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Original Article

Cardiovascular-kidney-metabolic syndrome in patients with acute forms of ischemic heart disease

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Abstract

The purpose of the study was to evaluate the cardiac and renal manifestations of cardiovascular-kidney-metabolic syndrome (CKMs) in patients of different glucometabolic categories. A total of 116 patients with ischaemic heart disease (IHD) and acute coronary syndrome aged 37 to 84 years were examined. Based on their carbohydrate metabolism status, they were divided into 5 groups: 24 patients with normal glucose regulation (NGR); 23 – with impaired fasting glycaemia (IFG); 21 – with impaired glucose tolerance (IGT); 24 – with a combination of IFG and IGT; 24 – with type 2 diabetes mellitus (DM). The patients underwent an oral glucose tolerance test, creatinine levels were determined by colorimetry, proteinuria was determined, and glomerular filtration rate (GFR) was calculated using the MDRD formula. In patients with acute forms of IHD, as carbohydrate metabolism deviated from NGR through IFG, IGT and combined prediabetic disorders leading to type 2 DM, a gradual stretching of the left heart chambers and an increase in their myocardial mass and indexed value were observed without affecting systolic function. At the same time, proteinuria and blood creatinine increased and GFR decreased, which may be manifestations of CKMs. Proteinuria directly correlated with total fibrinogen levels, and creatinine correlated with glucose at the end of the glucose tolerance test. Patients with acute forms of IHD may be diagnosed with CKMs, which manifests itself in gradual stretching of the left heart chambers and an increase in myocardial mass, increased proteinuria and blood creatinine with a decrease in GFR as carbohydrate metabolism deteriorates.

Keywords: cardiovascular-kidney-metabolic syndrome, creatinine, proteinuria, glomerular filtration rate, heart structure

Introduction

In 2023 the American Heart Association proposed a scientific rationale for the concept of cardiovascular-kidney-metabolic syndrome (CKMs) – a holistic systemic disorder characterised by the interaction of metabolic factors, the cardiovascular system and kidneys with multi-organ dysfunction and a significant number of adverse effects [1–3]. According to the *Euro Heart Survey*, only one third of patients with ischaemic heart disease (IHD) have normal glucose regulation (NGR), and all forms of diabetes mellitus (DM) develop in stages: impaired fasting glucose (IFG) → impaired glucose tolerance (IGT) → combined prediabetic disorder (CPD). It is believed that these metabolic disorders have different pathophysiological mechanisms and have different effects on cardiovascular diseases [4, 5]. Changes in carbohydrate metabolism deserve special attention because they are potentially reversible when active lifestyle modification and drug therapy can delay the development of diabetes or restore NGR [1, 6]. The problems in the management of patients with CKMs are identified that include ensuring an interdisciplinary approach, early prevention, strategies to support weight loss, the use of cardioprotective antihyperglycaemic therapy in patients with diabetes and

high cardiovascular risk and existing heart disease, and lipid-lowering therapy other than statins [6, 7]. Although the multiplicity of key mechanisms for the development and progression of CKMs has been proven [3, 8], a number of questions remain unanswered regarding the peculiarities of the manifestation of cardiovascular disease and metabolic dysfunction in CKMs, which determined the relevance and topicality of our study.

The purpose of the study was to assess cardiac and renal manifestations of cardiovascular-kidney-metabolic syndrome in patients of different glucose metabolic categories.

