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CLINICAL SIGNIFICANCE OF SERUM KLOTHO LEVELS IN PATIENTS WITH STEMI AND RENAL DYSFUNCTION

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Abstract

Introduction: Renal dysfunction is recognized as a major global public health issue, with an estimated worldwide prevalence of up to 13.4%. Patients with renal dysfunction represent a growing proportion of the PCI population. At the same time, patients with chronic kidney disease are at high risk of adverse cardiovascular events.

Objective: To evaluate the relationship between the Klotho protein and traditional cardiovascular risk markers in patients with ST-segment elevation myocardial infarction (STEMI) combined with renal dysfunction.

Materials and Methods:

Design: Cross-sectional clinical study.

Timeline: 2022–2023.

Location: The department of Cardiac surgery of the hospital at NJSC "Medical University of Semey."

The study methods included evaluation of residual platelet reactivity and measurement of serum Klotho protein levels.

Results: A total of 123 patients were included. An inverse correlation was found between age and Klotho protein level (Rho = –0.673; $p < 0.001$). A direct correlation was found between estimated glomerular filtration rate (GFR) and serum Klotho (Rho = 0.463; $p < 0.001$). Additionally, for the first time, a correlation between Klotho and total cholesterol (Rho = –0.417; $p < 0.001$) and C-reactive protein (Rho = –0.416; $p < 0.01$) was demonstrated.

Conclusion: In patients with ST-segment elevation myocardial infarction (STEMI) and GFR < 60 mL/min/1.73 m², assessment of serum Klotho levels may serve as an early and independent biomarker of renal dysfunction and a predictor of adverse cardiovascular outcomes.

Keywords: *Klotho protein, ST-segment elevation myocardial infarction, renal dysfunction, aggregometry, residual platelet reactivity.*

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Резюме

КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ СЫВОРОТОЧНОГО УРОВНЯ KLOTHO У ПАЦИЕНТОВ С ИНФАРКТОМ МИОКАРДА С ПОДЪЕМОМ СЕГМЕНТА ST И ПОЧЕЧНОЙ ДИСФУНКЦИЕЙ

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Введение: Почечная дисфункция признана ведущей проблемой общественного здравоохранения во всем мире, ее глобальная распространенность оценивается до 13,4%. Пациенты с почечной дисфункцией составляют все большую долю популяции ЧКВ. Между тем, пациенты с ХБП подвержены высокому риску неблагоприятных сердечно- сосудистых событий.

Цель: Оценка связи белка Klotho с традиционными маркерами сердечно - сосудистого риска у пациентов с инфарктом миокарда с подъемом сегмента ST в сочетании с почечной дисфункцией.

Материалы и методы: Дизайн: поперечное клиническое исследование. Сроки выполнения 2022-2023гг., проведено на базе кардиохирургического отделения университетского госпиталя НАО «Медицинский университет Семей». Методы исследования включали оценивание остаточной реактивность тромбоцитов и определение уровня белка Klotho.

Результаты исследования: В исследование были включены 123 пациента. Определены: обратная корреляционная взаимосвязь между возрастом и уровнем белка Klotho (Rho=-0,673; p<0,001), между величиной СКФ и сывороточным уровнем белка Klotho установлена прямая корреляционная зависимость (Rho=0,463; p<0,001). Кроме того нами впервые показано наличие корреляции Klotho с уровнем общего холестерина (Rho=-0,417; p<0,001) и показателями С - реактивного белка (Rho=-0,416;p<0,01).

Заключение: У больных с ИМпST при снижении СКФ менее 60 мл/мин/1,73м2 целесообразно изучение уровня морфогенетического белка Klotho, являющего ранним независимым маркёром почечной дисфункции и предиктором неблагоприятных кардиоваскулярных осложнений при ИМпST.

Ключевые слова: *белок Klotho, инфаркт миокарда с подъемом сегмента ST, почечная дисфункция, агрегометрия, остаточная реактивность тромбоцитов.*

Для цитирования:

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Түйіндеме

БҮЙРЕК ДИСФУНКЦИЯСЫ ЖӘНЕ ST СЕГМЕНТІНІҢ ЖОҒАРЫЛАУЫМЕН МИОКАРД ИНФАРКТІСІ БАР ЕМДЕЛУШІЛЕРДЕ KLOTHO САРЫСУ ДЕҢГЕЙІНІҢ КЛИНИКАЛЫҚ МАҢЫЗЫ

