UHTN plays a significant role in kidney damage due to increased oxidative stress resulting from the overproduction of reactive oxygen species (ROS) [10]. This, in turn, leads to the oxidation of plasma proteins, resulting in the formation of advanced protein oxidation products (AOPPs). AOPPs are biomarkers of protein damage and trigger further renal inflammation; furthermore, oxidative stress is not limited to this role; it also sustains a pivotal role in inducing apoptotic pathways as a result of cell damage [11]. Caspase-3 acts as the final executive protease of apoptosis, reflecting the final stage of cellular stress and irreversible tubular cell death [12].

Despite the high prevalence of hypertension, it presents a clinical challenge in managing its complications, which are proportional to the duration and severity of the condition. Therefore, the relationship between UHTN duration and these biomolecular markers warrants further investigation to clarify their interrelationship with disease complications. This study aimed to investigate the levels of specific biochemical markers for evaluating structural kidney damage, such as NGAL and KIM-1, in patients with UHTN. Furthermore, the study explored the interrelationship between these biochemical factors and the mechanisms of oxidative stress and cellular damage that result from the hemodynamic instability of UHTN. Finding the correlation between these biomarkers and disease duration can establish their early diagnostic accuracy and facilitate better control to prevent hypertensive complications. The study seeks

to enable the early detection of subtle renal progression resulting from UHTN, which is considered the most insidious form of the condition.

Materials and Methods.

Study design: The study was conducted at Al-Diwaniyah Teaching Hospital (the Outpatient Clinics of the Internal Medicine), and at the University of AL-Qadisiyah (College of Science/Advanced Research Laboratory), during the period between January and April 2026.

The study included 90 male participants recruited from hospital visitors, whether healthy or patients, categorised into three groups (n=30 for each group): Healthy control group with no history of hypertension and normal renal function tests. Uncontrolled Hypertensive Group 1 (G1): Patients who were diagnosed with hypertension for less than 5 years, and Uncontrolled Hypertensive Group 2 (G2): Patients who were diagnosed with hypertension for more than 10 years. Both patient groups with high blood pressure often had blood pressure readings>140/90 mmHg; patient groups not suffering from dyslipidemia depended on the analysis of the lipid profile.

The study protocol, including each procedure related to blood sample collection and laboratory analyses, was approved by the Ethical Committee of the College of Science / University of Al-Qadisiyah (QU/SC-IRB-916/ 20-1-2026). All participants were fully informed about the study, and written informed consent was obtained from each individual before enrollment in the study and sample collection.

Inclusion criteria: Patients with confirmed uncontrolled hypertension regardless of the type of medication used.

Exclusion criteria: Patients with secondary hypertension, chronic kidney disease (CKD), diabetes mellitus, inflammatory disorders, or any malignancy and Autoimmune diseases.

Sample collection and biochemical analysis: Serum obtained from venous blood after collection in gel tubes, allowed to clot for 15-20 minutes and then centrifuged at 3600 rpm. Serum was divided into parts and stored at -20°C for biochemical analysis. Serum creatinine (Cr) and blood urea (BU) were measured by an automated analyser (Abbott, USA). Quantification of Molecular Biomarkers: NGAL, KIM-1, Caspase-3, and AOPP were quantified using specific ELISA kits according to the manufacturer's protocols of BT Lab kits (China).

Statistical analysis: The collected data were analysed using the Statistical Package for the Social Sciences (SPSS) software, v. 28. The mean levels of biomarkers and differences across the study cohorts were determined via One-way Analysis of Variance (ANOVA). Tukey's post hoc test comparisons were applied to identify specific group differences. Additionally, correlation analyses were calculated using Pearson's correlation coefficient to assess the relationship between variables among groups. The predictive performance of biomarkers was assessed by calculating the area under the receiver operating characteristic (ROC) curve. Statistical significance was maintained at p-value <0.05.

Results.

Regarding age, there was no significant difference between all groups (P=0.729). The duration of UHTN was significantly lower in G1 compared to G2 (P=0.001). Regarding blood pressure, the result shows the mean of both SBP and DBP were significantly higher in both groups of patients (G1 and G2) compared to the control group (P>0.05). Also, SBP showed a significant difference between both groups of patients themselves (P>0.05). Regarding renal function tests (urea and Creatinine), results show the mean levels of both biomarkers were significantly higher in G1 and G2 compared to control (P<0.05), also between both groups of patients themselves (P<0.05) (Table 1).

