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Cardiorenal connections in patients with type 2 diabetes mellitus and hypothyroidism

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Summary

Objective. *To study the cardiorenal connections in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (DM) in combination with primary hypothyroidism.*

Materials and methods. *The study included 203 patients: group 1 (76 patients) with type 2 DM and primary hypothyroidism, group 2 (127 patients) with type 2 DM without thyroid disease. All the participants underwent standard clinical examination, determination of the glomerular filtration rate by the level of creatinine and cystatin C (GFR-creat, GFR-cys), echocardiography, doppler ultrasonography of the lower extremity arteries, 24-hour ambulatory blood pressure monitoring (ABPM), endothelium-dependent vasodilation (Δd) assessment.*

Results. *The prevalence of CKD was 64.47±5.49% in group 1, and 44.88±4.41% in group 2 (p= 0.0059); the frequency of normoalbuminuric CKD (NA-CKD) was 32.89±5.39% and 16.54±3.3%, respectively (p=0.0103). Cardiovascular pathology was significantly more common in patients with NA-CKD compared with patients with diabetic nephropathy.*

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According to echocardiography, the left ventricular (LV) ejection fraction correlated with the level of creatinine (r= –0.2737; p= 0.0470), in group 1 — with albuminuria (r= –0.7871, p= 0.0005); in group 2 — with GFR-creat (r= 0.2148, p= 0.0407). LV isovolumic relaxation was associated with GFR-creat (r= –0.299, p= 0.0365) and GFR-cys (r= –0.9064, p= 0.0093) in group 2; LV myocardial mass index — with GFR-creat in group 1 (r= –0.5410, p=0.0305), GFR-creat in group 2 (r= –0.4235, p= 0.0252), GFR-cys in group 2 (r= –0.4207, p= 0.0634) and with albuminuria in both groups (r=0.3843, p=0.0157).

The concentration of cystatin C in both groups positively correlated with several ABPM and echocardiography parameters and negatively correlated with Δd.

Conclusion. *The combination of primary hypothyroidism and type 2 DM contributes to the increase of risk of cardiovascular pathology and CKD incidence. The strongest cardiorenal connections were shown in patients with normoalbuminuric CKD. The obtained data showed the importance of screening for thyroid dysfunction in patients with type 2 DM and cardiorenal pathology.*

Keywords: *cardiorenal syndrome, chronic kidney disease, diabetes mellitus, hypothyroidism, cystatin C.*

Conflict of interest: None declared.

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Introduction

Today, the connections between cardiovascular disease (CVD) and chronic kidney disease (CKD) in patients with diabetes mellitus (DM) are thoroughly investigated. Epidemiologic studies have shown that CKD is an independent risk factor of congestive heart failure (CHF), cardiovascular mortality [1] and significantly reduced quality of life [2]. CKD is associated with myocardial infarction (MI), stroke, peripheral artery disease (PAD) [1].

Cardiorenal syndrome (CRS) is a term that defines "disorders involving both the heart and the kidneys in which acute or chronic dysfunction in 1 organ may induce acute or chronic dysfunction in the other organ" [3].

Reduced glomerular filtration leads to sodium and water retention and hypervolemia, arterial hypertension (AH), increased left ventricular (LV) afterload with LV hypertrophy (LVH) [4]. CVD progression in diabetic patients with diabetic nephropathy and CKD is caused by additional risk factors (RF) such as albuminuria, systemic inflammation, autonomic neuropathy, anemia, oxidative stress, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency [5].

Along with DM, thyroid disorders are also highly prevalent. According to epidemiological data, the incidence of hypothyroidism manifestation is up to 10 % in general population and up to 6.9–35 % in diabetic individuals [6, 7]. Thyroid hormones play a major role in normal kidney and CVS functioning. Studies have shown that diabetic patients with concurrent symptomatic and subclinical hypothyroidism have earlier development of albuminuria, proteinuria and reduced glomerular filtration rate (GFR) [8].

