Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Body-mass index and the risk of albuminuria in hypertensive patients with a poor estimated glomerular filtration rate and the potential role of diabetes mellitus

Vaia D. Raikou [a, *], Sotiris Gavriil [b]

[a] Dpt of Nephrology, DOCTORS' Hospital, Athens, Greece
[b] Dpt of Bariatric Surgery, DOCTORS' Hospital, Athens, Greece

ABSTRACT

Background: Obesity-related to metabolic syndrome was associated with a greater risk for development of chronic kidney disease (CKD). We aimed to assess the association between obesity and micro/macroalbuminuria in hypertensive patients with a poor estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.
Methods: One hundred old patients (median age 79 years ± inter-quartile range 68–84.7) with manifested hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg) and a permanently poor eGFR for a duration time more than 3 months were enclosed. Albuminuria was defined as urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/gr and it was classified according to KDIGO 2012. The obesity was defined by a high body mass index (BMI>30 kg/m^2). The waist circumference, HDL-C, triglycerides and serum glucose were measured. Chi-square tests and an adjusted model were performed.
Results: Chi-square tests showed significant association between classified albuminuria and both obesity and high serum triglycerides ($x^2 = 7.2$, $p = 0.02$ and $x^2 = 8.3$, $p = 0.01$ respectively). However, the adjusted model for the prediction of albuminuria showed that the presence of a high BMI was a non-significant risk factor, although diabetes mellitus and eGFR value were found to be significant risk factors ($p = 0.03$, OR = 4.3, 1.2−22.07 and $p = 0.04$, OR = 0.9, 0.9−1.007 respectively) adjusting to covariates including the high waist circumference.
Conclusion: Obesity defined by a high BMI was not found to be a significant risk factor for micro/macroalbuminuria in hypertensive patients with a poor estimated glomerular filtration rate, when diabetes mellitus and the low eGFR value act as confounders.

© 2019 Diabetes India. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Obesity confers an increased risk of chronic kidney disease (CKD) and the odds ratio is increased further by accompanying metabolic abnormalities through the metabolic syndrome including dyslipidemia (high triglycerides and low HDL cholesterol), elevated blood pressure and dysregulated glucose homeostasis [1−3]. Moreover, individuals with CKD have higher prevalence rates of metabolic disorders than individuals without CKD, due to potential pathophysiological mechanisms connected to

CKD including insulin resistance and inflammatory microenvironment [3,4].

Obesity, which is defined as the degree of fat storage related to elevated health risks, is commonly measuring by body mass index (BMI), waist to hip ratio (WHR) and/or waist circumference (WC) [5−7].

Chronic kidney disease is defined by a poor estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or the presence of albuminuria, both of which commonly are required for the diagnosis of CKD [8,9]. However, a few studies have been reported to the relationship between obesity and urinary protein excretion [10,11]. In the meantime, renal function plays an important role in initiating hypertension particularly during obesity by multiple mechanisms including increased renal tubular sodium

---

* Corresponding author. 26 Kefallinias, 11257, ATHENS, Greece.
 E-mail addresses: vraikou@med.uoa.gr (V.D. Raikou), sotiris@sgavriil.gr (S. Gavriil).

reabsorption and activation of the renin-angiotensin-aldosterone system (RAAS) [12]. Previously, it has been reported that the relationship between a high BMI and CKD risk and its progression was similar among subjects with and without hypertension, diabetes or cardiovascular disease, despite being overweight increases the risk of advanced CKD in people with these comorbidities [13]. However, the effect of obesity in population with both classified CKD based on eGFR categories and/or albuminuria categories and comorbidities, such as hypertension, is unclear.

Therefore, in this study, we aimed to assess the association between obesity defined by a high BMI and micro/macroalbuminuria in hypertensive patients with a permanently poor eGFR <60 mL/min/1.73 m^2 for a duration time more than 3 months.

