THE RELATION BETWEEN THE LEVEL OF URIC ACID AND REMODELING OF THE MYOCARDIUM AND CAROTID ARTERIES IN PATIENTS OF THE HOSPITAL OF THE MEDICAL CENTER OF THE ADMINISTRATIVE DEPARTMENT OF THE PRESIDENT OF THE REPUBLIC OF KAZAKHSTAN

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Abstract: The aim of the study was to establish and evaluate the character of associations between the level of uric acid (UA) and myocardial remodeling of (MR) and carotid remodeling (CR) in patients with arterial hypertension (AH). The authors used secondary data obtained from the hospital information database. Patients were divided into groups by sex, age, no remodeling, carotid remodeling (CR), myocardial remodeling (MR), and carotid and myocardial remodeling (CR and MR). The analysis showed that with aging, the share of patients without remodeling decreased (38.4% of patients younger than 45 years old vs 14.3% of patients aged 45 and older. The share of patients with RCA (38.4% vs 51.0%) and the share of patients with RM and RCA (11.15% vs 27.3%) increased, and the share of patients with RM decreased from 12.1% to 7.5%. One-sided ANOVA analysis for the evaluation of the levels of UA in groups divided by the parameter of remodeling showed that the level of UA was significantly different, $F(3, 374) = 2.895$, $p < 0.05$. In the group of patients that did not have remodeling, it was 341.84 ± 73.46; in the group with CR, it was 339.7 ± 78.69; in the group with MR, it was 343.39 ± 84.36; and in the group with CR and MR, it was 367.4 ± 71.18. Tukey's test showed that an increase in the level of UA in the group of patients with MR and CR (27.73, 95% CI (from 52.81 to 265)) was statistically significant ($p < 0.05$). The results of the present study indicate that, in the studied population, MR was performed earlier, and CR – later (the number of such patients was higher). Also, probably, the level of UA was not associated with MR and CR. However, it was significantly higher in the group of patients with MR and CR, which could be associated with the progressing of AH.

Keywords: uric acid, carotid remodeling, myocardial remodeling, Kazakhstan.

Introduction

The issue of cardiovascular diseases (CVD) is very acute in Kazakhstan because they represent the leading cause of lethality in the country. Thus, in 2017, the lethality rate from CVD was 174.83 per 100,000 and the morbidity rate was 2595.7 per 100,000

[1]. In the structure of CVD, AH is one of the significant but modifiable factors of the development of IHD and multifocal atherosclerosis [2,3]. One of the controversial factors of the development of AH is the level of uric acid (UA). Despite the fact that updated recommendations of the European Cardiologic Society acknowledge UA as a factor that influences the cardiovascular risk in patients with AH (2018) [4], until now, the influence of UA on the development of AH still provoke discussion. Some studies confirm the role of UA in the pathogenesis of AH. The mechanism of its action is unclear. However, there is a theory that UA exerts effect via the activation of the renin-angiotensin system [5]. Another possible explanation for the hypertensive effect of UA is the production of anti-inflammatory cytokines, like CRP, interleukins 1, 6, and TNF [6], which promotes the development of endothelial dysfunction and formation of vascular stiffness. One of the possible mechanisms of the damaging effect of UA is oxidative stress caused by hyperuricemia [7].

It should be mentioned that the ability of UA to affect the development of AH is well described in the publications [8] but the association between the level of UA and the damage of target organs is still understudied. In particular, the development of myocardial remodeling is probably associated with higher levels of UA. Such studies as LIFE [9], PAMELA [10], and others that were performed among the Italian [11], Chinese [12], and Taiwanese [13] population confirm this hypothesis. Nearly all of them demonstrated the association between the level of UA and the processes of myocardial remodeling. Moreover, a prognostic significance of UA is discussed. Besides, there is evidence that the indication of drugs that decrease the levels of UA can have a reverse influence on the processes of myocardial hypertrophy [14]. When it comes to the remodeling of the carotid artery, some studies confirm the influence of the level of UA on the increase in the thickness of the intima-media complex [15,16,17]. This effect could be provided by the atherogenic properties of UA that exerts an inflammatory effect on the vascular endothelium via the oxidative stress [18,19] or in addition to the harmful effect of urates that appear due to the excessive levels of UA in the blood [20]. Thus, the pathogenetic association between UA and the processes of remodeling is understudied. The studies of these aspects are ongoing and relevant for the prognosis of the damage of target organs in patients with AH with the possibility of its correction. In the present study, the authors tried to show the association between the level of UA and MR and CR among the studied Kazakhstani population.