Thyroid hormones not only directly regulate kidney function (filtration, secretion and reabsorption) but also have prerenal (indirect) effects on CVD and kidney perfusion [9].

Hypothyroidism is highly prevalent in diabetic patients. Negative effects of hypothyroidism include dyslipidemia, endothelial dysfunction, rise in peripheral vascular resistance and antidiuretic hormone production and are associated with CVD and CKD. Therefore, the objective of this study was to investigate cardiorenal connections in patients with CKD and coexistent DM and hypothyroidism; evaluate diagnostic values of cystatin C as a marker of CRS in this group of patients.

Materials and methods

Our study included 203 patients with DM that were divided into two groups: group I — 76 participants with type 2 diabetes (T2D) and primary hypothyroidism (PH) (T2D+PH) (n=76, 21 men, 55 women): autoimmune thyroiditis — n=45, postoperative hypothyroidism — n=31; group II — patients with T2D without thyroid disease (T2D) (n=127, 38 men, 89 women). The two groups didn't have any statistically significant differences in the age, sex and the duration of T2D of the participants (Table 1) and also in the type of antihypertensive, anti-anginal, hypoglycemic and hypolipidemic therapy.

We collected anthropometric parameters, evaluated the levels of hemoglobin A1C, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerids (TG), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), thyroid-stimulating hormone (TSH), thyroxine (T4). Cystatin C levels were evaluated using the Human Cystatin C ELISA. Albuminuria was evaluated in a single urine portion with the NycoCard reader. GFR was calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on the creatinine level (CKD-EPI-creat) and cystatin C (CKD-EPI-cys). 24-hour blood pressure monitoring was performed with Valento monitor, Russia. Echocardiography (Echo) was performed with the Acuson Sequoia 512 (Siemens, USA) system. PAD was verified using the LOGIQbookXP, China ultrasound machine. Endothelium-dependent vasodilation was assessed with the D. Celermajer (1999 r.) method based on the brachial artery diameter changes (Δd).

Patients with active urine tract infections (UTI) and CKD stages 4–5 were excluded from the study.

Statistical analysis was performed using the "Statistica 10.0" software. The Kolmogorov-Smirnov test was used to check if the set of data came from a normal distribution. Quantitative (numeric) values were summarized using the median with the upper and lower quartiles — Me [Q25; Q75]. Qualitative (ategorical) values summarized using the proportions (%). The Mann-Whitney U test was used to compare differences between two independent groups. The Spearman rank correlation coefficient (Spearman ρ) was used to determine the relation existing between two sets of numeric data.$p<0.05$ was considered statistically significant.

Study protocol was approved by the local Ethics Committee. Informed consents were obtained prior to participation in the study.

Results and discussion

The main clinical and laboratory values are presented in Table 1. The comparison of the two groups identified higher levels of hemoglobin A1c, lipids, HOMA-IR in group I that is similar to the data presented in other research works: most studies have shown that patients with T2D and hypothyroidism have increased insulin resistance and reduced glucose uptake. Primary hypothyroidism is associated with atherogenic dyslipidemia [10].

The prevalence of AH, CAD, PAD, as well as history of MI, arrythmias and AF was higher in patients with T2D and PH (Figure 1).

Today, along with the rising number of cases of classic albuminuria there's an increase in normoalbuminuric diabetic kidney disease (NADKD) prevalence especially in diabetic patients. This is possibly due to the use of antihypertensive medications with antialbuminuric effects; increased effectiveness of hypolipidemic therapy; the use of new hypoglycemic medications with nephprotective effects. On the one hand, NADKD is associated with lower risk of end-stage renal disease; on the other hand, the risks of MI, stroke, cardiovascular and all-cause mortality in T2D [11].