2. Materials and methods

2.1. Subjects

This is a single-center cross-sectional study in which one hundred hypertensive patients with chronic renal disease were enclosed. The participants were collected from the Department of Nephrology outpatient clinic of our Hospital.

We excluded subjects younger than 18 years old and uncooperative patients. Those with established dementia or psychiatric symptomatology diagnosed by neuropsychologists were also excluded from the study.

Fifty-two males and forty-eight females were enrolled in the study on median age 79 years ± inter-quartile range 68–84.7.

Detailed individual medical histories, family histories of kidney/cardiovascular diseases and the current pharmaceutical therapy were obtained from the patients. The causes for the development of a poor eGFR in our data included hypertensive nephrosclerosis (52%), type2 diabetes mellitus (29%), interstitial nephritis (7%), chronic glomerulonephritis (6%), polycystic disease (3%), other/unknown (3%). The total of the enrolled subjects was receiving antihypertensive medications including calcium channel blockers, beta-blockers, inhibitors of angiotensin II AT1 receptors or new central-acting.

Demographic data, including age, gender, marital status, education level, sleep and lifestyle characteristics regarding with active or passive smoking, alcohol drinking and physical activity were collected using interviews. Subjects who declared no alcohol consumption during the past month were considered non-drinkers. Physical activity was measured based on the World Health Organization (WHO) recommendations for healthy adults and physical inactive participants were considered sedentary [14].

Anthropometric measurements including height, body weight and waist circumference were recorded. Body mass index (BMI) was calculated and categorized based on the WHO classification into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) [15]. Waist circumference measurements made approximately at the midpoint between the lower margin of the last palpable rib and the top of iliac crest at the end of a normal expiration according to the WHO guidelines [16].

2.2. Biochemical measurements

Fasting plasma glucose, triglycerides, high-density lipoprotein-cholesterol (HDL-C) were recorded from the patient files using the latest results. Biochemical markers were measured using spectrophotometric technique by Chemistry Analyzer (MINDRAY BS-200, Diamond Diagnostics,USA) and were represented as mg/dL.

Spot urine samples from the first micturition after rising were used for the measurement of albumin and creatinine concentrations by the Chemistry Analyzer.

2.3. Definitions

We enclosed exclusively hypertensive subjects with an impaired eGFR for a duration time more than 3 months [17]. As hypertensive were defined the subjects with a systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg and/or with pre-existed individual history of hypertension and/or with taking antihypertensive therapy.

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) equation.

The enrolled subjects were also classified based on albuminuria, which was defined as urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/gr according to KDIGO 2012 [17]. ACR calculation by using a spot urine sample, such as in this study, is considered an acceptable calculation, as ACR is correlated well with 24-h urinary albumin excretion.

The obesity was defined by a high BMI (>30 kg/m^2).

3. Data analysis

Data were analyzed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, Illinois) and expressed as mean ± standard deviation or as median value ± inter-quartile range for data that showed skewed distribution. Differences between mean values were assessed by using unpaired *t*-test for two groups and data that showed skewed distributions were compared with Mann-Whitney *U*- test.

Correlations between variables were defined by Spearman coefficient and correlations between categorical variables were defined by chi-square tests. P values less than 0.05 were considered significant. We built a model using logistic regression analysis for the role of obesity defined by a high BMI on the development of albuminuria adjusting to the age, gender, physical activity, smoking, alcohol taking, diabetes mellitus, eGFR value and waist circumference.

4. Results

In Table 1 the differences between the groups of subjects with and without obesity (BMI > or < 30 kg/m^2) are shown. We observed that the patients with obesity had significantly elevated albuminuria, serum glucose and triglycerides than the patients without obesity.

In Table 2 the differences between the groups of subjects with and without albuminuria are shown. We observed that the group of patients with albuminuria (ACR>30mg/gr) had significantly higher waist circumference and serum triglycerides than the group of patients without albuminuria (ACR<30mg/gr).

The bivariate correlation between BMI value and albuminuria was found to be significant (r = 0.252, p = 0.01).