Material and methods

A total of 116 patients with IHD and acute coronary syndrome aged 37 to 84 years (median 63) were examined, including 51 women and 65 men. Based on their carbohydrate metabolism status, they were divided into 5 groups: 24 patients with NGR; 23 with IFG; 21 with IGT; 24 with CPD; 24 with type 2 diabetes mellitus. Glucose metabolism categories were determined based on the results of a fasting blood glucose test and a 120-minute oral glucose tolerance test in accordance with ESC/EASD recommendations. The patient groups did not differ significantly in terms of age (median test: $\chi2=1.4$, $p=0.78$), body mass index (BMI), waist circumference (WC) and hip circumference (HC), duration of hypertension, or blood pressure values (Table 1). Renal function was assessed by creatinine levels using a colorimetric method (normal range 50–100 μmol/L), urine analysis indicators, and glomerular filtration rate (GFR) calculated using the MDRD formula: $186.3\times (Kr/88.4)^{-1.154}\times(age)^{-0.203}\times(0.742$ for women). To determine the structural and functional condition of the heart, the results of standard echocardiography (Kontron Sigma 44 device; France) were used. The study was conducted in accordance with the principles of the Helsinki Declaration on Human Rights under the supervision of the Lviv National Medical University Bioethics Committee (protocol No. 2 as of 21.2.22) with the informed consent of the patients. The examination and treatment complied with national standards (Order of the Ministry of Health of Ukraine No. 1957 dated 15.9.21).

Statistical processing was performed using the software "Statistica for Windows 6.0" (Statsoft, USA). The distribution did not correspond to the Gaussian distribution, so the values are presented as the median [lower; upper quartiles]. Comparisons were made using the Mann-Whitney and $\chi2$ criteria. $p<0.05$ was taken as a level of significance.

Results

Analysis of the heart condition showed that as carbohydrate metabolism deteriorated, there was a gradual stretching of the left atrium (LA from 3.9 to 4.2 cm) and left ventricle (LVEDd from 5.6 to 6.1 cm) with less pronounced thickening of the interventricular septum (IVS from 1.1 to 1.2) and the posterior wall of the left ventricle (LVPW from 1.0 to 1.1 cm), while the ejection fraction (EF) remained in the moderate decrease zone (51% and 50%) (Table 2). This was accompanied by a significant increase in left ventricular myocardial mass (LVMM from 228 to 303 g) and its indexed value (iLVMM from 127 to 149 g/m^2).

Analysis of renal function showed that, unlike individuals with NGR, patients with any carbohydrate metabolism disorders had proteinuria of 0.021 [0.008; 0.049] *versus* 0 [0; 0.033] g/l. It was recorded significantly more often (87.7±3.4% *versus* 42.0±10.1%; $p<0.05$) and correlated with the content of the pro-inflammatory hepatokine of total fibrinogen ($r=0.39$; $p<0.05$). Serum creatinine was higher in cases of carbohydrate

Table 1: Comparative characteristics of patient groups.

Indicator	NGR	IFG	IGT	CPD	DM
Women/men	10/14	12/11	7/14	10/14	12/12
Median age	64.5	61.2	64.0	65.5	61.5
BMI, kg/m^2	27.4 [25.3; 33.5]	32.5 [27.8; 33.7]	29.2 [27.0; 31.9]	30.7 [28.7; 33.7]	30.5 [27.1; 36.2]
WC, cm	102 [89; 113]	108 [95; 117]	102 [98; 110]	109 [96; 115]	108 [99; 116]
WC/HC	0.95	0.96	0.96	0.96	0.94
Systolic pressure, mm Hg	138 [123; 150]	150 [120; 160]	140 [130; 150]	138 [128; 150]	155 [135; 160]

Table 2: Echocardiography, depending on the glucose metabolic state.