Materials and Methods

In the present study, the authors used secondary data obtained from the hospital database of the Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan (Hospital). The data included the results of biochemical, instrumental, and general clinical tests performed in 2018. The study included the data of 591 patients that were divided into two groups by age: young patients (younger than 44 years old) and senior patients (44 years old and older). The criterion for the entry to the study was diagnosed arterial hypertension and follow-up monitoring at the hospital. The level of UA was measured by the method of photometry with the analyzer Abbott Architect c 8000 (USA). The reference values of the norm for men were 210-420 μmol/L and for women - 150-350 μmol/L.

Carotid remodeling was diagnosed based on the results of color duplex scanning performed with a cardiovascular ultrasound scanner Vivid E9 (GE Healthcare's, USA). The thickness of the intima-media complex of the carotid arteries more than 0.9 mm indicated carotid remodeling (CR). Myocardial remodeling (MR) was diagnosed based on the results of echocardiography performed with an ultrasound scanner Vivid E9 (GE Healthcare's, USA). MR was registered based on the left ventricular mass index (LVMI) that was

calculated by the following formula: left ventricular weight / area of the body surface. Myocardial remodeling was registered at LVMI > 115 g/m^2 in men and at LVMI > 95 g/m^2 in women, and in cases, when relative myocardial wall thickness (RMWT) was ≥ 0.43. RMWT was calculated by the following formula: the thickness of interatrial septum + the thickness of left ventricular back wall / final diastolic size [2]. Statistical analysis was performed in the software package SPSS Statistics 24. The authors performed correlation analysis and one-sided ANOVA. The significance was established at $p < 0.05$.

Results

The data obtained from 333 men (56.3%) and 258 women (average age was 51 ± 7.3 years old) were used in the present study. The participants were divided into two groups by the parameter of age: young patients (younger than 44 years old (19.6%)) and 45 years old (Diagram 1). The analysis showed that in the case of the distribution by the type of remodeling, there were some gender-related differences. Thus, 17.4% of women and 29.4% of men had MR and CR; 23.7% of women and 15.2% of men did not have remodeling revealed. Age-related differences were in the decrease in the share of patients without remodeling (38.4% at the age of 44 and younger vs 14.3% at the age of 45 years old and older), the increase in the share of patients with CR (38.4% vs 51.0%) and CR and MR (11.1% vs 27.3%), and the reduction of the share of patients with MR from 12.1% to 7.5%. Table 1 shows the results obtained in the study groups divided by the parameter of sex, age, and some qualitative parameters. An average level of UA was higher in men than in women: 375.75 and 307.84 μmol/L, respectively ($p<0.01$), the difference remained in each of the age groups, but the level of UA was higher in men aged 44 years old and younger (395.65) than in men aged 45 years old and younger (371.55 μmol/L) ($p < 0.05$); in women, it was 273.11 and 311.10 μmol/L in groups aged 44 years old and younger and 45 years old and older, respectively ($p < 0.05$). LVMI was higher in men (91.14 g/m^2) than in women (76.72 g/m^2) ($p<0.01$), and in men 44 years old and younger, LVMI was lower than in men aged 45 years old and older (83.82 g/m^2 and 93.40 g/m^2, respectively. The thickness of IMC was higher in men (1.01 mm) than in women (0.98 mm) ($p < 0.05$).

