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Original Article

The Relationship Between Kidney Function and Peripheral Artery Diseases in Patients with Metabolic Syndrome In a Resource Limited Setup: A Retrospective Record Review

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Abstract
***Background**: Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors and has an impact on the prevalence of chronic kidney diseases (CKD). We aimed to investigate the association between CKD and peripheral arterial diseases (PAD) in MetS patients.*
***Patients and Methods**: This retrospective record review was performed among patients with and without MetS over seven months. MetS was defined according to NCEP ATPIII criteria, PAD was diagnosed by an ankle-brachial index (ABI) <0.9 and confirmed by angiography. Subjects were categorized on the basis of estimated Glomerular filtration rate (eGFR). The ANOVA test was applied to compare the three classes of eGFR. Boxplots were used to compare kidney biological parameters between males and females, MetS abnormalities and association of PAD with CKD.*
***Results**: From 342 patients, 56.40% were females, 77.8% with MetS, and 17.3% with PAD, 79.9% diabetics, 50.9% hypertensives, and 37.1% with dyslipidemia. The mean age was 61.56±17.30 years. Significant differences (p<0.05) were highlighted for age, anthropometric characteristics, diabetes, dyslipidemia, hypertension, PAD, family history and biochemical parameters. High levels of uric acid, albuminemia, micro-albuminuria and caliciumia in MetS patients were observed in both genders. These parameters increased with number of MetS components. CRP levels and lipid profile were significantly higher (p<0.05) in CKD patients. The prevalence of PAD in patients without CKD was 10.16% vs. 47.45 % in subjects with CKD.*
***Conclusion**: The coexistence of CKD and PAD was associated with MetS abnormalities and an inflammatory state, suggesting that the control of metabolic disorders may form part of the preventive measures for PAD and CKD.*

***Keywords**: CKD, Peripheral arterial disease, Metabolic syndrome, eGFR, Ankle-brachial index.*
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Introduction

Metabolic syndrome (MetS) is a cluster of various metabolic disorders including obesity (abdominal obesity), fasting or postprandial hyperglycaemia, hypertension and dyslipidaemia (high plasma triglycerides (TG) and low plasma high density lipoprotein cholesterol (HDL)). This clustering was first noted in 1923 by Kylin E (1). Subsequently, MetS was defined by several international bodies, including the WHO and EGIR (1999), Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATPIII) (2001), AACE (2003), NCEP-R (2004), and IDF (2005) (2). The most widely accepted definition is that of the NCEP-ATPIII, which identifies MetS as the combination of at least three of the following five risk factors: abdominal obesity defined as a waist circumference ≥102 cm for men and ≥88 cm for women, high triglyceride (TG) levels ≥ 1. 5 g/L, low high-density lipoprotein (HDL) cholesterol (≤ 0.4 g/L for men and ≤ 0.5 g/L for women, blood pressure ≥ 130/85 mmHg, and fasting blood glucose ≥1 g/L (3).

Metabolic syndrome has become a common phe-

nomenon in several countries, where its prevalence has reached epidemic proportions, not only in the United States and the urbanized world, as well as in developing countries (4, 5). There is growing evidence of an association between kidney disease and MetS components (6). Several studies have confirmed this association, in which the number of MetS components has a positive impact on the prevalence of chronic kidney disease (CKD) (7-9). In fact, these abnormalities may be involved in the development and progression of reduced estimated glomerular filtration rate (eGFR). For example, arterial hypertension may be a major risk factor for the progression of renal dysfunction, or even CKD (10). Fatty tissue expansion and insulin resistance (IR) promote the chronic inflammation and oxidative stress that lead to renal failure. These factors may induce endothelial dysfunction, activation of the renin-angiotensin-aldosterone system and imbalance of adipokines. Inflammation and IR are the most common causes of microvascular and podocyte damage. These events lead to hypertension, albuminuria and parenchymal lesions. In addition, dyslipidaemia and excess nutrients too can affect mitochondrial function and promote the progression of renal cell damage (11).

Metabolic syndrome is characterized by a cluster of cardiovascular risk factors that are associated with a high risk of developing coronary heart disease, stroke, heart disease and peripheral arterial disease (PAD) (4, 11-13). Over the last decade, the prevalence of PAD has increased by 25% worldwide, reaching more than 200 million people worldwide (14, 15), prompting the Kidney Disease / Improving Global Outcomes (KDIGO) association to organize a conference in 2020 on the clinical controversies surrounding central disease and PAD in renal failure. The KDIGO reported that cardiovascular events account for the majority of deaths in people with CKD (16). However, the link between MetS, PAD and KD is not fully understood. Hence, our focus is to examine the association between CKD and PAD with MetS.