Chi-square tests showed significant association between classified albuminuria and both obesity and high serum triglycerides (x^2 = 7.2, p = 0.02, Fig. 1 and x^2 = 8.3, p = 0.01 respectively).

The built adjusted model for albuminuria prediction showed that the presence of obesity defined by a high BMI was a non-significant risk factor, although diabetes mellitus and eGFR value were found to be significant risk factors (p = 0.03, OR = 4.3, 1.2–22.07 and p = 0.04, OR = 0.9, 0.9–1.007 respectively) adjusting to the age, gender, smoking, alcohol intake, physical activity and waist circumference (Table 3).

Table 1
Differences between groups of patients with (n = 46) and without (n = 54) obesity (BMI > or < 30 kg/m^2) (*: p < 0.05).

Characteristic	Patients with BMI >30 kg/m^2 (n = 46) *mean ± SD/mean Rank*	Patients with BMI < 30 kg/m^2 (n = 54) *mean ± SD/mean Rank*	P value
Sex (%males/%females)	24 (52%) −22 (48%)	28(52%) − 26 (48%)	0.1
Age (years)	/47.04	/53.44	0.3
BMI (Kg/m^2)	32.3 ± 2.5*	26.7 ± 1.7	**0.001**
ACR (mg/gr)	/58.55*	/43.64	**0.001**
eGFR (ml/min/1.73m^2)	35.06 ± 11.1	37.7 ± 12.03	0.2
HDL (mg/Dl)	/45.8	/54.4	0.2
Triglycerides (mg/Dl)	178.8 ± 70.4*	153.5 ± 47.5	**0.03**
Waist circumference (cm)	114.7 ± 10.4*	99.01 ± 8.5	**0.001**
Glucose (mg/Dl)	/59.9*	/42.5	**0.003**

Table 2
Differences between groups of patients with (n = 81) and without (n = 19) albuminuria defined by urinary albumin-to-creatinine ratio ≥ 30mg/gr or < 30mg/gr (ACR ≥ or < 30mg/gr) (*: p < 0.05).