For the evaluation of the differences by the type of remodeling (no remodeling (n=66), CR (n=186), MR (n=33), CR and MR (n=93)), the authors used Kruskal-Wallis test (Diagram 2). During the test, the missing values on the type of remodeling were excluded. Median values were significantly different between the types of remodeling: $\chi 2$ (3) = 48.271, $p<0.001$. Further, paired comparisons were performed with Dunn's test (1964) with Bonferonni adjustment for multiple comparisons. Corrected p-values were presented. This analysis revealed statistically significant differences in the mean age between the groups without remodeling (48 years old) and CR (54 years old) and CR and MR (56 years old) ($p < 0.001$), as well as between the groups with CR and MR (56 years old) and the group with MR (50 years old) ($p = 0.001$), and the group with CR (54 years old) ($p < 0.05$). Table 2 demonstrates Spearman correlation analysis between the main parameters, which revealed weak correlation between MR and LVMI ($r=0.16$, $p < 0.01$), between MR and BMI ($r=0.25$, $p < 0.01$), and medium correlation between MR and waist circumference ($r=0.30$, $p < 0.01$) and between LVMI and BMI ($r=0.26$, $p < 0.01$). Weak correlation between waist circumference and BMI and RWT ($r=0.18$, $p < 0.01$) was revealed. For the evaluation of the significance of the difference of UA level in the groups divided by the type of remodeling, one-sided ANOVA analysis was performed (Diagram 3). The data are presented as the mean ± standard deviation. The level of UA was significantly different between the groups: $F (3, 374) = 2.895$, $p < 0.05$. The level of UA was 341.84 ± 73.46 in the group without remodeling, 339.67 ± 78.69 in the group with CR, 343.39 ± 84.36 in the group with MR, and 367.4 ± 71.18 in the group with CR and MR. Tukey test showed that the increase in the level of UA in the group with CR and MR (27.73,

95% CI (from 52.81 to 265)) was statistically significant ($p<0.05$), but the differences in all the other groups were statistically insignificant.

Discussion

Among all the patients observed at the Hospital, there are only 44% of men. However, among the studied population with AH, the majority of patients were men, which can be probably explained by the fact that male sex is a risk factor for cardiovascular diseases [21]. The same factor can explain the fact that the majority of patients with AH and remodeling of target organs were men. Another gender-related peculiarity is an increase in the average level of UA in women and its decrease in men with age. The former should be explained by menopause and associated hormonal factors typical for women of older age [22]. A decrease in the level of UA in men could be associated with the intake of xanthine oxidase inhibitors that are indicated to patients with an elevated level of UA. With patients' age increase, the share of patients in the group with CR and the group with CR and MR increased. However, the share of patients in the group with MR decreased. This was observed because of earlier development of MR. It should be mentioned that in the studied population, first, MR developed and, then, CR followed. This conclusion can be based on the mean age in the groups and their ratio depending on the age: 44 years old and younger and 45 years old and older.

Besides, the number of patients with CR prevailed over the number of patients with MR. Probably, this is a peculiarity of the studied population. In other words, it cannot be excluded that in a certain group of patients MR develops earlier, which could be determined by genetic factors. In the majority of the population, CR develops in older age under the influence of AH and simultaneous development of atherosclerosis, which explains a larger number of patients in the group with CR. No significant correlations were revealed between the parameters indicating remodeling and the level of UA. This also agrees with the intergroup comparison of the levels of UA depending on the remodeling. There are no significant changes in the level of UA in patients without remodeling, CR and MR. However, there is a difference between the level of UA in the group with CR with the lowest level and highest number of patients and the group with CR and MR, wherein the level of UA is higher than in the other groups. In other words, the level of UA does not change in patients with "isolated" CR or MR. However, the level of UA increases when these two processes "combine". All these factors indirectly indicate that an increase in the level of UA in the studied population occurs after the processes of remodeling develop and cannot be considered as its predictor [23,24,25], and probably, it can be caused by damage of another target organ – kidneys [26]. The present study had some limitations. In particular, the authors performed a retrospective evaluation of the secondary data. Besides, a cross-sectional study does not provide highly reliable results. However, as far as the authors know, this was the only attempt to search for the association between the processes of CR and MR and the level of UA among the Kazakhstani population, which makes this study relevant.