Patients and methods

Study design and area

A retrospective record review was conducted on individuals with and without MetS, who were admitted to the internal medicine unit of the "Ben Badis" public hospital and the Larbi Ben M'hidi Diabetes Centre in the Sidi-Bel-Abbes province in northwestern Algeria between between January 2019 and April 2022.

Data collection

During the 17-month study period, thorough medical records containing details of all hospitalized patients were reviewed to collect information on medical history (including diabetes, hypertension, dyslipidemia, and cardiovascular conditions) and a range of biochemical parameters (such as HbA1c, fasting glucose levels, HDL, LDL, total cholesterol (TC), triglycerides (TG), creatinine, urea, albumin levels, microalbuminuria, uric acid, calcemia, C-reactive protein, Na, K, chloride, and Cl). A total of 516 files were collected, excluding patients who met the exclusion criteria, leaving 315 files for this study.

Inclusion and Exclusion criteria

This study included adult men and women with and without MetS. Participants had to agree to take part in the interview and have a complete medical file.

Individuals suffering from cancer, autoimmune diseases, infectious diseases, HIV or HCV, pregnant women and patients with incomplete medical records were excluded.

Anthropometric measurements

Anthropometric measurements, including body weight (in kilograms), height (in meters), and waist circumference (in cm), were obtained using an electronic balance, a body meter and a tape measure, respectively.

The body mass index (BMI) was calculated as follows: BMI (Kg/m2) = weight (Kg) / height 2 (m2).

Blood pressure was measured using a manual handheld sphygmomanometer.

MetS, PAD and CKD definition

NCEP ATP III criteria were used to defined MetS, waist circumference ≥ 102 cm for men or ≥88 cm for women, triglycerides ≥1.5g/l, HDL <0.4g/l, for men or <0.5g/l for women, hypertension (systolic blood pressure ≥13cmHg or diastolic blood pressure ≥ 8.5 cmHg) and impaired glucose tolerance (fasting plasma glucose ≥1.1g/l) or diabetes (3). PAD was diagnosed by an ankle-brachial index (ABI) <0.9 and confirmed by angiography. Kidney function was categorized on the basis of eGFR >90, 60 to 89 and 15 to 59 ml/min per 1.73 m2 for non-kidney diseases (NKD), moderate kidney diseases (MKD), and chronic kidney diseases (CKD), respectively.

Calculation of eGFR

Estimated glomerular filtration rate was calculated according to Modification of Diet in Renal Disease study formula (MDRD) (17).

MDRD formula: eGFR =186.3 * (serum creatinine-1.154) * (age-0.203) *1.212 (if black) * 0.742 (if female).

Statistical analysis

Data were analysed using SPSS 20.0. Results are expressed as means ± standard deviations. The comparison of mean values and qualitative variables between group of patients without MetS (without MetS) and with MetS (with MetS) was performed using independent student's t test and Chi-square test, respectively. ANOVA test was applied to compare the three classes of eGFR. Box plots were used to compare kidney assessment between males and females, MetS abnormalities and association of PAD with CKD.

Ethical consideration

Ethical clearance was obtained from the Human Resources Sub-Management (HRSM) of Ben Badis in the Sidi-Bel-Abbes (Reference number: / 2021/م ف م ب .(1661

Results

The basic characteristics of the patients are shown in table 1. Following the exclusion and inclusion criteria, 315 participants were chosen from a pool of 516 files, 56.40% of whom were women and 43.6% men. Among the individuals included, 77.8% were diagnosed with MeS and 17.3% with PAD. The overall of mean age was 61.56 ± 17.30 years (51.80± 22.13 in patients without MetS and 64.35± 14.54 in patients with MetS), with a significant difference (p<0.001) between the two groups. Our results revealed that 79.9% of patients were diabetics, 50.9% were hypertensives and 37.1% were with dyslipidaemia.