Table 1. **The main clinical and laboratory values**

Value	Group I (T2D+PH)	Group II (T2D)	p*
Age, years	60.5 [55.0;66.0]	59.0 [53.5;63.0]	0.4118
Duration of T2D, years	11.0 [5.0;16.0]	10.0 [7.0;14.0]	0.6209
TSH, mU/L	5.51 [2.93;11.08]	1.655 [1.26;2.5]	0.00000000007
T4., nmol/L	12.7 [10.8;14.1]	13.85 [12.3;15.8]	0.0404
HbA1c, %	8.9 [7.9;11.3]	8.0 [7.1;9.0]	0.0253
HOMA-IR	5.7 [3.14;8.32]	2.83 [1.9;9.36]	0.027
Total cholesterol, mmol/L	6.29 [5.55;7.43]	5.75 [5.0;6.6]	0.0011
LDL, mmol/L	3.84 [3.38;4.58]	3.41 [2.8;4.0]	0.0062
HDL, mmol/L	1.1 [0.89;1.22]	1.27 [1.05;1.46]	0.0062
TG, mmol/L	2.27 [1.76;2.8]	1.635 [1.225;2.15]	0.0012
Albuminuria, mg/L	16.0 [5.0;50.0]	5.5 [0;20.0]	0.018
Creatinine, μmol/L	88.0 [78.0;99.0]	85.5 [72.0;95.0]	0.044
GFR, ml/min/1.73 m^2 (CKD-EPI-creat)	59.0 [50.0;72.0]	66.0 [54.0;81.0]	0.0281
Cystatin, ng/ml	1058.0 [976.55;1110.0]	1282.5 [1087.0;1417.0]	0.0321
GFR, ml/min/1.73 m^2 (CKD-EPI-cys)	67.0 [63.0;74.0]	51.5 [45.0;65.0]	0.0271

Note. CKD — EPI — The CKD Epidemiology Collaboration, GFR — glomerular filtration rate, HbA1c — hemoglobin A1c, HDL — high-density lipoprotein, HOMA-IR — Homeostatic Model Assessment for Insulin Resistance, LDL — low-density lipoprotein, PH — primary hypothyroidism, T2D — type 2 diabetes, T4 — free thyroxine, TSH — thyroid-stimulating hormone. * — $p<0.05$ is considered statistically significant.