| Characteristic	Patients with ACR≥ 30mg/gr (n = 81) *mean ± SD/mean Rank*	Patients with ACR <30mg/gr (n = 19) *mean ± SD/mean Rank*	P value
Sex (%males/%females)	45 (55.6%) −36 (44.4%)	7(36.8%) − 12(63.2%)	0.1
Age (years)	/49.3	/55.2	0.4
BMI (Kg/m^2)	29.6 ± 3.6	28 ± 2.8	0.07
ACR (mg/gr)	/60*	/10	**0.001**
eGFR (ml/min/1.73m^2)	35.9 ± 11.6	39.0 ± 11.7	0.3
HDL (mg/Dl)	/48	/61.1	0.07
Triglycerides (mg/Dl)	171.8 ± 61.7*	136.4 ± 43.4	**0.02**
Waist circumference (cm)	107.7 ± 12.1*	100.05 ± 10.8	**0.01**
Glucose (mg/Dl)	/52.7	/40.9	0.1
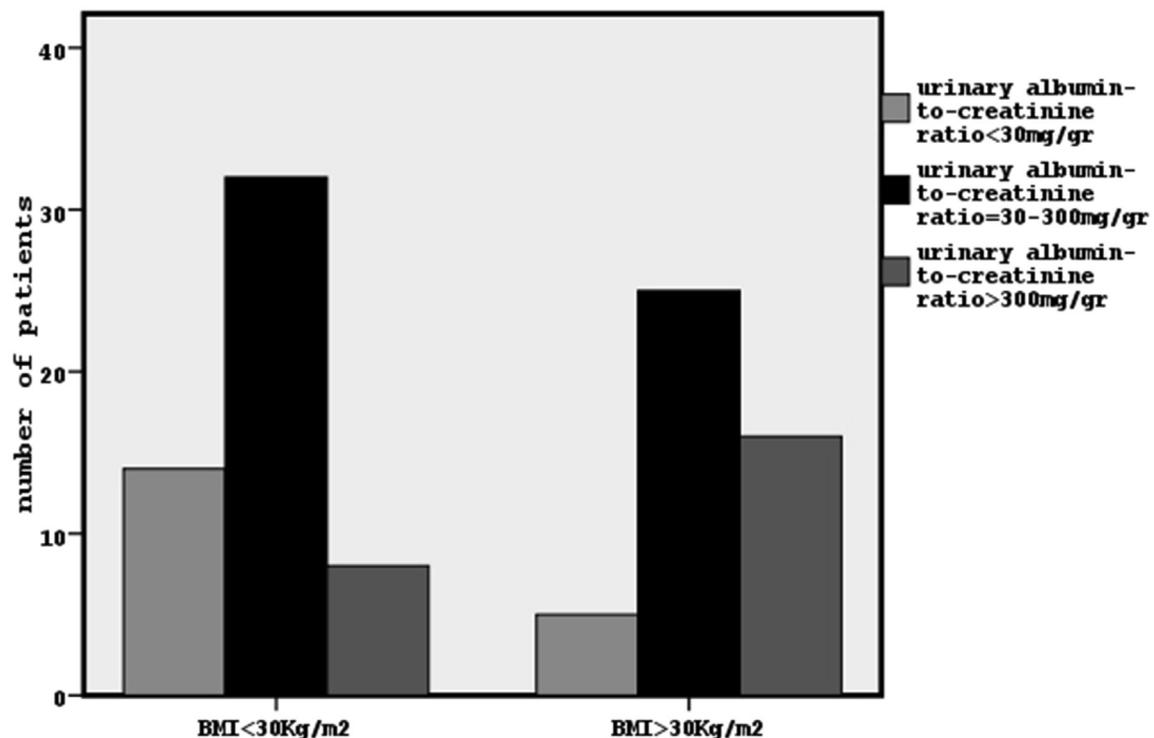
Fig. 1. The association between classified albuminuria and obesity defined by a high BMI (BMI < or > 30 Kg/m^2) in our subjects (x^2=7.2, p=0.02).

Table 3
Logistic regression analysis showing the predictors for the manifestation of albuminuria in hypertensive patients with eGFR< 60 mL/min/1.73 m² (n = 100).

Characteristic	p-value	Odds ratio	Confidence interval
age	0.4	0.9	0.9–1.03
gender	0.4	0.6	0.2–2.1
smoking	0.9	0.8	0.1–5.6
Alcohol intake	0.2	3.5	0.6–19.9
Physical activity	0.4	2.1	0.4–11.5
Diabetes mellitus	0.03	4.3	1.2–22.07
eGFR	0.04	0.9	0.9–1.007
High waist circumference	0.6	1.8	0.2–13.5
BMI < or >30 kg/m²	0.2	2.2	0.6–7.8

The classification of renal function based on eGFR value for our subjects in relation with classified albuminuria is depicted in Fig. 2.

5. Discussion

Our participants with obesity defined by a high BMI had significantly elevated albuminuria, serum glucose and triglycerides than the patients without obesity. Moreover, we noted a significant correlation between BMI value and albuminuria.

The unadjusted association between classified albuminuria and both high BMI and high triglycerides was found to be significant.

In agreement with our findings, the obesity had been already associated with proteinuria in a few previous reports [18,19] and it has been reported that hypertriglyceridemia was associated with increased risk for CKD development and high triglycerides were a prevalent risk factor for proteinuria [20,21].

On the other hand, we observed that the patients with albuminuria had significantly higher triglycerides serum concentrations and significantly higher waist circumference than the patients without albuminuria (ACR<30 mg/gr), despite they did not had significantly higher BMI.

Previously, it has been reported limitations of BMI to define obesity in CKD patients. Hence BMI does not evaluate the muscle wasting usually seen in patients with CKD, it may misclassify patients with CKD with sarcopenic obesity as normal, although their body fat would classify them as obese [22]. It seems that adipose tissue is an active organ during central obesity, which is mainly connected to the manifestation of albuminuria in patients with a poor eGFR rather than a high BMI.