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Кіріспе: Бүйрек қызметінің бұзылуы бүгінде жаһандық денсаулық сақтау саласындағы басты мәселелердің бірі ретінде танылып отыр. Эпидемиологиялық зерттеулерге сәйкес, оның жаһандық таралуы 13,4%-ға дейін жетеді. Шеткері коронарлық араласу (ШКА) жүргізілетін науқастар арасында бүйрек қызметі бұзылғандардың үлесі артып келеді. Бұл халықтың қартаюымен және қатар жүретін аурулардың жиі кездесуімен байланысты. Сонымен қатар,

созылмалы бүйрек ауруы (СБА) жүрек-қантамыр жүйесінің жағымсыз асқынуларының даму қаупін айтарлықтай арттырады, сондықтан мұндай науқастарды емдеу және бақылау стратегиясын таңдауда ерекше назар қажет.

Мақсаты: ST сегментінің жоғарылауымен жүретін миокард инфарктісі және бүйрек қызметінің бұзылысы бар науқастарда Klotho ақуызы мен жүрек-қантамыр ауруларының дәстүрлі қауіп факторлары арасындағы байланысты бағалау.

Әдістер мен материалдар: Зерттеу дизайны: көлденең клиникалық зерттеу. Зерттеу 2022–2023 жылдары "Семей медицина университеті" КЕАҚ университеттік госпиталінің кардиохирургия бөлімшесінде жүргізілді. Зерттеу әдістеріне тромбоциттердің қалдық реактивтілігін бағалау және Klotho ақуызының деңгейін анықтау кірді.

Зерттеу нәтижелері: Зерттеуге 123 пациент қатыстырылды. Klotho ақуызы деңгейі мен жас арасындағы кері корреляциялық байланыс анықталды (Rho = –0,673; p < 0,001).

Сонымен қатар, жылдамдықты шумақтық сүзілу (ЖШС) көрсеткіші мен сарысулық Klotho деңгейі арасында тура корреляциялық байланыс анықталды (Rho = 0,463; p < 0,001).

Бұған қоса, біз алғаш рет Klotho деңгейінің жалпы холестерин мөлшерімен (Rho = –0,417; p < 0,001) және С-реактивті ақуыз көрсеткіштерімен (Rho = –0,416; p < 0,01) арасындағы корреляцияны көрсеттік.

Қорытынды: СКФ деңгейі 60 мл/мин/1,73 м²-ден төмен болған жағдайда ST сегментінің жоғарылауымен жүретін миокард инфаркті бар науқастарда морфогенетикалық Klotho ақуызының деңгейін зерттеу орынды. Бұл ақуыз бүйрек функциясының ерте және тәуелсіз маркері болып табылады, сондай-ақ ST сегментінің жоғарылауымен жүретін миокард инфарктісі кезіндегі жүрек-қантамырлық асқынулардың болжамдық көрсеткіші ретінде қарастырылады.

Түйінді сөздер: *Klotho ақуызы, ST сегментінің жоғарылауымен жүретін миокард инфаркті, бүйрек қызметінің бұзылысы, агрегометрия, тромбоциттердің қалдық реактивтілігі.*

Дәйексөз үшін:

Жунуспекова А.С., Каражанова Л.К., Мансурова Д.А., Орехов А.Ю., Аккалиев М.Н., Қожабаева А.Д., Капакова М.А., Сатиева Г.С., Аширов Б.А. Бүйрек дисфункциясы және ST сегментінің жоғарылауымен миокард инфарктісі бар емделушілерде kKotho сарысу деңгейінің клиникалық маңызы // Ғылым және Денсаулық [Science & Healthcare]. 2025. Vol.27 (2), pp. 62-69. *doi 10.34689/SH.2025.27.2.008*

Introduction

Renal dysfunction (RD) is recognized as a major global public health issue, with its global prevalence estimated at up to 13.4%. Studies have shown that patients with chronic kidney disease (CKD) make up an increasing proportion of the population undergoing percutaneous coronary intervention (PCI). Meanwhile, RD patients are at high risk for adverse cardiovascular events such as recurrent myocardial infarction, heart failure, and stroke [4]. RD is one of the most common comorbidities in this patient population and occurs significantly more frequently than in the general population [8]. To date, evidence has confirmed an inverse relationship between cardiovascular morbidity and mortality and kidney function, particularly when the glomerular filtration rate (GFR) drops below 15 mL/min/1.73 m² [17]. Currently, it is well-established that RD negatively affects both in-hospital prognosis and long-term outcomes, and it is associated with poor results following myocardial revascularization [2]. Given these facts, it is necessary to identify new and early predictors of RD in order to improve the detection of patients at high risk of complications. In this context, the morphogenetic protein Klotho has attracted increasing scientific interest.