The oxidative stress AOPP and apoptotic Caspase-3 levels were higher in both groups of patients (G1 and G2) compared to the control group, and there is a significant difference between G1 and G2 (P>0.05) (Table 2).

Functional marker (eGFR) and structural markers (NGAL and KIM-1) were compared in Table 3 and Figure 1. Both groups of patients exhibited significantly elevated major parameters (NGAL and KIM-1) levels compared with healthy

Table 1. *Characteristics of patients and healthy control groups.*

Characteristic	G1 Patients	G2 Patients	Healthy	P value
Age, years	49.50 ±4.18	49.76±3.54	48.93 ±4.62	0.729
BMI, kg/m^2	27.17 ±1.19	27.36±1.35	26.49 ±1.27	0.129
Duration of HTN, years	3.2±1.1 ^{A}	14.6±3.^{5}B	--	0.001
Systolic blood pressure, mmHg	149.57 ±5.36^A	162.70 ±10.4^B	119.76±3.71^C	0.001
Diastolic blood pressure, mmHg	94.90±3.35^A	102.97±4.87^A	79.03±2.61^B	0.001
Blood Urea, mg/dl	34.64±2.87^A	55.63±6.36^B	27.79±4.99^C	0.001
Serum Creatinine, mg/dl	1.00±0.07^A	1.14±0.11^B	0.83±0.07^C	0.001
Means followed by different letters are significantly different according to Duncan's multiple range comparisons (DMRT); means followed by the same letter are not significantly different.				

Table 2. *Comparison of AOPP and Caspase-3 in patients and healthy control groups.*

Groups	AOPP, µmol/l	Caspase-3, ng/ml
G1 patients	52.94±6.73^A	2.39±0.4^{7}A
G2 patients	106.97±10.28^B	4.05±0.62^B
Control	26.31±2.98^C	1.26±0.11^C
p-value	0.001**	0.001**
Data expressed as mean		

Table 3. *Comparison of measured parameters in patients and healthy control groups.*

Groups	eGFR, mL/min/1.73 m²	NGAL, ng/ml	KIM-1, ng/ml
G1 patients	87.63±3.9[1]A	76.66±8.81[A]	0.28±0.08[A]
G2 patients	79.97±8.31[B]	132.44±14.29[B]	0.64±0.17[B]
Control	101.37±5.89[C]	54.57±8.12[C]	0.12±0.03[C]
p-value	0.001**	0.001**	0.001**

Table 4. *Correlation between measured parameters in G1 patient group.*

	eGFR		NGAL		KIM-1	
	r	P	r	P	r	P
eGFR	1					
NGAL	-0. 570	0.050	1			
KIM-1	-0. 510	0.031	0.276	0.061	1	
SBP	-0. 459	0.044*	0.57	0.042*	0.45	0.057
DBP	-0.280	0.053	0.460	0.0798	0.430	0.082
BMI	0.026	0.890	0.113	0.553	0.092	0.628
Urea	-0.493	0.041*	0.094	0.620	0.359	0.051
Creatinine	-0.523	0.011*	0.472	0.063	0.656	0.085
AOPP	-0.365	0.047*	0.375	0.058	0.238	0.060
Caspase-3	-0.252	0.179	0.417	0.041*	0.679	0.079

Table 5. *Correlation between measured parameters in G2 patient group.*

	eGFR		NGAL		KIM-1	
	R	P	r	P	r	P
eGFR,	1					
NGAL	-0.577	0.034*	1			
KIM-1	-0.427	0.05*	0.514	0.001*	1	
SBP	-0. 574	0. 029*	0. 594	0. 025*	0. 582	0. 042*
DBP	-0.380	0.041*	0.301	0. 046*	0.422	0.052
BMI	0.112	0.557	0.183	0.334	0.143	0.450
Urea	-0.479	0. 047*	0.334	0.039*	0. 393	0. 042*
Creatinine	-0.626	0.036*	0.518	0.011*	0.409	0.025*
AOPP	-0.353	0.047*	0.274	0.043*	0.216	0.059*
Caspase-3	-0.459	0.034*	0.588	0.039*	0.382	0.037*

Table 6. *ROC curve of measured parameters in G1 patient group.*

Characteristic	eGFR	NGAL (ng/ml)	KIM-1 (ng/ml)
Cutoff value	>94.74	<59.67	<0.133
P value	0.001	0.001	0.001
Sensitivity %	90.0 %	90.0%	83.3 %
Specificity %	93.3 %	86.7 %	86.7 %
PPV %	93.1 %	87.1 %	86.2%
NPV %	90.3 %	89.7 %	83.9 %
AUC (95% CI)	0.901 (0.814- 0.986)	0.893 (0.810- 0.976)	0.882 (0.796- 0.968)
CI: Confidence interval, AUC: Area under curve.			

