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Can body shape index indicate obesity-associated inflammation and cardiovascular diseases in stage 3-4 chronic kidney disease patients?

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Abstract. *The incidence and prevalence of obesity are increasing rapidly throughout the world. Various methods have been developed to evaluate obesity. A body shape index (aBSI) is based on waist circumference adjusted for height and weight. High BSI values have been found to be associated with early mortality. It is known that obesity is associated with inflammation and cardiovascular diseases. In this study, we examined the relationship between aBSI, inflammatory markers such as C-reactive protein and interleukin-6 and cardiovascular disease in patients with stage 3-4 chronic kidney disease.*

Methods. One hundred twenty patients were enrolled in this cross-sectional observational study. The mean aBSI value was 0.0870. Patients were divided into 2 groups according to the mean value of aBSI as there is no currently defined cut-off value for BSI. Those with aBSI ≤ 0.087 were allocated to group I, and those with aBSI > 0.0870 to group II.

Results. Patients in group II had more cardiovascular disease than in group I. In partial Spearman correlation analysis, the presence of cardiovascular disease was correlated with aBSI ($r = 0.36$, $p = 0.0001$). aBSI higher than 0.0986 predicted cardiovascular disease in our cohort: the area under the curve (CI 95%) for aBSI was 0.715 (0.602-0.829).

Conclusions. The relationship between aBSI and inflammation could not be shown. But we found that high aBSI is associated with increased cardiovascular disease. Further studies are needed to recommend the routine clinical use of aBSI as a cardiovascular disease marker.

Keywords: *chronic kidney disease, inflammation, cardiovascular disease, obesity, body shape index.*

Conflict of interest statement. The authors declare no competing interest.

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Чи може індекс форми тіла вказувати на запалення, асоційоване з ожирінням і серцево-судинні захворювання у пацієнтів з хронічною хворобою нирок III-IV стадій?

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Резюме. *Захворюваність і поширеність ожиріння швидко зростають в усьому світі. Для оцінки ожиріння розроблено різні методи. Індекс форми тіла (aBSI) базується на окружності талії з урахуванням зросту та ваги. Було продемонстровано, що високі значення BSI пов'язані з ранньою смертністю. Відомо, що ожиріння пов'язане із запаленнями та серцево-судинними захворюваннями. У цьому дослідженні ми вивчали зв'язок між aBSI, маркерами запалення, такими як С-реактивний білок та інтерлейкін-6, і серцево-судинними захворюваннями у пацієнтів із хронічною хворобою нирок III-IV стадії.*

Методи. До одномоментного обсерваційного дослідження залучено 120 пацієнтів. Середнє значення aBSI становило 0,087. Пацієнти були розділені на 2 групи відповідно до середнього значення aBSI, оскільки на даний момент не визначено порогове значення BSI. Група I включала пацієнтів з aBSI ≤ 0,087, до групи II увійшли хворі з aBSI > 0,087.

Результати. Пацієнти групи II мали більше серцево-судинних захворювань, ніж у групі I. Наявність серцево-судинних захворювань корелювала з aBSI (r = 0,36; p = 0,0001). Значення aBSI вище за 0.0986 прогнозувало розвиток серцево-судинних захворювань:площа під ROC-кривою (CI 95%) склала 0,715 (0,602-0,829).

Висновки. Високе значення aBSI асоційовано зі збільшенням серцево-судинних захворювань у хворих на хронічну хворобу нирок III-IV стадії. Необхідні подальші дослідження, щоб рекомендувати рутинне клінічне використання aBSI як маркера серцево-судинних ускладнень.

Ключові слова: *хронічна хвороба нирок, запалення, серцево-судинні захворювання, ожиріння, індекс форми тіла.*

Introduction. The incidence and prevalence of obesity are increasing rapidly throughout the world. Obesity is associated with an increase in the frequency of hypertension (HT), diabetes mellitus (DM) and cardiovascular disease (CVD) [1]. CVD is the main cause of mortality in patients with chronic kidney disease (CKD). Obesity also plays an important role in the development and progression of CKD. However, the underlying mechanism is not fully understood [2-4]. Inflammatory cytokines (adipokines), which are released by visceral fat tissue in particular play a role in the pathogenesis of CKD and CVD. These adipokines cause a persistent, low-grade inflammation [5]. Computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy x-ray absorptiometry (DXA) can accurately assess body fat composition. These methods are expensive and their use in the routine clinical setting is difficult. Different methods are used to evaluate obesity (e.g body mass index (BMI) such as waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR), waist to height ratio (WHtR)). BMI cannot differentiate fat tissue (FM) from muscle and peripheral fat tissue from visceral fat tissue [6, 7]. Krakauer et al suggested a method for determining central obesity which is called 'A Body Shape Index (aBSI)' [8]. Recent studies showed that aBSI is associated with DM, metabolic syndrome (metS), and HT [9, 10, 11]. aBSI has also been found to be related to a higher mortality rate compared to other anthropometric measures [8,12]. High aBSI values have been found to be associated with early mortality in the US population [8]. Sato et al. [13] assessed the relationship between aBSI and all-cause mortality, they found that

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aBSI increased the mortality in men with CKD (HR 1.16, 95% CI 1.01 to 1.34).