In recent years, the prognostic role of morphogenetic proteins has become increasingly important. The Klotho gene was discovered by Japanese researcher Makoto Kuro-o in 1997. Klotho is a 130-kDa transmembrane protein produced primarily in the distal convoluted tubules of the kidneys and in various other organs involved in regulating the aging process in humans [6, 16]. Currently, two forms of the Klotho protein have been identified: membrane-bound and secreted, each performing different functions. The secreted form of Klotho has been associated with cardiovascular events and mortality in the general population. The relationship between secreted Klotho and cardiovascular diseases and mortality was initially studied in populations without RD. In a cohort of 804 elderly individuals (>65 years) followed for six years, patients with low serum Klotho levels had a higher risk of death. Klotho deficiency leads to atherosclerosis, skin atrophy, osteoporosis, and aging-like syndromes. Interestingly, these phenotypes resemble those of patients with RD, suggesting that Klotho is closely linked to the pathogenesis of CKD [11, 13]. It is important to emphasize that previous studies have shown that low serum Klotho levels are associated with a higher risk of cardiovascular complications and mortality in patients with renal dysfunction [1].

Materials and Methods

This cross-sectional study included 123 consecutive patients with ST-segment elevation myocardial infarction who were admitted to the cardiac surgery department of the university hospital of NJSC "Medical University of Semey" between 2022 and 2023. All patients underwent percutaneous coronary intervention (PCI), and residual platelet reactivity (RPR) was assessed using optical aggregometry.

Inclusion criteria: STEMI with estimated glomerular filtration rate (GFR) ≤ 60 mL/min/1.73 m² following PCI with stenting; Use of dual antiplatelet therapy (DAPT) with a P2Y12 receptor inhibitor and acetylsalicylic acid (ASA).

Exclusion criteria: Patients with end-stage renal disease who were already receiving hemodialysis; Presence of oncological diseases; Antiplatelet drug intolerance; Refusal to participate in the study.

The study was conducted in accordance with the Declaration of Helsinki. The study design was approved by the local ethics committee (Protocol No. 6 dated March 16, 2022). All patients provided written informed consent prior to participation.

To determine renal filtration function, GFR was calculated using the Cockcroft–Gault formula [12]. Traditional cardiovascular risk markers were also assessed, including lipid profile, blood glucose, and complete blood count (CBC) with platelet count following myocardial revascularization.

Residual platelet reactivity (RPR) was measured using an AggRAM aggregometer (Helena) with 10 µg/mL ADP stimulation and reagents from "Technology-Standard" (Barnaul, Russia).

All patients received 325 mg of aspirin and a loading dose of 600 mg clopidogrel or 180 mg ticagrelor, followed by maintenance doses of 100 mg/day aspirin and 75 mg/day clopidogrel or 90 mg/day ticagrelor.

Prior to PCI, venous blood was collected in EDTA tubes to determine serum Klotho levels. Serum Klotho was analyzed using a Bio-RAD Model-680 spectrophotometer and an ELISA kit (SEH757Hu, China).

Statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Quantitative variables with a normal distribution were presented as mean ± standard deviation (M ± SD), along with minimum and maximum values. Between-group comparisons were performed using the independent samples Student's *t*-test. For non-normally distributed variables, data were presented as median and interquartile range (Me, IQR), together with minimum and maximum values, and compared using the Mann–Whitney *U* test. Dichotomous variables were expressed as frequencies and percentages (n, %). Associations between categorical variables were analyzed using Pearson's chi-square test; where applicable, Yates' continuity correction or Fisher's exact test was employed. Differences were considered statistically significant at $p < 0.05$.

Results

A total of 123 patients with STEMI and concurrent renal dysfunction were included in the study. The mean age of the patients was 64.7 ± 8.9 years; the youngest was 43 years old, and the oldest was 87. The mean age for men was 63.6 ± 8.9 years, and for women — 67.9 ± 8.4 years (Figure 1).

Among the participants, 92 (74.8%) were men and 31 (25.2%) were women. Men were significantly younger than women (p = 0.031) (*Table 1).*

Correlation analysis showed a moderate negative correlation between age and serum Klotho levels (Rho = –0.673; p < 0.01), suggesting that Klotho concentrations decrease with age (p < 0.001).