Conclusion

The present study revealed certain peculiarities in the damage of target organs in the studied population. In particular, MR develops earlier and in a lower number of patients, while CR develops later and in bigger number of patients with AH. Besides, it should be mentioned that, probably, the level of UA elevates at later stages of AH after the development of remodeling and could indicate the progression of AH in the studied population. These conclusions are valuable in the clinical management of AH and require further investigation in this area.

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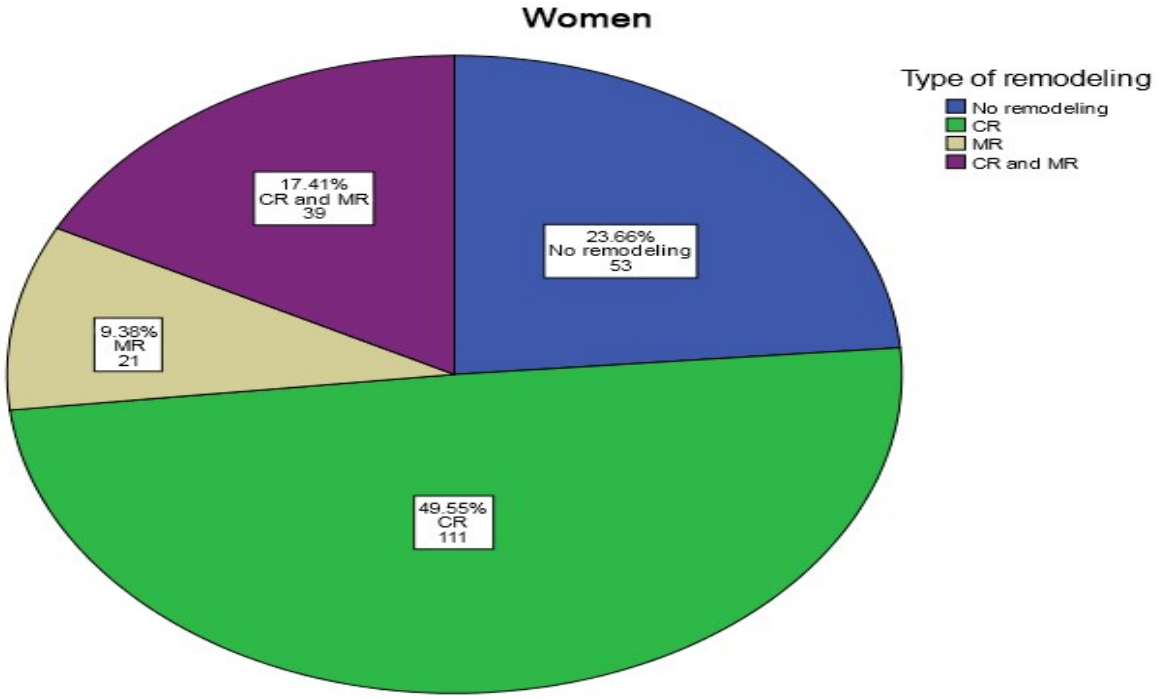
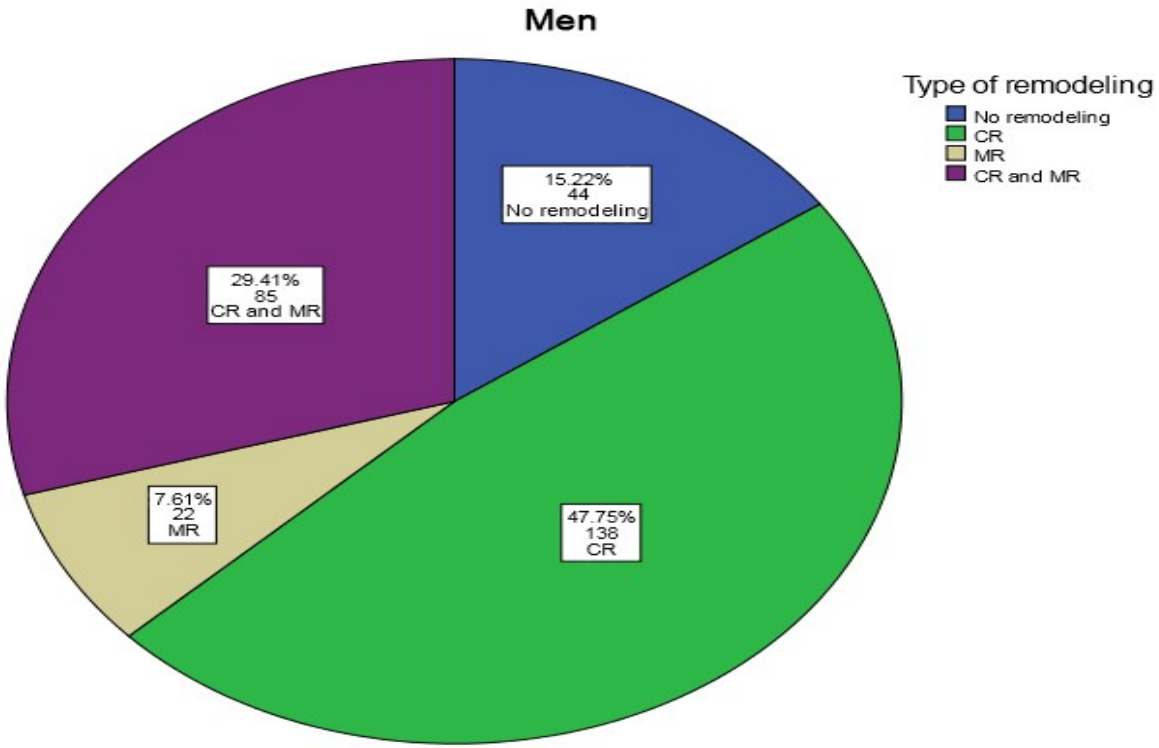
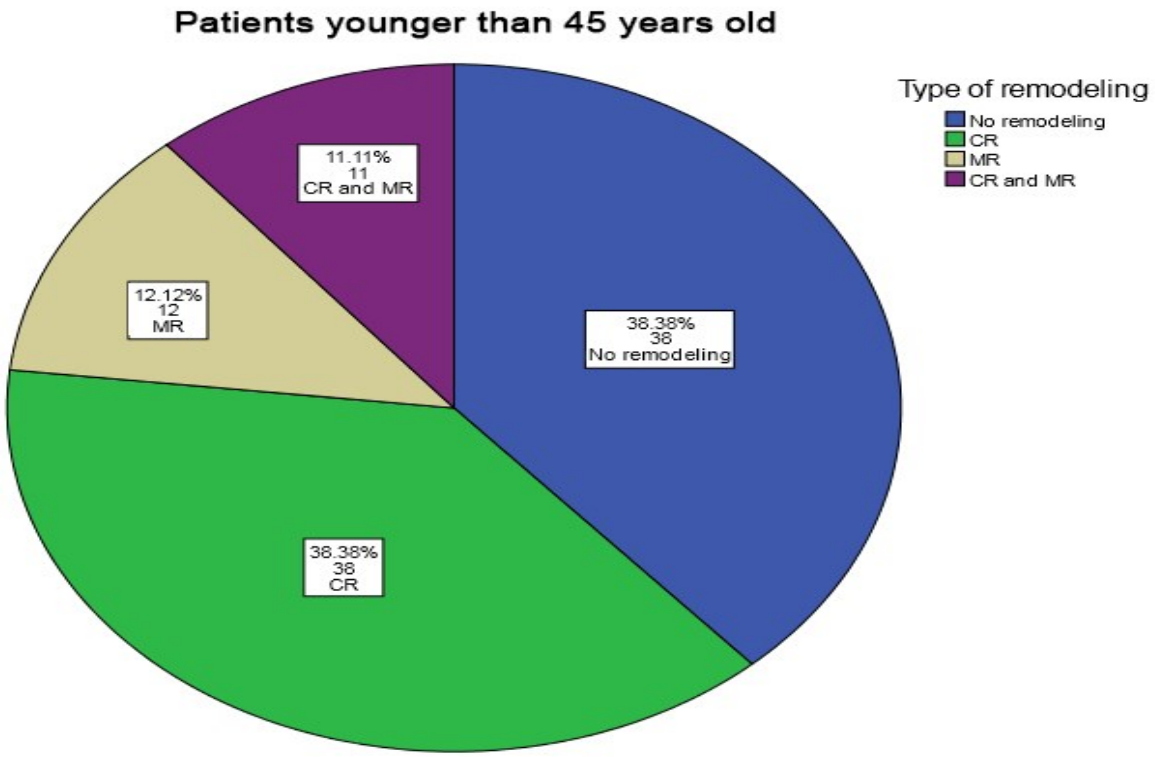
Diagram 1. The distribution of the participants by the presence and type of remodeling, by sex, and by age