The present study aimed to examine aBSI and its association with inflammatory markers and CVD presence in stages 3-4 CKD patients.

Materials and Methods. This cross-sectional observational study was approved by the hospital ethics committee (2013/0106). Patients with CKD but not on dialysis who were admitted to our nephrology clinic were included in the study. Those who had infections within the six months prior or active infections during the study, malignancy, rheumatic disease, age < 18 years, and those who refused to participate in the study, were not included. After written consent was obtained, age, sex, CKD etiology, co-morbidities and medications for all patients were recorded.

Biochemical measurements. *Blood samples.* For routine hemogram and biochemical evaluations, blood was taken after at least 8 hours of fasting. Venous blood samples were collected into a plain blood tube to obtain serum samples for measuring CRP and IL-6. After blood collection, samples were centrifuged at 2000x g for 10 minutes and the serum was stored at -80°C until further analyses.

Analytical methods. All the samples were measured together to avoid inter-assay variation. For all commercial kits, manufacturers' protocols were followed.

A commercial ELISA kit was used for serum C-reactive protein (CRP) determination (catalog no. EC1001-1; Assaypro LLC, MO, USA). The assay's limit of detection was 0.25 ng/mL. The intra-assay and inter-assay coefficients of variation (CVs) for CRP were 5.0% and 7.1%, respectively.

Serum interleukin (IL)-6 was measured with the IL-6-EASIA ELISA kit (catalog no. KAP1261; DIAsource Immunoassays S.A., Belgium). The lowest level of detection was 2 pg/mL. The intra-assay CVs at 147 and 623 pg/mL mean concentrations for IL-6 were 4.2% and 4.3%, respectively. The inter-assay CVs of the test were 4.4% and 5.4% at the mean concentrations were 114 and 270 pg/mL, respectively.

aBSI was calculated using the formula:

$$\text{aBSI: Waist circumference } (BMI^{2/3} X Height^{1/2})$$

Glomerular filtration rate (GFR) was calculated by the CKD-EPI formula. CKD was defined as GFR <60 ml/min/1.73 m^2 for more than 3 months according to KD GO guidelines [**14**]. The presence of CVD was evaluated by the file, self-report and assessment of the patient's file.

Statistical Analysis. Statistical analyses were performed with the SPSS software ver. 15.0 (SSPS, Chicago, IL, USA). The type of the distribution was evaluated using the Kolmogorov-Smirnov test. Distributions of aBSI, CRP and IL-6 were not normal. The median value was calculated for aBSI. The rank conversion was made for CRP and logarithmic conversion for IL-6 to make these variables distributed normally.

Comparisons of the groups were assessed with the Student's t test for continuous variables and with the χ^2 test for categorical variables. Multivariate linear regression analysis was used to determine the effect of aBSI on IL-6, CRP and CVD (after adjustment for age, sex, eGFR and the presence of diabetes mellitus and hypertension). Roc curve analysis was used to determine the sensitivity and specificity of aBSI measurements in detecting CVD. A p-value below 0.05 was considered statistically significant.

Results. A total of 120 patients with stage 3-4 CKD were enrolled in this study. The mean age of the patients was 59.6 ±11.8 years and GFR of 27, 1±9,6 ml/min/1.73 m^2, and the female to male ratio was 54/66. The etiology of CKD was hypertension (HT) (n = 48, 40%), diabetes (DM) (n = 37, 30.8%), glomerulonephritis (n =12, 10%), polycystic kidney disease (n = 4, 3.3%) and other causes (n = 19, 15.8%). The demographic and laboratory characteristics of the patients are shown in Table 1.