Figure 2 shows serum Klotho levels by age. The analysis confirms a trend toward decreasing levels of this morphogenetic protein with age in patients with RD, likely due to decreased Klotho gene expression and the development of chronic low-grade inflammation, including in Klotho-producing cells.

A positive correlation was observed between GFR and serum Klotho levels (Rho = 0.463; p < 0.01). The lowest Klotho levels were recorded in patients with the lowest GFR (Figure 3).

Anemia (Hb < 120 g/L) was diagnosed in 9 patients (7.3%). A significant positive correlation was found between hemoglobin levels and serum Klotho (Rho = 0.247; p < 0.01) (Figure 4).

Additionally, there was a negative correlation between serum Klotho and: Hypercholesterolemia (Rho = –0.417; p < 0.01), Elevated blood glucose (Rho = –0.315; p < 0.01), High C-reactive protein (CRP) compared to normal levels (Rho = –0.416; p < 0.01)

A weak negative correlation was also found between platelet aggregation activity (residual platelet reactivity, RPR) and serum Klotho levels (Rho = –0.339; p < 0.01). (Figure 5).

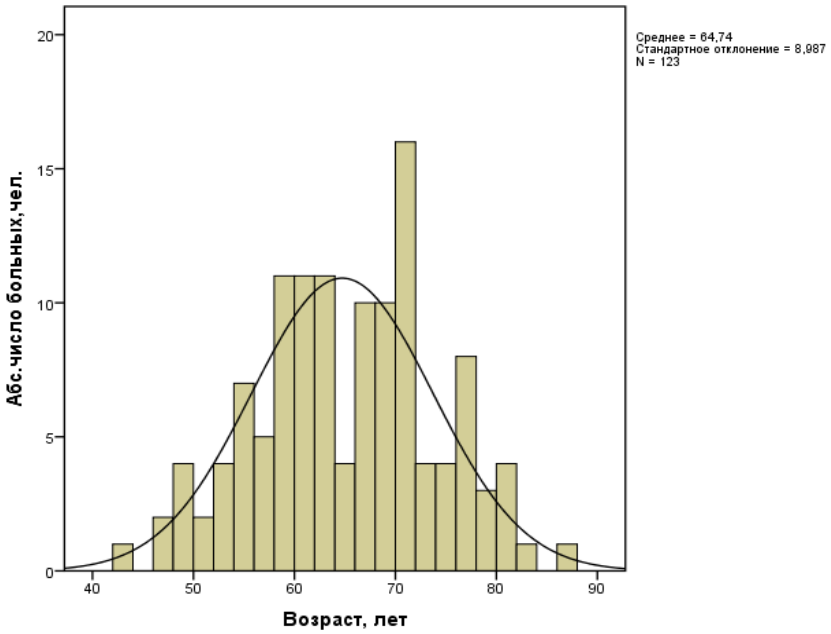

Figure 1. Distribution of patients by age.

Table 1.

General clinical and laboratory characteristics of the patients.

Indicator	Patients (n = 123; 100%)
Age, years	65 ±9 (43 - 87)
Body Mass Index, kg/m²	27,8±4,2 (19,4-39,9)
Overweight, n (%)	86(75%)
Smoking, n (%)	50(40,7%)
Family history, n (%)	35(28,5%)
Arterial hypertension (Grade I–II), n (%)	121(98,4%)
Compensated diabetes mellitus in anamnesis, n (%)	28(22,8%)
Iron deficiency anemia in anamnesis, n (%)	9 (7,3)
Systolic BP, mmHg	127,8 ±22,1
Diastolic BP, mmHg	76,6 ±17,1
Heart rate, bpm	76,1±14,7 (42-153)
Killip I, n (%)	5(42,3%)
Killip II, n (%)	56(45,5%)
Killip III n (%)	1(0,8%)
Killip IV, n (%)	14(11,4%)
Left ventricular EF, %	50,2±7,0 (29-66)
Hemoglobin, g/L	143,6±18,7 (80-180)
GFR, mL/min/1.73 m²	49,4±10,4 (21-60)
Glucose, mmol/L	6,4±1,6 (3,0-14,3)
Cholesterol, mmol/L	6,1±1,8
Triglycerides, mmol/L	1,9±0,9
LDL, mmol/L	2,8±1,0