Comparing patients with MetS to those without MetS,

Table 1: Baseline characteristics of the Study population according to presence or absence of Metabolic Syndrome at Ben Badis" public hospital from January 2019 to April 2022

Parameters	Total	Without MetS	With MetS	p value
n (%)	342	76 (22.20)	266 (77.80)	
Age (years)	61.56±17.30	51.80±22.13	64.35±14.54	<0.001*
Patient's systolic pressure (cmHg); Mean ±S.D	12.51±2.35	11.28±1.84	12.85±2.37	0.070*
Patient's diastolic pressure(cmHg); Mean ±S.D	6.9±1.43	6.7±1.35	7.04±1.42	0.586*
HbA1c (%); Mean ±SD	8.66±2.12	7.65±2.16	8.20±2.09	0.803*
Fasting glycaemia (g/l); Mean ±S.D	1.56±0.71	1.56±0.76	1.56±0.69	0.298*
HDLc (g/l); Mean ±S.D	0.44±0.14	0.50±0.11	0.42±0.14	0.209*
LDLc (g/l); Mean ±S.D	0.98±0.47	1.07±0.31	1.11±0.39	<0.001*
TC (g/l); Mean ±S.D	1.71±0.48	1.63±0.36	1.73±0.51	0.009*
TG (g/l); Mean ±S.D	1.38±0.70	1.04±0.45	1.48±0.73	<0.001*
Creatinine (g/l); Mean ±S.D	14.57±10.42	12.62±8.22	15.14±10.92	0.007*
Urea (g/l); Mean ±S.D	0.71±0.71	0.51±0.40	0.77±0.76	0.007*
Albuminemia (g/dl); Mean ±S.D	39.05±24.8	31.24±18.76	41.26±25.87	0.017*
Micro-Albuminuria (g/24h); Mean ±S.D	2.27±12.88	51.69±34.34	91.00±78.46	<0.001*
Uric acid (g/l); Mean ±S.D	58.28±23.79	40.97±17.82	63.22±22.97	0.023*
eGFR (mL/min/1.73m^2); Mean ±S.D	62.73±38.29	71.57± 40.22	60.17±37.40	0.267*
Calcemia; Mean ±S.D	77.90±20.49	69.49±21.92	80.30±19.45	0.032*
CRP (g/l); Mean ±S.D	42.70±41.37	45.51±45.26	42.01±40.41	0.048*
Na (g/l); Mean ±S.D	133.26±10.00	133.02±8.71	133.33±10.35	0.709*

K (g/l); Mean ±S.D				
	3.91±1.19	3.92±1.09	3.91±1.22	0.601*
Cl (g/l); Mean ±S.D				
	95.35±95.35	98.83± 9.02	94.26±16.18	0.037*
P (g/l); Mean ±S.D				
	48.96±33.090	46.11±22.03	49.58±35.06	0.093*
Patients' gender; n (%)				
Female	193 (56.4)	46 (13.5)	147 (43)	0.247#
Male	149 (43.6)	30 (8.8)	119 (34.8)	
Corpulence; n (%)				
Normal weight	90 (29)	39 (12.6)	51 (16.5)	<0.001#
Overweight	125 (40.3)	19 (6.1)	106 (34.2)	
Obese	95 (30.6)	7 (2.3)	88 (28.4)	
Diabetes; n (%)				
No	59 (20.1)	24 (8.2)	35 (11.9)	<0.001#
Yes	235 (79.9)	28 (9.5)	207 (70.4)	
Dyslipidaemia; n (%)				
No	215 (62.9)	71 (20.8)	144 (42.1)	<0.001#
Yes	127 (37.1)	5 (1.5)	122 (35.7)	
Hypertension; n (%)				
No	168 (49.1)	66 (19.3)	102 (29.8)	<0.001#
Yes	174 (50.9)	10 (2.9)	164 (48)	
PAD; n (%)				
No	283 (82.7)	70 (20.5)	213 (62.3)	0.008#
Yes	59 (17.3)	6 (1.8)	53 (15.5)	
Family history (CVD, Hypertension, Diabetes, Dyslipidaemia); n (%)				
No	64 (58.1)	26 (38.2)	38 (19.9)	0.003#
Yes		42 (61.8)	153 (80.1)	
Waist circumference classes				
Normal	92 (27.8)	45 (13.6)	47 (14.2)	<0.001#
Obese	239 (72.2)	25 (7.6)	214 (64)	

(*) p value for student t test; (#) p value for Chi-square test; p ≤ 0.05 was considered as statistically significant. MetS: metabolic syndrome, HbA1c: glycated haemoglobin, HDLc: high-density lipoproteins, LDLc: low-density lipoprotein, TC: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, PAD: peripheral arterial diseases, CVD: cardio-vascular diseases.

Our finding about the comparison of renal parameters between patients with and without MetS highlighted high levels of uric acid, albuminemia, micro-albuminuria and calicaemia in MetS patients, similar values were emphasized in male and female gender (figure 1). Figure two shows comparison of renal parameters (urea, creatinine, uric acid, albuminemia, micro-albuminuria and calcaemia) according to number of MetS abnormalities, our finding revealed that levels of al most of these parameters increased with number of MetS abnormalities.