Table 7. *ROC curve of measured parameters in G2 patient group.*

Characteristic	eGFR	NGAL (ng/ml)	KIM-1 (ng/ml)
Cutoff value	>94.74	<67.00	<0.132
P value	0.001	0.001	0.001
Sensitivity %	96.7 %	93.3 %	93.3 %
Specificity %	93.3 %	93.3 %	90.0%
PPV %	93.5 %	93.3 %	90.3 %
NPV %	96.6 %	93.3 %	93.1 %
AUC (95% CI)	0.977 (0.946- 1.000)	0.934 (0.883- 0.991)	0.911 (0.841- 0.981)

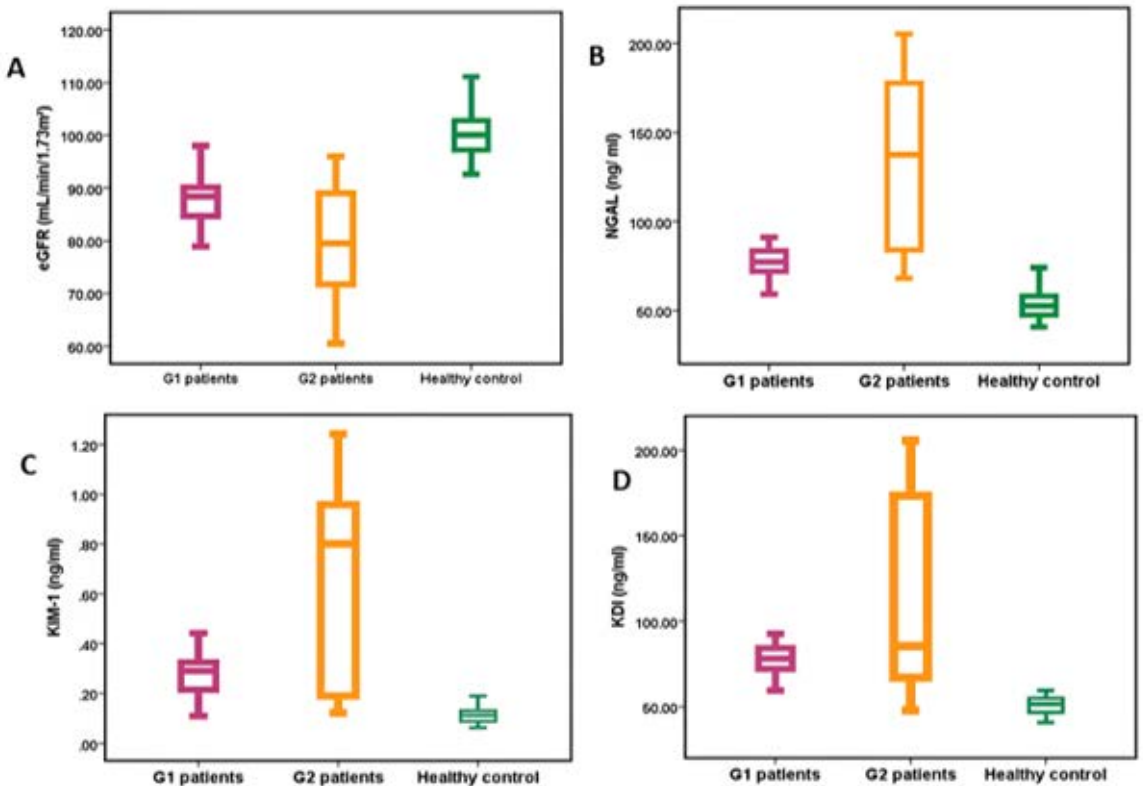

Figure 1. *The means level of eGFR (A), NGAL(B), KIM-1(C), and KDI(D) in patients and control groups.*

controls(P>0.05). Also, there is a significant difference between both groups of patients themselves (P<0.05). The eGFR level was lower in both groups of patients (G1 and G2) compared to the control group, and the difference was significant (P<0.05). Also, there was a significant difference between patient groups themselves (P<0.05).