Indicator	NGR	IFG	IGT	CPD	DM
LA, cm	3.9 [3.7; 4.2] [3, 4]	3.9 [3.8; 4.1] [6, 7]	4.0 [3.7; 4.2]	4.2 [4.0; 4.5] [3, 6]	4.2 [3.8; 4.5] [4, 7]
LVEDd, cm	5.6 [4.8; 5.8] [3, 4]	5.5 [5.1; 5.8] [7]	5.8 [5.2; 6.3]	5.8 [5.5; 6.5] [3]	6.1 [5.4; 6.7] [4, 7]
LVPW, cm	1.0 [0.9; 1.15] [1, 3, 4]	1.1 [1.0; 1.2] [1]	1.1 [1.0; 1.2]	1.1 [1.1; 1.2] [3]	1.1 [1.0; 1.2] [4]
IVS, cm	1.1 [0.9; 1.20] [3]	1.2 [1.1; 1.30]	1.1 [1.0; 1.2]	1.2 [1.1; 1.3] [3]	1.2 [1.0; 1.2]
EF, %	51 [39; 60]	55 [50; 60] [6, 7]	55 [45; 60]	48 [43; 57] [6]	50 [45; 54] [7]
IVS relative thickness	0.39 [0.37; 0.46]	0.42 [0.39; 0.47] [7]	0.38 [0.37; 0.46]	0.39 [0.35; 0.44]	0.38 [0.34; 0.41] [7]
LVPW relative thickness	0.38 [0.32; 0.42] [1]	0.43 [0.36; 0.44] [1, 6, 7]	0.38 [0.33; 0.43]	0.38 [0.34; 0.41] [6]	0.35 [0.33; 0.42] [7]
LVMM, g	228 [159; 270] [1, 2, 3, 4]	272 [217; 310] [1, 6]	271 [250; 324] [2]	302 [257; 354] [3, 6]	303 [250; 353] [4]
iLVMM, g/m²	127 [87; 140] [3, 4]	127 [107; 156]	136 [125; 164]	157 [125; 178] [3]	149 [127; 165] [4]

Note: The difference is significant (p<0.05) between the groups: [1] – NGR and IPG; [2] – NGR and IGT; [3] – NGR and CPD; [4] – NGR and DM; [5] – IFG and IGT; [6] – IFG and CPD; [7] – IFG and DM.

metabolism abnormalities (78.0 [70.1; 83.2] *vs.* 72.5 [64.0; 86.5] μmol/L; p<0.05), and GFR was lower (83.5 [69.5; 98.8] *vs.* 90 [74; 105] ml/min/1.73 m²; p<0.05). Creatinine levels correlated significantly with glucose levels at 120 minutes of the oral glucose tolerance test (r=0.21; p<0.05).

The division of patients into groups with progressive deterioration of carbohydrate metabolism showed that patients with concomitant diabetes mellitus had significantly more pronounced proteinuria (p_{DM-NGR}=0.001; p_{DM-IFG}=0.003; $p_{DM-IGT, CPD}$=0.007), higher creatinine levels (p_{DM-NGR}=0.026; p_{DM-IFG}=0.001; p_{DM-IGT}=0.041) and minimal GFR values (p_{DM-NGR}=0.078; p_{DM-IFG}=0.053; p_{DM-IGT}=0.036). First of all, these changes concerned men (for proteinuria indicators: p_{DM-IGT}=0.018, $p_{DM-NGR, CPD}$=0.064; creatinine: p_{DM-IFG}=0.051; GFR: p_{DM-NGR}=0.053, p_{DM-IFG}=0.019). Women with IGT, CPD and DM also had higher levels of protein in urine and creatinine in blood, and cases of proteinuria were more frequently recorded among them (Table 3).

An increase in GFR >120 ml/min/1.73 m² was found in 6% of the examined patients (all men), normal GFR values were found in 33.6% (4 women, 35 men); a decrease within the range of 60–89 ml/min/1.73 m² was

Table 3: Kidney function depending on glucose metabolism status.