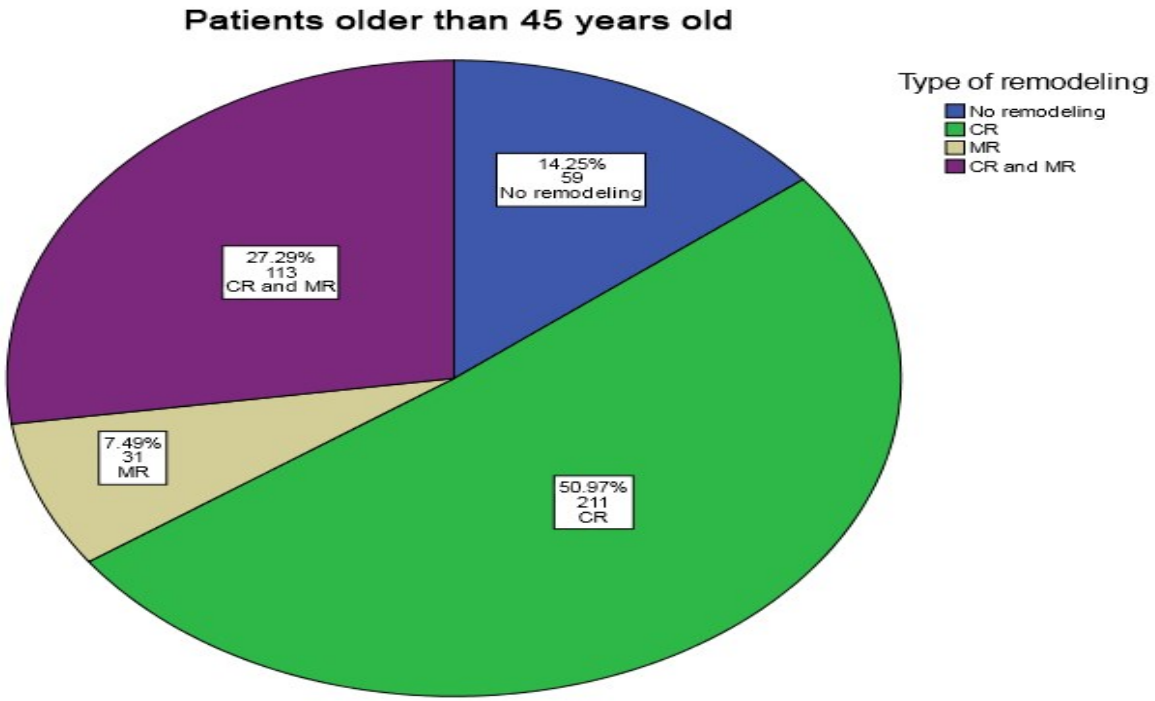
The distribution of women by the presence and type of remodeling.