Comparison between the three eGFR classes through ANOVA test reveals significant differences ($p<0.05$) in CRP levels and lipid profile (HDL, LDL, TC, TG) with higher values in patients of the first class.

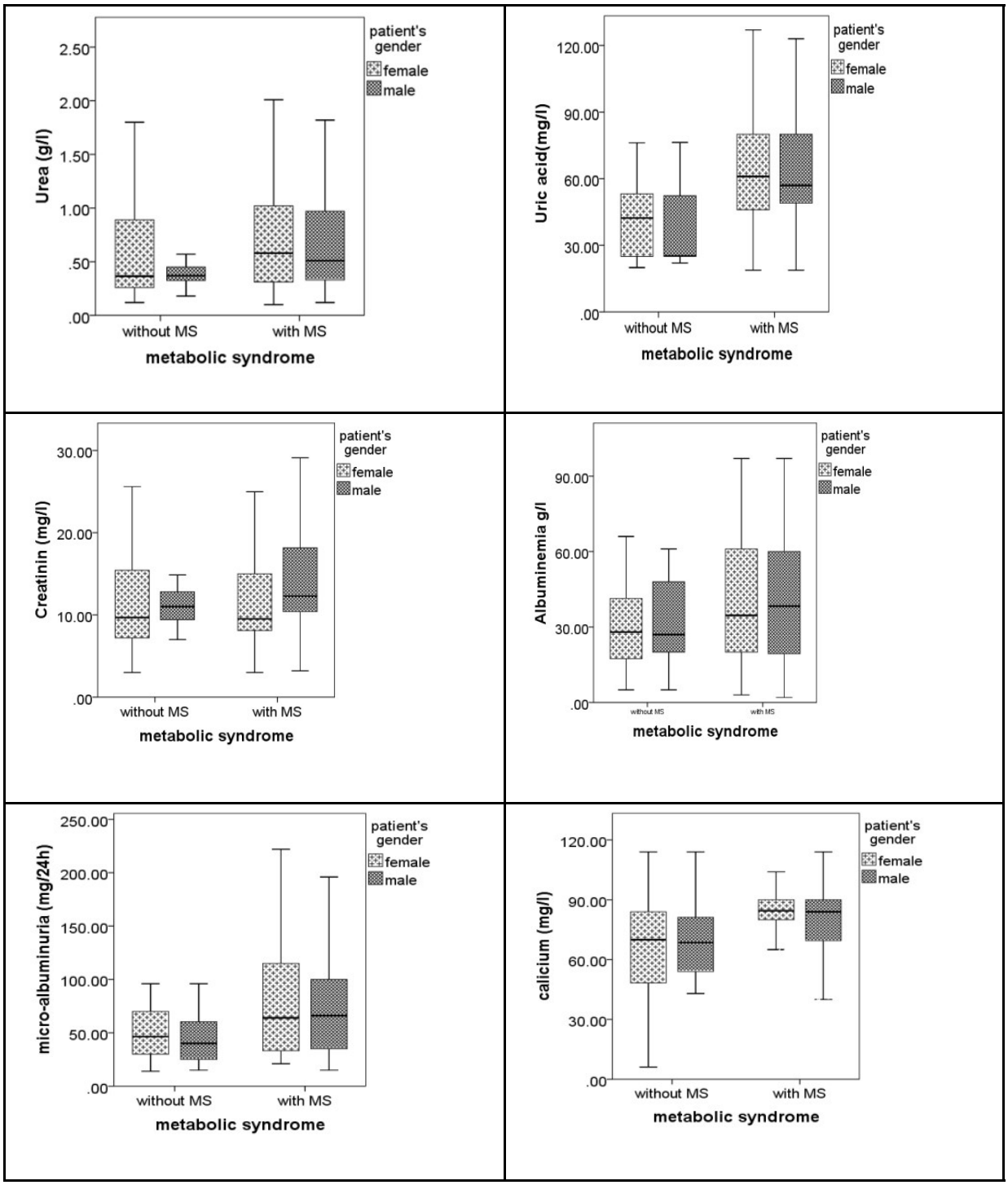


Figure 1: comparison of kidney assessment between males and females according to the metabolic syndrome profile at Ben Badis" public hospital from January 2019 to April 2022