Indicators	NGR, n=24	IFG, n=23	IGT, n=21	CPD, n=24	DM, n=24
Proteinuria, g/l	0 [0; 0.033] [2]	0 [0; 0.033] [5]	0.033 [0; 0.033] [6]	0 [0; 0.033] [7]	0.050 [0.033; 0.099] [2, 5, 6, 7]
Women	0.033 [0; 0.033] [1, 2]	0 [0; 0.033] [3, 5]	0.033 [0.033; 0.066] [1, 3]	0 [0.033; 0.066]	0.033 [0.033; 0.083] [2, 5]
Men	0 [0; 0.033]	0.033 [0; 0.033]	0 [0; 0.033] [6]	0 [0; 0.033]	0.066 [0; 0.099] [6]
Proteinuria, n/%	10/42 [2]	10/43.5 [5]	12/57	11/46 [7]	19/79 [2, 5, 7]
Women	5/50 [1, 2]	3/25 [3, 5]	7/100 [1, 3]	7/70	12/100 [2, 5]
Men	5/36	7/64	5/36	4/29	7/58
Creatinine, μmol/L	72.5 [64.0; 86.5] [2]	75.0 [66.0; 79.0] [5]	78.0 [67.0; 80.0] [6]	78.0 [71.5; 85.0]	81.0 [76.0; 89.0] [2, 5, 6]
Women	73.5 [64.0; 88.0]	75.0 [66.5; 77.5] [4, 5]	79.0 [63.0; 5.0]	80.5 [75.0; 5.0] [4]	82.0 [78.5; 9.0] [5]
Men	71.5 [64.0; 80.0]	76.0 [65.0; 80.0]	78.0 [67.0; 80.0]	76.0 [70.0; 80.0]	79.0 [72.5; 89.0]

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Table 3: Continued.

Indicators	NGR, n=24	IFG, n=23	IGT, n=21	CPD, n=24	DM, n=24
GFR, ml/min./1.73 m²	90 [74; 105]	91 [71; 113]	87 [76; 95] [6]	79 [66; 97]	77 [65; 90] [6]
Women	70 [57; 83]	71 [66; 80]	64 [59; 86]	66 [60; 74]	63 [52; 75]
Men	103 [91; 17]	95 [91; 115] [5]	92 [85; 104]	93 [85; 104]	88 [77; 101] [5]
↓ GFR, n/%	12/50	12/52	11/52	16/67	19/79
Women	9/90	10/83	6/86	10/100	12/100
Men	3/21	2/18	5/45	6/43	7/58

Note: Significant discrepancy ($p<0.05$) among the groups: [1] – NGR and IGT; [2] – NGR and DM; [3] – IFG and IGT; [4] – IFG and CPD; [5] – IFG and DM; [6] – IGT and DM; [7] – CPD and DM.

found in 50% (37 women, 21 men), and within the range of 59–45 ml/min/1.73 m² – in 10.3% (10 women, 2 men) (Figure 1). It should be noted that GFR was decreased in 92.2% of women ($p_{women.-men.}<0.0001$). That is, as carbohydrate metabolism deteriorated from NGR to diabetes mellitus, the proportion of patients with hyperfiltration and normal filtration progressively decreased (50.0% – 47. 8% – 47.6% – 33.3% – 20.8%) and the proportion with slight and moderate decrease in GFR increased (50.0% – 52.2% – 52.4% – 66.7% – 79.2%) (Figure 1).

Discussion

Thus, we found that as carbohydrate metabolism is disrupted from NGR through IFG, IGT, CPD, and DM, there are changes in the structural and functional condition of the heart and kidneys, which also progress in stages with minimum expression under NGR conditions and maximum expression in patients with diabetes type 2. This proves the existence of a pathogenetic combination such as CKMs in patients with acute IHD forms. According to epidemiological studies, a combination of atherosclerotic cardiosclerosis with chronic heart failure and metabolic disorders and progression of CKMs from stage 0 to stage 5 renal dysfunction is often recorded [5, 9, 10]. Previously, this was considered in terms of paired interactions: heart-metabolic disorders, heart-kidneys, kidneys-metabolic disorders, but the combination into a general syndrome explains the deepening of pathogenetic changes and rapid progression, which occurs through various mechanisms [5, 10].