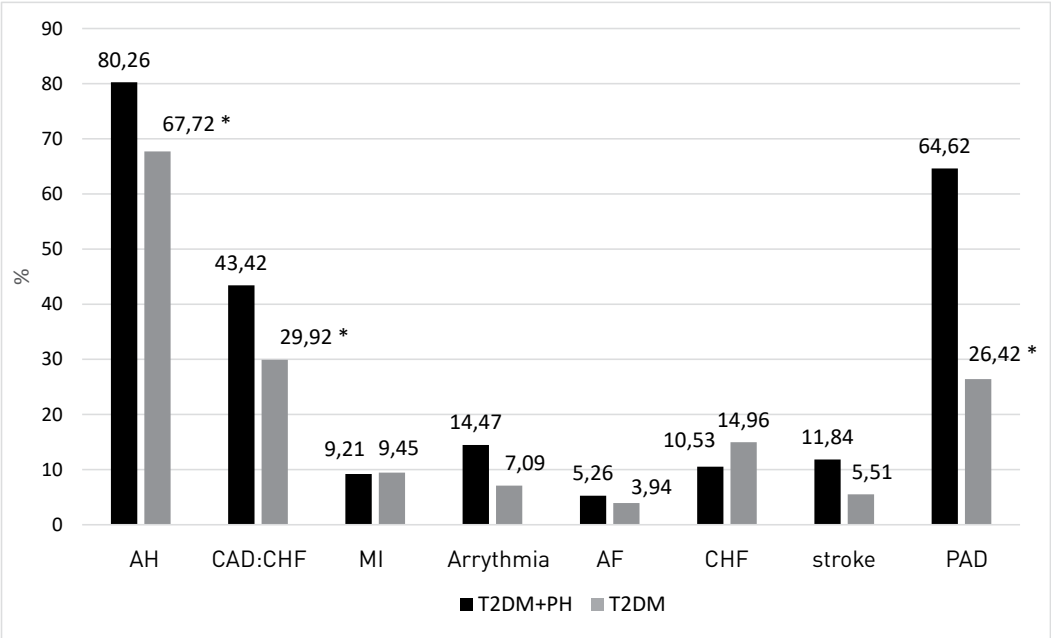

Figure 1. Cardiovascular disease prevalence in the T2D+PH and T2D groups.
Note. AF — atrial fibrillation, AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, PAD — peripheral artery disease, PH — primary hypothyroidism. T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

In this study, the prevalence of CKD in the 1st group was higher than in the 2nd group. The prevalence of classic albuminuric diabetic nephropathy was similar in both groups, and the prevalence of NADKD was twice as high in T2D-PH group as in T2D group (Table 2).

More patients with NADKD had CVD (Figures 2, 3). Diabetic nephropathy often co-existed with diabetic retinopathy — in 43.75±12.81 % and 72.73±9.72 % cas-

Table 2. **Kidney dysfunction in patients with T2D and PH**

Value	Group I (T2D+PH)	Group II (T2D)	p*
Diabetic nephropathy, %	21.05±4.68	17.32±3.36	0.518
NADKD, %	32.89±5.39	16.54±3.3	0.0103
Kidney stones, chronic pyelonephritis, %	10.53±3.52	11.02±2.78	0.9129
Total cases of CKD, %	64.47±5.49	44.88±4.41	0.0058

Note. CKD — chronic kidney disease, NADKD — normoalbuminuric diabetic kidney disease, PH — primary hypothyroidism. T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

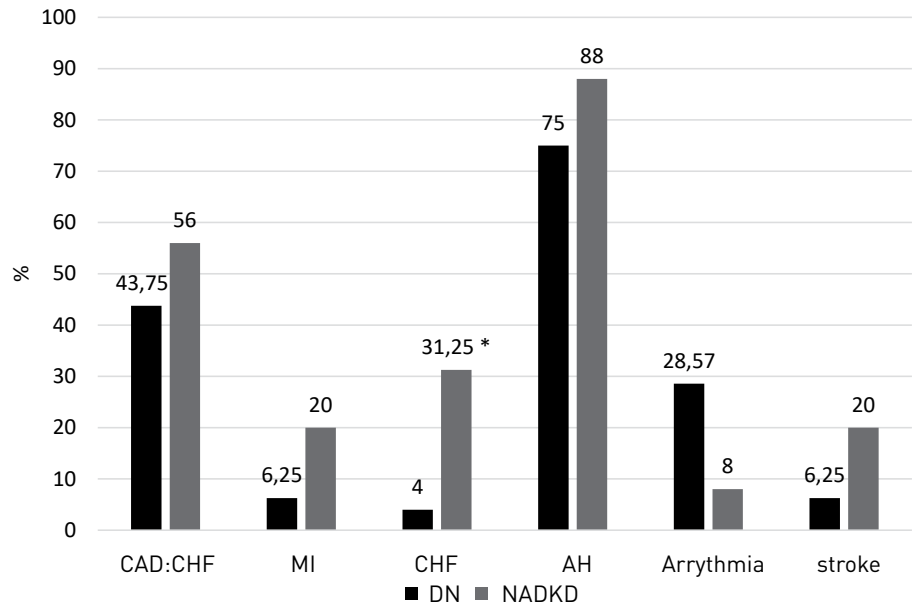

Figure 2. Prevalence of cardiovascular disease in patients with DN and NADKD in the T2D group.
Note. AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, DN — diabetic nephropathy, NADKD — normoalbuminuric diabetic kidney disease, T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