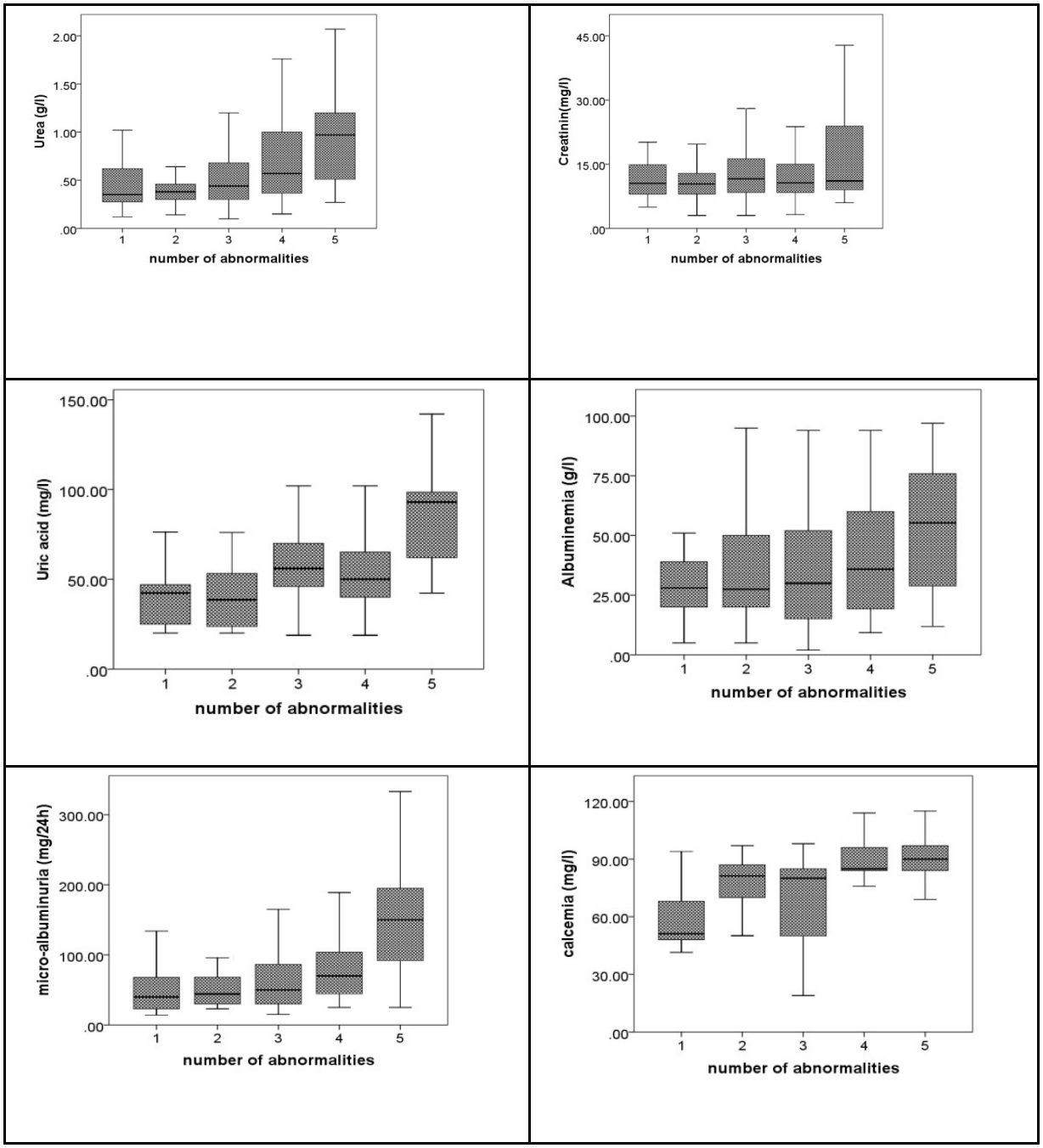


Figure 2: comparison of kidney assessment between metabolic syndrome classes at Ben Badis" public hospital from January 2019 to April 2022

No significant differences ($p>0.05$) were observed in age, urea, uric acid, micro-albuminuria, fasting glycaemia, HbA1c levels, BMI, systolic and diastolic pressure.

The group of patients with eGFR between 15 and 59 mL/min/1.73 m2 had higher percentage of diabetes, dyslipidaemia, hypertension, PAD and MetS compared to other groups, with a significant value ($p<0.05$) for hypertension and MetS (Table 2).