The distribution of men by the presence and type of remodeling.



The distribution of patients younger than 45 years old by the presence and type of remodeling.



The distribution of patients older than 45 years old by the presence and type of remodeling.

Table 1. Characteristics of the main parameters by sex and age

Parameters	Younger than 45 years old				45 years old and older				All ages					
	Male		Female		Male		Female		Male		Female		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Uric acid, µmol/L	395.65	75.14	273.11	66.42	371.55	73.86	311.10	59.23	375.75	74.49	307.84	61.04	345.66	76.62
Waist circumference, cm	101.18	8.083	93.58	12.894	104.69	10.65	92.43	11.81	103.58	10.02	92.57	11.88	98.68	12.17
Left ventricular mass index (LVMI), g/m^2	83.82	30.522	76.45	26.55	93.40	24.24	76.76	25.22	91.14	26.13	76.72	25.35	84.78	26.75
RWT	0.39	0.13	0.38	0.11	0.41	0.10	0.39	0.10	0.40	0.11	0.39	0.10	0.40	0.10
IMC, mm	0.94	0.36	0.84	0.39	1.04	0.41	0.10	0.37	1.01	0.40	0.97	0.38	0.10	0.39
BMI	29.72	4.23	28.60	5.55	30.14	3.60	29.24	5.13	30.04	3.75	29.15	5.19	29.64	4.47

Mean – Mean Arithmetic
SD – Standard Deviation
LVMI – Left Ventricular Mass Index
RWT – Left Ventricular Relative Wall Thickness
IMC – Complex Intima-Media
BMI – Body Mass Index

Table 2. Correlation analysis of the main parameters

Correlations			LVMI	RWT	Thickness of IMC	Uric acid	Waist circumference	BMI
Po Spearman	LVMI, g/m²	Correlation coefficient	1.000	0.449**	0.090*	0.158**	0.303**	0.264**
		Value (two-sided)	0.	0.000	0.030	0.001	0.000	0.000
		N	583	583	583	422	229	535
	RWT	Correlation coefficient	0.449**	1.000	0.094*	0.067	0.179**	00.183**
		Value (two-sided)	.000	0.	0.023	0.170	0.007	0.000
		N	583	583	583	422	229	535
	Thickness of IMC, mm	Correlation coefficient	0.090*	0.094*	1.000	0.082	0.061	0.073
		Value (two-sided)	0.030	0.023	0.	0.094	0.362	0.090
		N	583	583	583	422	229	535
	Uric acid, µmol/L	Correlation coefficient	0.158**	0.067	0.082	1.000	0.363**	0.252**
		Value (two-sided)	0.001	0.170	0.094	0.	0.000	0.000
		N	422	422	422	422	178	399
	Waist circumference, cm	Correlation coefficient	0.303**	0.179**	0.061	0.363**	1.000	0.782**
		Value (two-sided)	.000	.007	.362	.000	.	.000
		N	229	229	229	178	229	229
	BMI	Correlation coefficient	.264**	.183**	.073	.252**	.782**	1.000
		Value (two-sided)	.000	.000	.090	.000	.000	.
		N	535	535	535	399	229	535

**. The correlation was significant at 0.01 (two-sided).
*. The correlation was significant at 0.05 (two-sided).

LVMI – Left Ventricular Mass Index
RWT – Left Ventricular Relative Wall Thickness
IMC – Complex Intima-Media
BMI – Body Mass Index