Correlation analysis for the G1 group (Table 4) revealed that NGAL exhibited significant positive correlations with SBP (r=0.553, P=0.039 and (r=0.570, P=0.042, respectively. In contrast, eGFR showed a significant inverse correlation with SBP (r=-0.459, P=0.044). Regarding oxidative and apoptotic pathways, AOPP demonstrated a significant negative correlation with eGFR (r=-0.365, P=0.047), while Caspase-3 exhibited significant positive associations with the primary injury markers, NGAL (r=0.417, P=0.041).

NGAL and KIM-1 were significantly positively correlated with Urea (r=0.303, 0.334, 0. 393), Creatinine (r=0.575, 0.518, 0.409), and Caspase (r=0.501, 0.588, 0.382) at P<0.05. Additionally, there is a positive correlation of NGAL with DBP (r= 0.424, r=0.301) and AOPP (r=0.363, 0.274) at P<0.05. In contrast there is negative correlation between eGFR with DBP (r=-0.380), Urea, (r=-0.479), Creatinine (r=-0.626), AOPP (r=-0.353), and Caspase-3 (r=-0.459), with P<0.05.

In the G2 group (Table 5), the association between blood pressure and renal injury intensified. SBP maintained strong positive correlations with KIM-1 (r=0.582, P=0.042), whereas eGFR was significantly negatively correlated with SBP (r = -0. 574, P=0.029). Notably, the structural markers (NGAL and KIM-1) showed robust positive correlations with traditional indicators Urea and Creatinine as well as the apoptotic marker Caspase-3 (P<0.05). Conversely, eGFR demonstrated consistent negative correlations across all parameters, including DBP (r=-0.380), Urea (r=-0.479), Creatinine (r=-0.626), AOPP (r=-0.353), and Caspase-3 r=-0.459), at P<0.05.

Table 6. illustrates the ROC curve of eGFR, NGAL, and KIM-1. These markers exhibited the highest diagnostic Discriminatory power from all variables with AUC=0.913 (95% CI: 0.830–0.994), Exhibited greater predictive accuracy than the traditional test of eGFR (AUC = 0.901), as well as the structural individual biomarkers NGAL (AUC = 0.893) and KIM-1 (AUC = 0.882), all findings were reached statistical significance with a P-value of 0.001.

In Table 7, G2 of the chronic stage of UHTN, eGFR exhibited the highest diagnostic performance, with an AUC = 0.977 (95% CI: 0.946–1.000). Nevertheless, NGAL (AUC = 0.934) and KIM-1 (AUC = 0.911). All results were statistically significant at P<0.05.

Discussion.

No significant differences were found in age and BMI across the study groups. This consistency in demographic variables such as age and weight ensures that they do not influence biochemical parameters. Renal deterioration is a direct result of hypertension, not a physiological decline associated with ageing [13]. Regarding hemodynamic state, results showed both systolic and diastolic blood pressure were significantly higher in the two UHTN groups, G1 and G2, compared to the control group (P<0.05). Furthermore, the large differences in systolic blood pressure between G1 and G2 (P<0.05) reflect progressive vascular damage associated with the prolonged duration of hypertension, resulting in a loss of vascular elasticity [14].

The renal function parameters gradually increased with the chronicity of hypertension, reflecting a progressive decline in glomerular filtration competence related to the duration of HT [15]. Chronic UHTN is considered the major cause of the deterioration, which is primarily attributed to vascular remodelling and structural thickening [16]. It is important to depend on a more sensitive biomarker for early detection, as creatinine is a late indicator that typically rises only after approximately 50 % of nephron function deficiency [17].

The increase in AOPP and caspase-3 levels was observed across the patient groups, which suggests a prolonged duration of UHTN significantly exacerbates protein oxidation. In turn, the oxidative stress triggers systemic apoptosis, as evidenced by the progressive increase of Caspase-3 levels. These results align with a previous study suggesting that high AOPP levels can promote podocyte apoptosis, subsequently accelerating renal tissue damage in hypertension patients [15].

The findings of the present study illustrated an important gap between functional (eGFR) and structural (NGAL and KIM-1) biomarkers. In G1, eGFR remained quite preserved, whereas NGAL and KIM-1 were elevated; this disparity between functional and structural biomarkers confirms that tubular injury precedes the decline in glomerular filtration in UHTN patients, even in the short duration of UHTN, less than five years.

The traditional indicators such as urea and creatinine levels often stay within a near-normal range until substantial nephron damage occurs [17,18], whereas results from new markers offer a more comprehensive assessment of the renal status compared to the assessment by either marker alone. These findings support the practical application of these structural markers as a reliable early warning marker for detecting and revealing early subclinical damage in hypertensive nephropathy.