CKMs begins with excess adipose tissue, the dysfunction of which (abdominal obesity) leads to hypersecretion of pro-inflammatory and pro-oxidative products that damage arterial, cardiac and renal tissue [8],

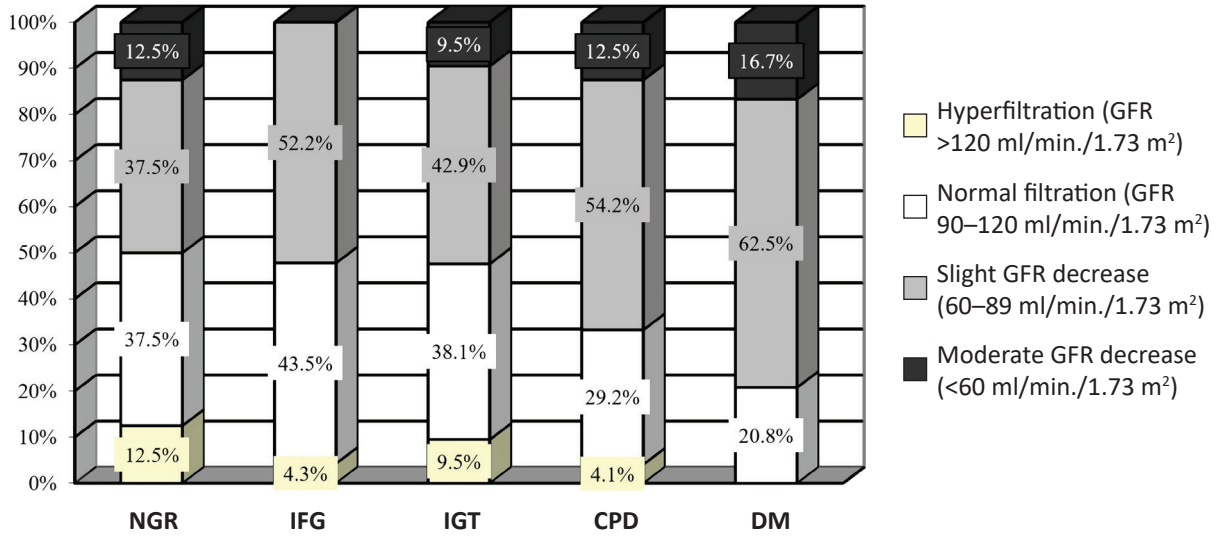

Figure 1: Frequency of detection (%) of rGFR changes in patients with IHD.

activate atherogenesis and myocardial damage, cause glomerulosclerosis, inflammation of the renal glomeruli, renal fibrosis, and activation of the renin-angiotensin-aldosterone system [11]. At the same time, there is progression of lipid metabolism disorders with manifestations of lipotoxicity [12]. In its turn, the inflammatory process reduces insulin sensitivity, leading to the progression of carbohydrate metabolism disorders and an increase in the number of glycated products [12]. Hyperglycaemia causes hyperfiltration in the glomeruli and arterial hypertension, which further damages the kidneys. Endoplasmic reticulum stress, abnormal calcium metabolism, and mitochondrial dysfunction with altered energy production are also observed [12]. In other words, the mechanisms of CKMs pathogenesis include metabolic, inflammatory, fibrotic, and haemodynamic components [11–13], which necessitates a review of the management strategy for such patients [6, 7].

Conclusion

In patients with acute forms of IHD, as carbohydrate metabolism deviates from normal glucose regulation through impaired fasting glycaemia, impaired glucose tolerance, and combined prediabetic disorders leading to type 2 diabetes mellitus, a gradual stretching of the left heart chambers and an increase in their myocardial mass and indexed value were observed without affecting systolic function. At the same time, proteinuria and blood creatinine increased and glomerular filtration rate decreased, which may be manifestations of cardiovascular-kidney- metabolic syndrome. Proteinuria directly correlated with total fibrinogen levels, and creatinine correlated with glucose at the end of the glucose tolerance test. Prospects for further research include the mechanisms of CKMs development and progression.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Danylo Halytsky Lviv National Medical University (Approval ID: 371).

Consent to participate

Written informed consent was obtained from all the participants.

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