Diagram 2. Medians of the age in groups with different types of remodeling

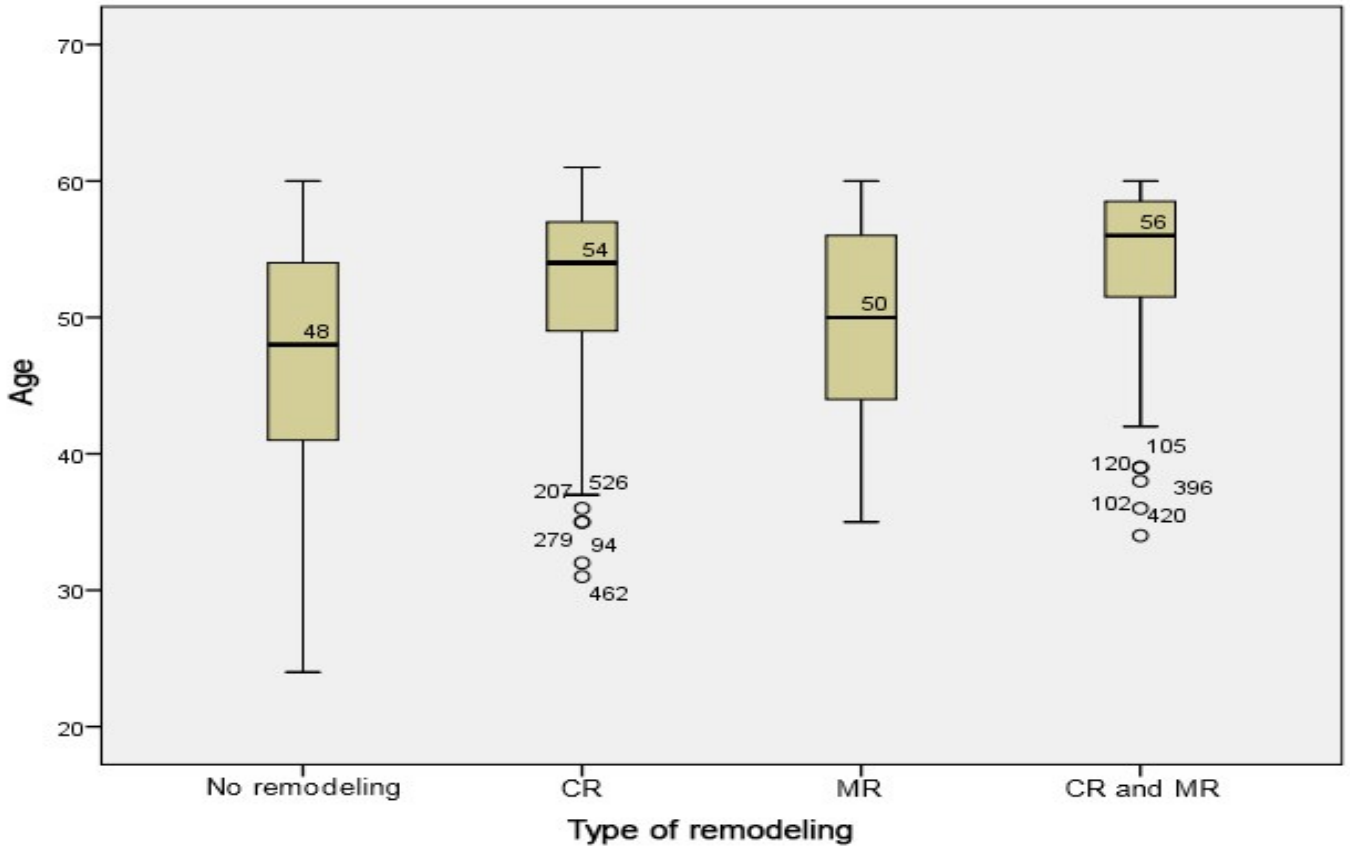


Diagram 3. Mean levels of uric acid in groups with different types of remodeling