Comprehensive correlation analysis revealed that these structural markers serve as a sensitive indicator of early renal stress in patients with UHTN, even within a short disease duration (<5years). A significant positive correlation between SBP and these structural markers confirms that early-stage hemodynamic stress is sufficient to induce structural damage to renal tubules [19]. Although serum creatinine and eGFR remained within near-normal ranges, these structural markers correlated with the concept of 'subclinical acute kidney injury'. In this state, tubular structural abnormalities precede any apparent decline in glomerular function [17].

Furthermore, the moderate positive correlation between these structural markers and Caspase-3 demonstrates a link between structural damage and apoptosis; consistent with studies indicating that the kidneys in this chronic stage of hypertension undergo significant structural remodelling as a result of programmed cell death [20], and oxidative stress mechanisms play a key role in induced apoptosis by activation of caspase-3 in hypertension state [21]. Additionally, the inverse relationship between the oxidative marker AOPP and eGFR highlights the role of protein oxidation products as mediators of podocyte injury, contributing to the gradual erosion of the glomerular filtration barrier [22,23]

The correlation Analysis reflects the cumulative effect of persistent hypertension for more than 10 years, with the result showing a clear shift toward chronic renal changes. The strong positive correlation between these structural markers and SBP, along with a strong significant inverse correlation with eGFR, indicates that chronic UHTN over long periods makes kidney tissue more susceptible to damage, which in turn facilitates the constant release of tubular injury markers like NGAL and KIM-1 [24]. Furthermore, there was a correlation between these structural markers, serum creatinine and blood urea, suggesting that the accumulation of the toxic waste products is directly related to the structural damage detected by these structural markers.

These structural markers demonstrated a positive correlation with Caspase-3 and AOPP, reflecting that chronic oxidative stress stemming from chronic UHTN causes renal cellular dysfunction, subsequently leading to renal impairment and apoptosis [25,26]. These structural markers correlated with these biomarkers and can be considered a robust indicator reflecting the damage resulting from the interplay between prolonged UHTN and the gradual decline in eGFR, driven by hemodynamic changes and continuous oxidative stress.

These structural markers demonstrated superior diagnostic performance and outperformed all parameters related to the renal status of UHTN patients suffering for less than 5 years, such as eGFR, NGAL, and KIM-1. These results highlight that these structural markers have exceptional efficiency in detecting subclinical renal insult when the traditional markers such as creatinine still remain insensitive. Renal damage became more established with the chronicity of UHTN; therefore, the diagnostic power of all markers increased in the ROC curve analysis. These structural markers maintained their robust accuracy with high sensitivity and specificity. While traditional markers like eGFR became highly indicative in this advanced stage, the results consistently demonstrate the important role of these structural markers as a more sensitive and reliable tool for identifying hypertensive nephropathy across different disease stages of UHTN, with particular clinical utility in early-stage intervention.

Despite integrated molecular evaluation of subclinical renal injury using NGAL and KIM-1 in uncontrolled hypertension, several limitations should be acknowledged. The study is cross-sectional, limiting the determination of the relationships between the duration of hypertension and the patterns of NGAL and KIM-1 expression. The assay for NGAL and KIM-1 reflects tubular injury rather than differentiating between hypertensive nephrosclerosis or other coexisting glomerular or interstitial pathologies. Being a single-centre study and the restriction of samples to males limits the ethnicity and gender generalizability. Early renal damage or subclinical stages are well correlated with the levels of NGAL and KIM-1; however, these structural markers are non-specific and cannot rule out infection, diabetes, or other chronic systemic diseases.

Conclusion.

Depending on the results, this study concludes that NGAL and KIM-1 offer important clinical value as an early diagnostic tool for nephropathy resulting from UHTN, and suggests that structural tubular damage occurs independently and prior to the alterations in conventional markers like serum creatinine and eGFR, particularly in the early stages of HTN. These structural

markers demonstrate high predictive power for identifying subclinical renal impairment, facilitate early diagnosis, enable timely intervention, and ensure better control of disease progression.

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Authors' Contributions.

Nawal K. Jabbar: Conceptualization, methodology, Statistical analysis, and writing – original draft. Rasha A.H. Al-Athari: Resources (sample collection), investigation (ELISA laboratory analyses), and writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest.

None.

Ethical Clearance.

The project was approved by the local ethical committee at the University of Al-Qadisiyah/ College of Science.

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