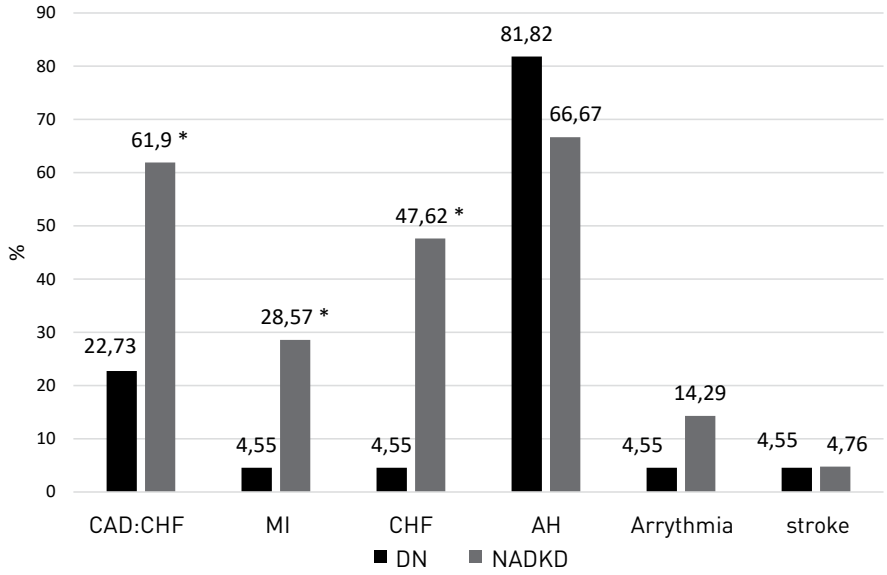

Figure 3. Prevalence of cardiovascular disease in patients with DN and NADKD in the T2D group.
Note. AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, DN — diabetic nephropathy, NADKD - normoalbuminuric diabetic kidney disease, T2D — type 2 diabetes. * — p<0,05 is considered statistically significant.

es in groups 1 and 2, respectively (p=0.0801). That is a sign of the nephron-retinal syndrome development.

The analysis of AH and CKD connection using the 24-hour blood pressure monitoring has shown that the 24-hour systolic and diastolic blood pressure indices were higher in patients with stage C3a and C3b CKD compared with in those with GFR>60 ml/min/1.73 m^2 in both groups. This is a sign of the 24-hour blood pressure rhythm imbalance and insufficient blood pressure decrease during nighttime (Figure 4). Patients with stage C3a and C3b CKD had faster and more pronounced systolic and diastolic blood pressure elevation in the morning.

According to echocardiography findings in patients with stage C3 CKD the median thickness of interventricular wall was 13.0 [12.0; 14.0] mm, the median thickness of left ventricular posterior wall was 12.85 [12.0;13.5] mm; in patients with GFR>60 ml/min/1.73 m^2–12.0 [11.0; 13.0] mm (p=0.0462) and 12.0 [11.0;13.0] mm (p=0.0593), respectively. The maximal IVRT was identified in patients with stage 3 CKD — –0.12 [0.10; 0.12] sec, in СКФ≥90 ml/min/1.73m^2–0.095 [0.09; 0.1] sec (p=0.0296).

Left ventricular ejection fraction (LVEF) reversely correlated with creatinine level (r=–0.2737, p=0.047) and with albuminuria in group I (r=–0.7871, p=0.0005);