The pathophysiological mechanisms of obesity-induced kidney disease are still unclear. The increased renal blood flow during obesity in conjunction with a decreased renal vascular resistance causes renal hyperfiltration. Such changes lead to glomerulomegaly, focal segmental glomerulosclerosis and fibrosis that characterize the renal damage in obese hypertensive subjects [23]. Additionally, visceral obesity and adipose tissue expansion is highly correlated with insulin resistance [24]. Adipose tissue promotes chronic inflammation and oxidative stress that exacerbate insulin resistance. Insulin resistance and inflammation are associated with multiple abnormalities including endothelial dysfunction, reduced synthase of endothelial nitric oxide, worsening of renal hemodynamic and injury of podocytes resulting in hypertension and albuminuria [18,19]. Moreover, it has been reported that insulin resistance is associated with hyperlipidemia defined by overproduction of low-density lipoprotein cholesterol and hypertriglyceridemia, which may impair the mitochondrial function and promote the kidney cell damage [25].
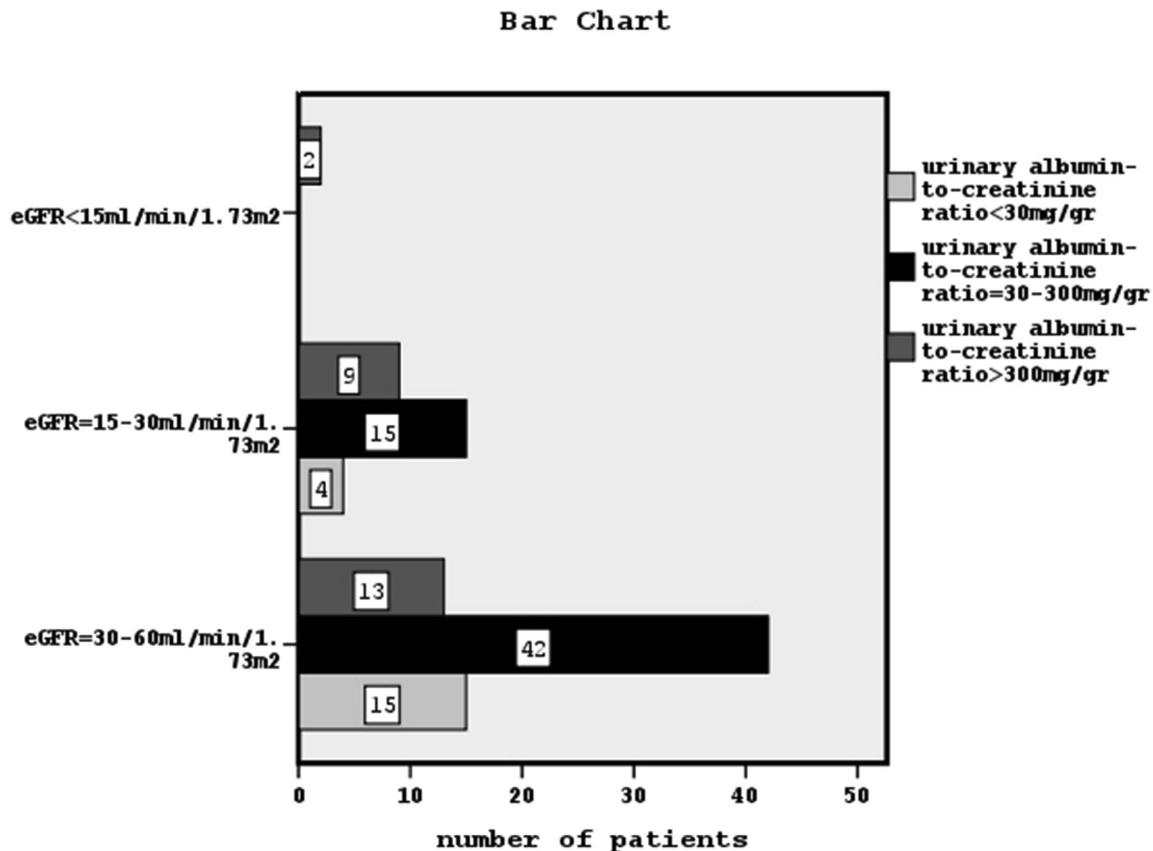

Fig. 2. Bar chart showing the classification of renal function based on eGFR value in relation with classified albuminuria in our subjects (n=100).