Table 2: Comparison of renal parameters, CRP and metabolic syndrome components between eGFR classes.at Ben Badis" public hospital from January 2019 to April 2022

Parameters	15< eGFR≤ 59 121(45%) CKD	60<eGFR≤89 101 (37.5 %) MKD	eGFR≥ 90 47(17.5%) NKD	P value*
Age(year)	68.60 ± 13.93	59.5 ± 11.03	63 ± 19.53	0.068*
Urea (g/l); Mean ±S.D	0.71 ± 0.45	0.47 ± 0.27	0.98 ± 1.43	0.160*
Uric acid(g/l); Mean ±S.D	64.24 ± 23.94	61.62 ± 22.5	55.91 ± 16.87	0.709*
Micro-Albuminuria (g/24h); Mean ±S.D	102.19 ± 82.35	74.24 ± 52.53	49.22 ± 33.7	0.147*
CRP (g/l); Mean ±S.D	54.14 ± 34.64	59.88 ± 25.74	23.10 ± 24.90	0.041*
Fasting glycaemia (g/l); Mean ±S.D	1.45 ± 0.56	1.63 ± 0.74	1.58 ± 0.42	0.608*
HbA1c (%); Mean ±SD	7.70 ± 2.22	8.6 ± 2.56	9.46 ± 2.31	0.174*
HDLc(g/l); Mean ±SD	0.37 ± 0.12	0.37 ± 0.10	0.61 ± 0.09	$<10^{-3}$*
LDLc(g/l); Mean ±SD	1.36 ± 0.56	1.27 ± 0.64	0.38 ± 0.24	0.002*
TC(g/l); Mean ±SD	2.20 ± 0.62	2 ± 0.56	1.30 ± 0.35	0.004*
TG(g/l); Mean ±SD	2.38 ± 0.79	1.86 ± 0.56	1.55 ± 0.58	0.007*
BMI (kg/m²)	29.39 ± 6.39	29.52 ± 4.07	26.80 ± 3.09	0.523*
Patient's systolic pressure (cmHg); Mean ±S.D	12.68 ± 2.10	13.68 ± 3.41	12.83 ± 1.16	0.410*
Patient's diastolic pressure(cmHg); Mean ±S.D	7.08 ± 1.45	7.59 ± 2.07	7.16 ± 1.16	0.580*
Diabetes; n (%)	93 (44.07%)	81(38.38%)	37 (17.53%)	0.833#
Dyslipidaemia; n (%)	57 (48.71%)	45 (38.46%)	15 (12.82%)	0.138#
Hypertension; n (%)	88 (56.05%)	53(33.57%)	16 (10.19%)	$<10^{-3}$#
MetS; n (%)	121 (45%)	101(37.5%)	47(17.5%)	0.014#
PAD; n (%)	28 (47.45%)	22(37.28%)	6(10.16%)	0.255#