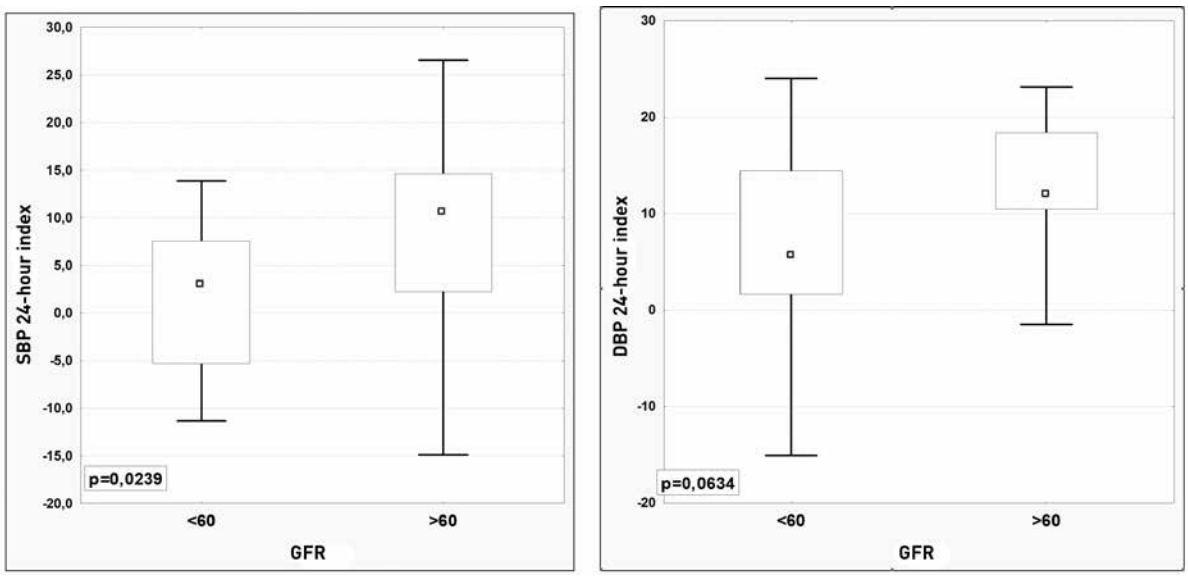

Figure 4. Systolic (SBP) and diastolic (DBP) blood pressure 24-hour indices in patients with different glomerular filtration rate (GFR) values

and positively correlated with GFR-creat in group II (r=0.2148, p=0.0407). IVRT correlated with GFR-creat and GFR-cys in group II: r=–0.299 (p=0.0365) и r=–0.9064 (p=0.0093), respectively. A strong correlation between the left ventricular (LV) mass with GFR-creat in group I (r=–0.541, p=0.0305), GFR-creat in group II (r=–0.4235, p=0.0252), GFR-cys in group II (r=–0.4207, p=0.0634); with albuminuria in both groups (r=0.3843, p=0.0157).