However, our adjusted model for the predicted albuminuria showed the high BMI to be non-significant risk factors, in contrast to diabetes mellitus and low eGFR value adjusting for covariates including the high waist circumference. The presence of diabetes mellitus was found to be a prevalent risk factor for manifested albuminuria in combination with the low eGFR in our data.

Commonly, albuminuria is associated with a low eGFR in chronic kidney disease. In our data microalbuminuria was a prevalent manifestation (a ratio equal to 57%), macroalbuminuria was presented in a ratio of 24%, although a ratio of 19% had no albuminuria despite the poor eGFR, as it is depicted in Fig. 2, in agreement with previous reports [26].

Hypertension and diabetes mellitus and their combination are worldwide the main leading causes for development of CKD defined by both a poor eGFR and/or albuminuria [27,28]. Indeed, in our data hypertensive nephrosclerosis was the main cause of chronic renal disease, although type 2 diabetes mellitus was the second cause in agreement with recent previous study [29].

According to the findings of this study we could suggest that the presence of diabetes mellitus in conjunction with the low eGFR value could be the main risk factors for manifested albuminuria in aging hypertensive patients with a poor eGFR rather than the obesity defined by a high BMI. Given that the BMI is an invalid marker of obesity in CKD patients due to commonly seen sarcopenia, the definition of central obesity should be applied in these patients to avoid the confusion regarding with both the risk for CKD progression and mortality risk.

6. Limitations

The main limitation of this study is the small number of enclosed patients by the Department of Nephrology of one single-center.

7. Conclusion

Obesity defined by a high BMI was not found to be a significant risk factor for micro/macroalbuminuria in hypertensive patients with a poor eGFR, when diabetes mellitus and the low eGFR value act as confounders.

Declarations

Ethical approval and consent to participate

The study was conducted in Doctors' Hospital and it was approved by the Hospital Institutional Review Board. All procedures performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed oral consent was obtained from all individual participants included in the study.

Consent for publication

I have obtained consent to publish from the participant (or legal parent) to report individual patient data.

Availability of supporting data

Not applicable.

Authors' contributions

Vaia Draikou: research plan, data collection, statistic analyses and manuscript writing.

Sotiris Gavriil: research plan, data collection, approval of written manuscript.

Conflicts of interest

None.

References

[1] Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on Epidemiology and prevention; national heart, lung, and blood institute; American heart association; World heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120:1640—5.

[2] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. J Am Med Assoc 2002;287:356—9.

[3] Zammit RA, Katz JM, Derby C, Bitzer M, Lipton BR. Chronic kidney disease in non-diabetic older adults: associated roles of the metabolic syndrome, inflammation, and insulin resistance. PLoS One 2015;10(10):e0139369.

[4] Cheng H-T, Huang J-W, Chiang C-K, Yen C-J, Hung K—Y, Wu K—D. Metabolic syndrome and insulin resistance as risk factors for development of chronic kidney disease and rapid decline in renal function in elderly. JECM 2012;97:1268—76.

[5] Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and metaregression analysis. Epidemiol Rev 2007;29:6—28.

[6] Chang HC, Yang HC, Chang HY, et al. Morbid obesity in Taiwan: prevalence, trends, associated social demographics, and lifestyle factors. PLoS One 2017;12. e0169577.