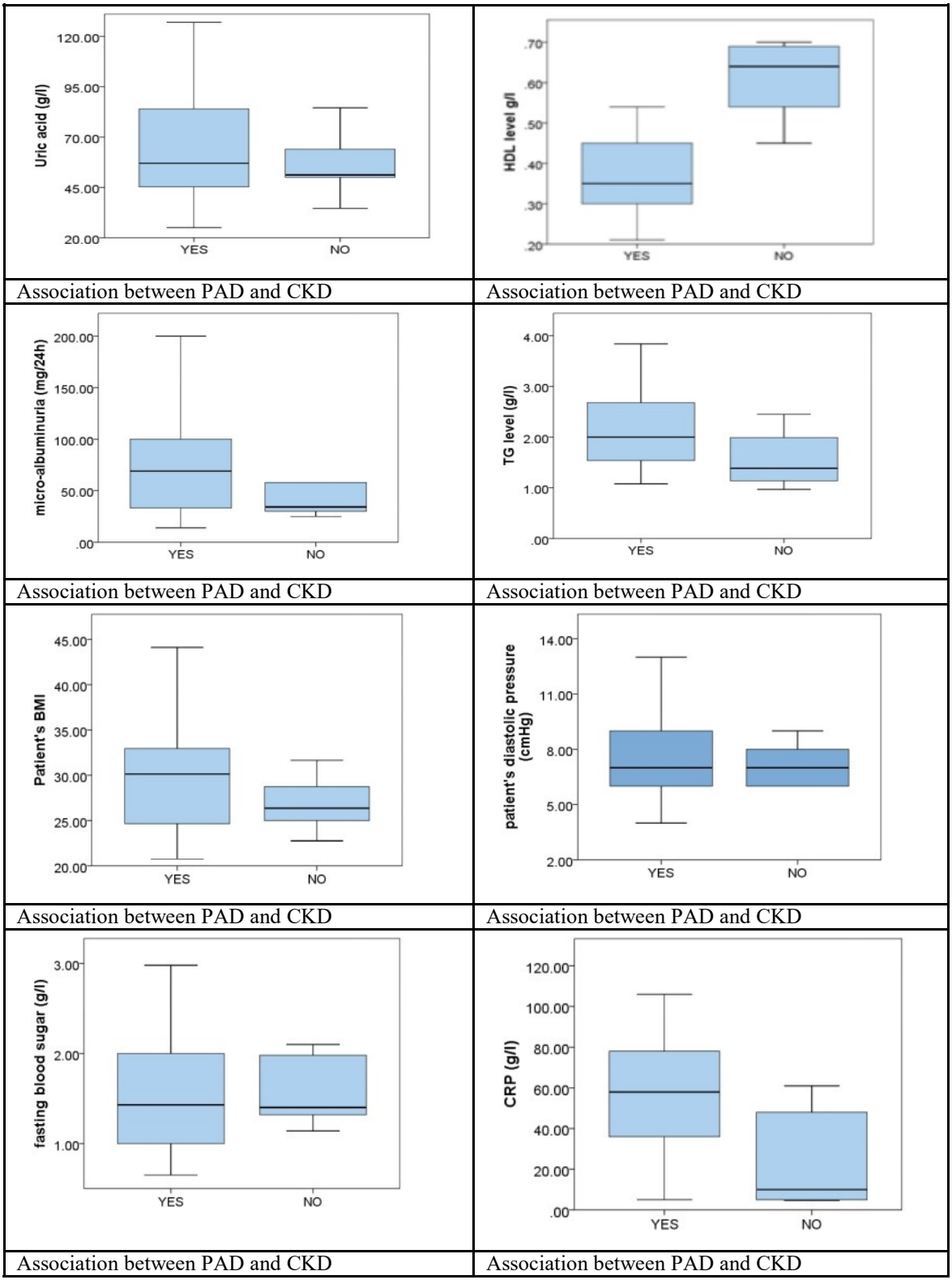
(*) Comparison between eGFR classes using ANOVA test, (#) p value for Chi-square test; p ≤ 0.05was considered as statistically significant. eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; HbA1c: glycated haemoglobin, HDLc: high-density lipoproteins; LDLc: low-density lipoprotein; TC: total cholesterol; TG: triglyceride; BMI: body mass index; MetS: metabolic syndrome; PAD: peripheral arterial diseases. The eGFR unit is expressed as: ml/min per 1.73 m2, NKD: non-kidney diseases, MKD: moderate kidney diseases, CKD: chronic kidney diseases.

The prevalence of PAD in patients without kidney diseases was 10.16% vs. 47.45 % in subjects with CKD (Table 2). The uric acid, micro-albuminuria, CRP, TG levels and BMI were elevated in the group of patients with PAD associated with CKD. However, HDL levels were higher in second group. Fasting glycaemia and diastolic pressure were nearly equal in both groups. The coexistence of KD and PAD was associated with MetS abnormalities and an inflammatory state (elevated CRP) (Figure 3).

Discussion

In the present study, we set out to investigate the complex interconnection between PAD and CKD with presence of MetS. A cross-sectional and longitudinal study involving a nationwide population in Taiwan pointed that having five abnormalities was associated with a more than twofold increase in odds of Kidney stone (KS) and all components of the MetS were associated with a higher prevalence of KS (18). A study of 3872 Korean men without KS underscored an elevated risk of KS in individuals with MetS at 1.77 times higher (1.157-2.711) (19). In 2004, Chen et al. reported that MetS was an independent risk factor of CKD (20). The Finding by Chang, et al demonstrated a strong association between MetS and KS (18), these findings were confirmed in recent studies (9, 21).

In our study population of adults with a mean age of 61.56 years, the prevalence of MetS was 77.80%, with women accounting for 56.4% of participants.



Association between PAD and CKD	Association between PAD and CKD
Association between PAD and CKD	Association between PAD and CKD
Association between PAD and CKD	Association between PAD and CKD
Association between PAD and CKD	Association between PAD and CKD

Figure 3: comparison of renal parameters, CRP and metabolic syndrome components according to association of peripheral arterial diseases with kidney diseases *at Ben Badis" public hospital from January 2019 to April 2022*