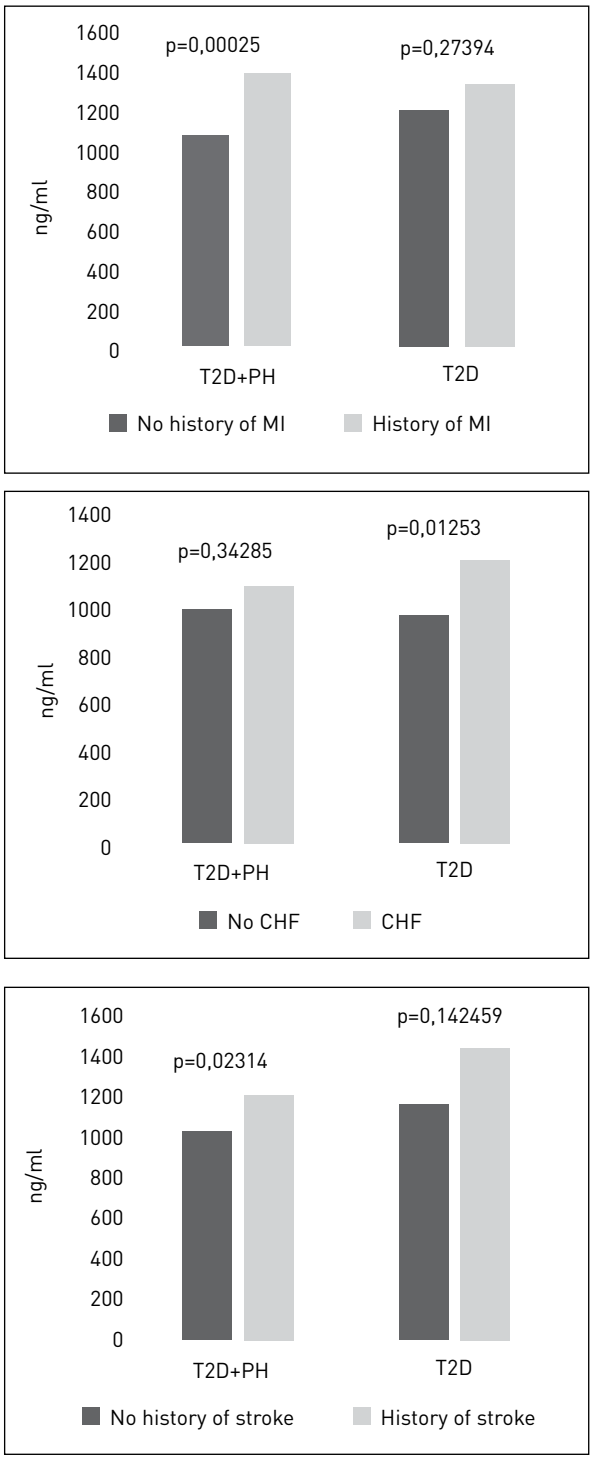

Figure 5. Cystatin C values in patients from T2D+PH and T2D groups with cardiovascular disease

The latest data show that cystatin C is not only an early marker of kidney dysfunction but also of cardiorenal syndrome, CHF, ACS, and a cardiovascular risk factor in general. Cystatin C is thought to play a role in systemic inflammation [12]. Some studies have also shown that thyroid hypothyroidism is associated with lower levels of Cystatin C [13].

According to our results, the levels of cystatin C were lower in group I compared with group II — 1019.0 [976.55;1097.5] and 1350 [1087.0;1485.0] ng/ml, respectively, (p=0.008542) and correlated with T4 levels (r=0.5798, p=0.0278).

In group II cystatin C levels correlated with age (r=0.5934, p=0.0032), 24-hour blood pressure monitoring parameters: DBP variability (r=0.585, p=0.0269), DBP index (r=0.6585, p=0.0269), 24-hour SBP index (r=–0.4661, p=0.0028); echocardiography parameters — IVS thickness (r=0.3625, p=0.1243) and left ventricular posterior wall thickness (r=0.4566, p=0.0033), LV IVRT (r=0.7121, p=0.0679), LV mass (r=0.5666, p=0.0056), endothelium-dependent vasodilation parameter Δd (r=–0.6868, p=0.0332).

In T2D+PH group cystatin C levels correlated with DBP (r=0.4958, p=0.0044), LVEF (r=–0.3633, p=0.0764), LV IVRT (r=0.3286, p=0.0893), aortic wall thickness (r=0.7595, p=0.0028), and Δd (r=–0.2765, p=0.1386).

Cystatin C levels were increased in patients with CHF with a history of prior MI and with a history of stroke (Figure 5). Cystatin C levels were also increased in patients with LVH and LV diastolic dysfunction according to echocardiography. However, these differences weren't statistically significant.

Conclusion

Primary hypothyroidism together with type 2 diabetes causes increased insulin resistance, lipid and carbohydrate imbalance, increased risk of cardiovascular and chronic kidney disease. There is also a mild risk of CVD and CKD in normoalbuminuric CKD.

High prevalence of CKD and CVD in patients with co-existent T2D and hypothyroidism means that PH screening is necessary in patients with T2D and CVD.

The associations between cystatin C and 24-hour blood pressure monitoring and echocardiography parameters allow us to recommend it as a cardiorenal syndrome marker in patients with T2D.

Conflict of interest: none declared.

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