[7] Ladhani M, Craig JC, Irving M, Clayton PA, Wong G. Obesity and the risk of cardiovascular and all-cause mortality in chronic kidney disease: a systematic review and meta-analysis. Nephrol Dial Transplant 2017;32(3):439—49.

[8] Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. J Am Med Assoc 2015;313:837—46.

[9] Jerums G, Panagiotopoulos S, Premaratne E, MacIsaac RJ. Integrating albuminuria and GFR in the assessment of diabetic nephropathy. (glomerular filtration rate) (Report). Nat Rev Nephrol 2009;5:397—406.

[10] Bonnet F, Marre M, Halimi JM, et al. Waist circumference and the metabolic syndrome predict the development of elevated albuminuria in non-diabetic subjects: the DESIR Study. J Hypertens 2006;24:1157—63.

[11] Thomas G, Sehgal RA, Kashyap RS, Srinivas RT, Kirwan PJ, Navaneethan DS. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2011;6:2364—73.

[12] Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 2015;116(6):991—1006.

[13] Herrington William G, Smith Margaret, Clare Bankhead, Matsushita Kunihiro, Stevens Sarah, Tim Holt, Richard Hobbs FD, Coresh Josef, Woodward Mark. Body-mass index and risk of advanced chronic kidney disease: prospective analyses from a primary care cohort of 1.4 million adults in England. PLoS One 2017;12(3):e0173515.

[14] Organization WH. Global recommendations on physical activity for health. World Health Organization; 2010.

[15] Organization WH. BMI classification. Global database on body mass index: an interactive surveillance tool for monitoring nutrition transition. Geneva: World Health Organization; 2006.

[16] Consultation WE. Waist circumference and waist-hip ratio. Report of a WHO expert consultation geneva. World Health Organization; 2008. p. 8—11.

[17] Kdigo CKD, Work Group KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013 2012;3:1—150.

[18] Zhang X, Lerman LO. The metabolic syndrome and chronic kidney disease.

Transl Res 2017;183:14–25.

[19] Hsu CC, Chang HY, Huang MC, et al. Association between insulin resistance and development of microalbuminuria in type 2 diabetes: a prospective cohort study. Diabetes Care 2011;34:982–7.

[20] Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S. Triglyceride, but not total cholesterol or low-density lipoprotein cholesterol levels, predict development of proteinuria. Kidney Int 2002;62:1743–9.

[21] Chen J, Kong X, Jia X, et al. Association between metabolic syndrome and chronic kidney disease in a Chinese urban population. Clin Chim Acta 2017;470:103–8.

[22] Wang YW, Lin TY, Peng CH, et al. Factors associated with decreased lean tissue index in patients with chronic kidney disease. Nutrients 2017;9:434.

[23] Reisin E, Jack AV. Obesity and hypertension: mechanisms, cardio-renal consequences, and therapeutic approaches. Med Clin 2009;93(3):733–51.

[24] Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792–800.

[25] Gluba A, Mikhailidis D, Lip GYH, Hannam S, Rysz J, Banach M. Metabolic syndrome and renal disease. Int J Cardiol 2013;164:141–50.

[26] Moţa E, Popa SG, Moţa M, et al. Prevalence of chronic kidney disease and its association with cardio-metabolic risk factors in the adult Romanian population: the PREDATORR study. Int Urol Nephrol 2015;47(11):1831–8.

[27] Michishita R, Matsuda T, Kawakami S, et al. Kidney disease (CKD) in middle-aged and older males. Clin Exp Hypertens 2017;7:1–10.

[28] Kurata M, Tsuboi A, Takeuchi M, Fukuo K, Kazumi T. Association of metabolic syndrome with chronic kidney disease in elderly Japanese women: comparison by estimation of glomerular filtration rate from creatinine, cystatin C, and both. Metab Syndrome Relat Disord 2016;14(1):40–5.

[29] Alswat KA, Althobaiti A, Alsaadi K, et al. Prevalence of metabolic syndrome among the end-stage renal disease patients on hemodialysis. J Clin Med Res 2017;9(8):687–94.