Our estimate was comparable to that reported in a cross-sectional and longitudinal cohort study of 121,579 participants registered at the Taiwan Biobank (mean ages were 54 ± 10 and 49 ± 11 years in the MetS and non-MetS groups, respectively, comprised 64% of the population, and 67% were affected by MetS), on the other hand, our figures were higher than those reported in a national cross-sectional study of 97,098 Chinese adults aged 18 years or older in 2010, in which the prevalence of MetS was 33.9% (31.0% in men and 36.8% in women) (18, 22). Our MetS participants had higher risk of CKD (45% of MetS patients had CKD and 37.5% had MKD) compared to those without MetS. Moreover, they had high BMI, blood pressure, HbA1c, LDL, CT, TG, serum creatinine, urea, serum albumin, Micro-Albuminuria, uric acid, serum calcium and serum phosphor levels and low eGFR, HDL-C and CRP levels. Similar results were reported by Wu N et al. (23), participants with MetS were 1.82 times as likely to develop CKD compared to those without MetS (OR: 1.82, 95% CI: 1.19–2.78). In which the risk of CKD increased with the number of MetS components ($p < 0.001$). ORs for CKD were 1.25 (95% CI: 0.74–2.11), 1.95 (95% CI: 1.11–3.43), 2.29 (95% CI: 1.20–4.39), 4.28 (95% CI: 1.98– 9.25), and 4.93 (95% CI: 1.87–13.03) for one, two, three, four, and five MetS components versus zero (23). Our finding revealed elevated levels of uric acid, albuminemia, microalbuminuria and calcaemia in patients with MetS compared to those without MetS (figure 1). Similar values were underlined in males and females. Levels of all most of renal assessment parameters increased with number of MetS abnormalities.

It is well-known that diabetes and hypertension represent the most common drivers of reduced kidney function in the general population. Moreover, it is known that high triglyceride levels and low HDL-cholesterol levels are associated with an increased risk of CVD and may contribute to kidney dysfunction through their pro-inflammatory and atherogenic effects or by acting as a marker for insulin resistance in kidney diseases (24, 25). Two previous studies likewise outline an enhanced risk of KS in hypertensive patients. Furthermore, familial hypertensive patients tend to have hypercalciuria and hyperuricosuria, leading to KS (26-29).

Several epidemiological studies have established a link between low HDL levels and poor renal function or progression to CKD (30, 31). Interestingly, our results showed a high proportion of diabetes, dyslipidaemia, hypertension, PAD and MetS in patients with eGFR between 15 and 59 ml/min/1.73. Indeed, subjects in this eGFR class had high levels of LDL, TG and TC. Bowe et al estimated that patients with HDL-C concentrations below 30 mg/dL had a 10-20% higher risk of CKD than individuals with concentrations above 40 mg/dL (32). Our results likewise highlight the reduced levels of HDL in the group of people with chronic kidney disease.

The prevalence of PAD has increased over the last decade by more than 25% from about 160 million to over 200 million, particularly in low-income countries (15). Numerous studies have revealed a close correlation between PAD and components of MetS, as well as between lipid profile disorders and PAD in patients with MetS. In addition, CKD is now recognized as a significant independent risk factor for PAD (4, 33). Foley et al. In study of 1,091,201 subjects pointed out that, the prevalence of PAD was threefold higher in patients with CKD (35% in CKD patient vs. 9.6% in patient without CKD) (34). Abu et al. (35) established an association between age, duration of CKD, length of time on dialysis, PAD and cardiovascular risk. Consistent with these previous studies, we found that 47.45% of patients with CKD developed PAD compared to only 10.16% of patients without CKD. We found that uric acid, microalbuminuria, CRP, TG levels and BMI were elevated when CKD and PAD coexisted. However, HDL levels were lower. The association of CKD and PAD was linked to MetS abnormalities and an inflammatory state (high CRP).

Our investigation faced some problems that must be indicated. First, the sample size was limited since the cases were collected in a short period. Second, the generalization of our results to other populations may be limited because the prevalence of components of the MetS varies across population. Fourth, most patients already under antihypertensor, statins and oral antidiabetic drug these treatments may improve renal function, lower the risk of vascular events and improve the survival of PAD (36, 37). Whereas those with incomplete medical records were excluded.

Conclusion

High levels of LDL, TC, TG, and low HDL levels were associated with an eGFR between 15 and 59 mL/min/1.73 m2. Diabetes, dyslipidaemia, hypertension, obesity (components of MetS) and PAD were closely linked with kidney dysfunction. The coexistence of CKD and PAD was associated with MetS abnormalities and an inflammatory state (elevated CRP levels). We conclude that MetS can be considered as a potential risk factor for CKD and PAD, suggesting that correction of metabolic disorders could be part of preventive measures against the recurrence of CKD and PAD.

Conflict of interest

The authors declare that they have no known competing interests.

Funding

We have not received any fund for this study.

Data availability

Data can be shared up on reasonable request

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