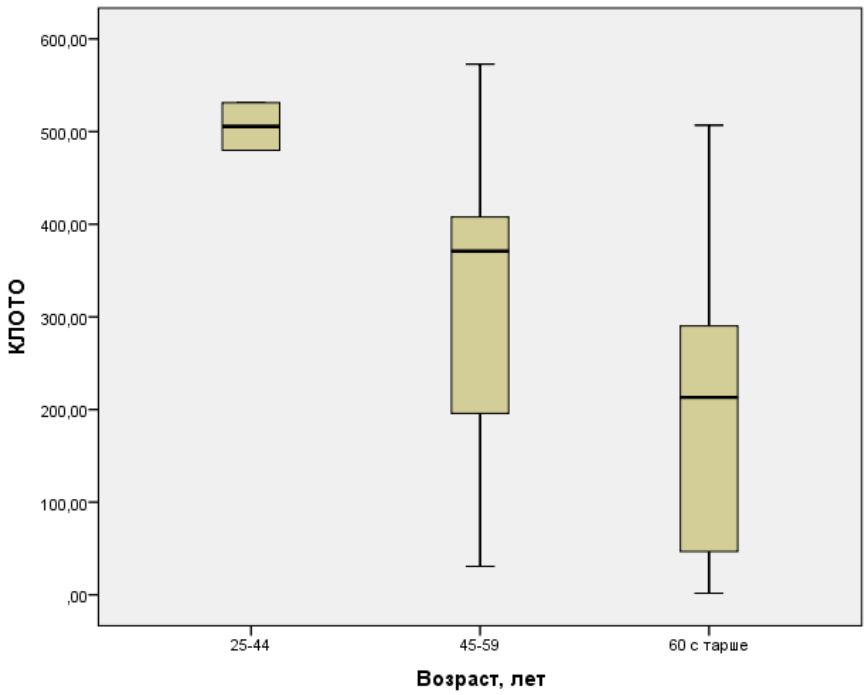

Figure 2. Serum Klotho levels in relation to age.

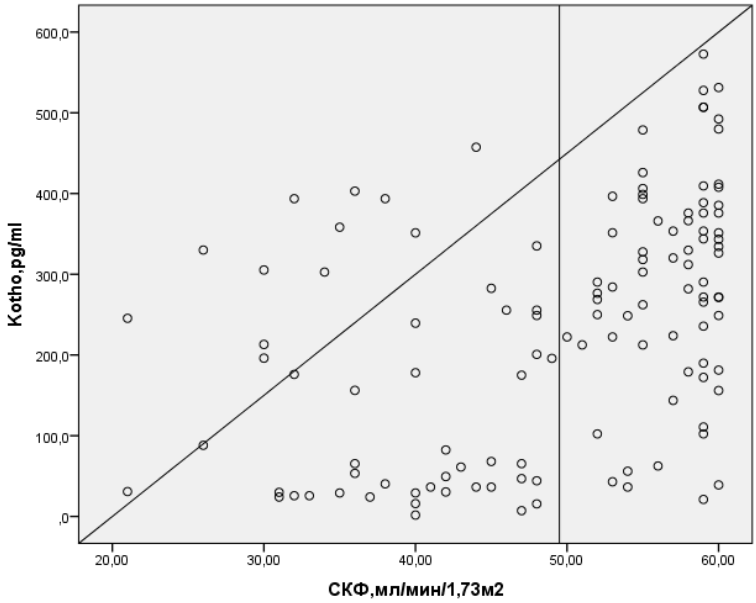

Figure 3. Relationship between serum Klotho levels and GFR.

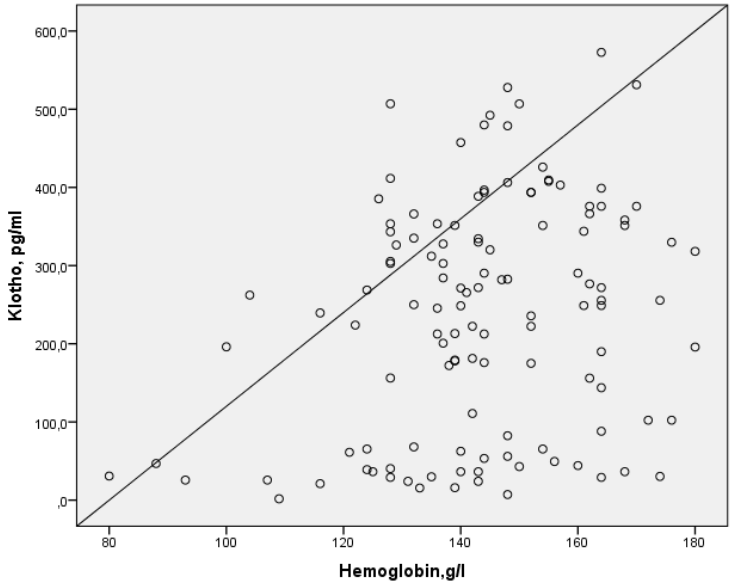

Figure 4. Relationship between Klotho and hemoglobin levels.

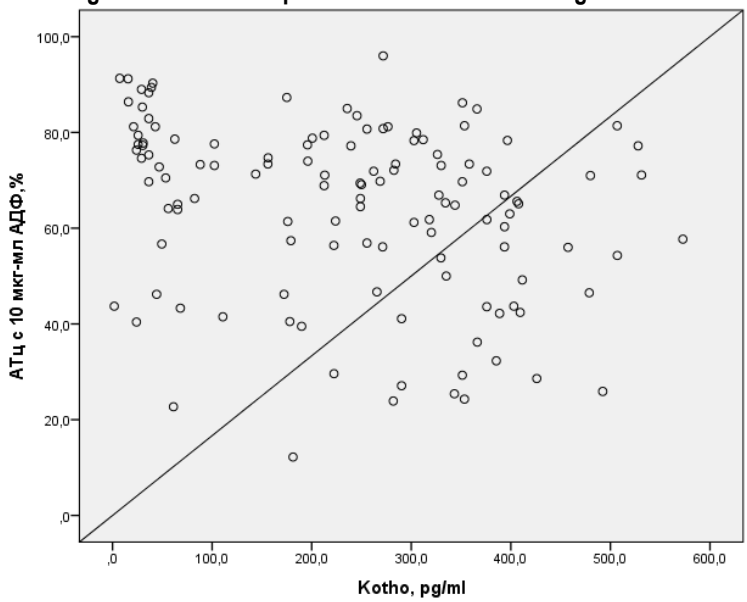

Figure 5. Correlation between RPR and serum Klotho levels.

Discussion

Renal dysfunction in patients with STEMI is one of the key predictors of mortality both during hospitalization and in the long-term perspective.

In studying the relationship between Klotho protein levels and age in STEMI patients with RD, it was found that the highest serum Klotho levels were observed in patients aged 25–44 years. Our findings are consistent with other researchers who have referred to Klotho as the "protein of youth" [14, 20].

In our study, a reduction in serum Klotho levels was found in STEMI patients with RD. Ivana Pavik and colleagues also noted that with every 1 mL/min/1.73 m² decrease in GFR, the average Klotho level decreased by 4.8 pg/mL [15]. Renal dysfunction is an independent predictor of major adverse cardiovascular events (MACE) in myocardial infarction patients. For example, a cohort study conducted in Denmark from 2010 to 2022 showed that mortality in MI patients with RD was significantly higher than in those with normal kidney function—21% (95% CI 20–22%) versus 16.4% (95% CI 16–17%), respectively [3].

Our study group deserves special attention because all patients underwent PCI, which is the gold standard for STEMI treatment. One important component of our evaluation was the inclusion of residual platelet reactivity (RPR), assessed using ADP-induced optical aggregometry. While the clinical effectiveness of DAPT with aspirin and clopidogrel has been proven in many studies, some patients still experience ischemic or recurrent events despite DAPT use [5, 18, 19]. The need for and safety of DAPT is well-established, but factors such as coronary blood flow anatomy, non-specific inflammatory processes, and comorbidities including RD can affect its efficacy [9].

Despite these facts, patients with RD remain an under-researched group, often excluded from randomized clinical trials due to non-compliance with inclusion criteria [7].

This study represents the first phase of a project investigating the role of Klotho protein in heart disease patients with RD. It is important to note that our analysis included only patients with STEMI and RD. To further explore the potential of Klotho as a biomarker, its prognostic value in patient survival should be assessed in future studies.

Conclusion

Thus, based on the conducted study, serum Klotho protein levels are not only a marker of renal dysfunction severity but also, apparently, a pathogenic factor in its progression. Further research into Klotho protein changes in renal dysfunction is necessary, and the implementation of Klotho measurement as an early diagnostic marker of cardiorenal injury should be considered.

Determining residual platelet reactivity (RPR) in the context of antiplatelet therapy in STEMI patients with renal dysfunction, in addition to standard clinical tests, helps identify patients at high risk of cardiovascular complications early during hospitalization. The results of this study highlight the need for further prospective research in this area.

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