Table 1

Laboratory and clinical characteristics of the enrolled patients

	Patients (n =120)
Sex (M/F)*	54/66
Age (years)	59.6±11.8
CKD etiology	
DM (n, %)	37 (30.8%)
HT (n, %)	48 (%40)
Glomerulonephritis (n, %)	11(9.2%)
Other causes	24 (20%)
KAD (n, %)	28 (23.3%)
DM (n, %)	35 (29.2%)
HT (n, %)	101(84.2%)
eGFR (ml/min/1.73 m^2)	27.1±9.6
Creatinine (mg/dl)	2.3±0.6
Glucose (mg/dl)	107.8±35.5
Waist(centimeter)	102.9±13.1
Waist-hip ratio	0.96±0.08
Waist-height ratio	0.63±0.08
Body mass index (kilogram/meter^2)	28.6±5.8
Body shape index$^{\alpha}$	0.087 (0.061-0.113)
CVD** (number, %)	28 (23. 3%)
Rank CRP$^{\infty}$ (nanogram/mililiter)	97.75±45.8
Log IL-6$^{£}$ (picogram/mililiter)	1.32±0.76
Neutrophil count (milimeter^3)	4823±1538
Albumin(gram/liter)	3.9±0.4

Abbreviations: *M/F: Male/Female, **CVD: cardiovascular disease, $^{\infty}$CRP: C reactive protein, $^{£}$ IL-6: Interleukin 6, MPV: Mean platelet volume.

The median aBSI value was 0.087. Patients were divided into two groups according to this median value as there is no currently defined cut-off value for BSI. Those with aBSI <0.087 were the group I, and those with aBSI ≥ 0.087 were group II. Patients in group II had more CVD than those in group I (p = 0.029). The results are shown in Table 2.

Table 2

Comparison of clinical and laboratory data of CKD patients according to median aBSI value

	Group 1 (n = 66) aBSI < 0.087	Group 2 (n = 54) aBSI ≥ 0.087	P-value
Sex(M/F)[£]	36/30	18/36	0,200
Age3 (years)	58.8±10.9	60.5±12.9	0.135
Presence of hypertension (n, %) *	20 (30.3)	15 (27.7)	0.762
Presence of diabetes mellitus (n, %) *	55 (83.3)	46 (85.1)	0.782
Presence of CVD[∞] (n, %) *	10 (15.1 %)	18 (33.3%)	0.029
Waist (centimeter)	101.7± 14.3	104.5±11.5	0.248
Waist-hip ratio	0.93±0.08	1.00±0.008	0.000
Waist-height ratio	0.62±0.09	0.64±0.08	0.497
BMI (kilogram/meter^2)	30.6±5.9	26.1±4.77	0.000
Rank CRP **(nanogram/mililiter)	91.39±46.4	105.5±44.3	0.094
Log IL-6 (picogram/mililiter)	1.21±0.78	1.4±0.74	0.094
Neutrophil count (mililiter^3)	4752±1473	4910±1623	0.57
Albumin (gram/ liter)	4.01±0.37	3.9±0.43	0.696
Proteinuria (gram/day)	1.7±2.2	1.98±2.4	0.590

Abbreviations: [£] M/F: Male/Female, *n: number,** CRP: C reactive protein, ∞CVD: Cardiovascular disease. p < 0.05 is statistically significant.

Table 3 shows the results of partial Spearman correlation coefficients aBSI with inflammatory markers and presence of CVD after adjustment for age and sex. CVD was correlated with aBSI (r = 0.36, p = 0.0001).

Table 3

Partial correlation analysis between aBSI* and inflammatory markers and presence of CVD∞ after adjustment for age and sex

	aBSI*	
	r	p-value
CRP**	0.11	0.235
IL-6[£]	0.06	0.502
Albumin	0.00	0.971
CVD∞	0.36	0.000

Abbreviations: *aBSI: A body shape index, **CRP: C reactive protein, [£]IL-6: Interleukin 6, [∞]CVD: cardiovascular disease. p < 0.05 is statistically significant.

The multivariate regression analysis assessing the effect of aBSI on IL-6 and CRP after adjustment for age, gender, eGFR, the presence of DM and HT, showed that aBSI had no effect on log IL-6 (β: 0.162, 95% Confidence interval: -56.231-88.092 p = 0.92) or rank CRP (β: 0.284, 95% Confidence interval: -2433.19-5754.83, p = 0.423). However, the relationship with aBSI and CVD was still present (β: 0.323, 95% Confidence interval: 9.377-23.883, p = 0.000) after adjustment (Table 4).

Table 4

Multivariate regression analysis to identify factor aBSI effect on IL-6, CRP and CVD after adjusted for sex, age, eGFR, and DM and HT

	aBSI		
	Beta	p-value	(95% Confidence interval)
IL-6	0.162	0.663	-56.231-88.092
CRP	0.284	0.423	-2433.19-5754.83
CVD	0.323	0.000	9.377-23.883

Abbreviations: IL-6: Interleukin 6, aBSI: A body shape index, CRP: C-reactive protein, CVD: Cardiovascular disease

ROC-curve analysis showed that aBSI higher than 0.098 can predict CVD development in CKD patients. The area under the curve was 0.715 (0.602-0.829) (p<0.001) (Fig. 1).

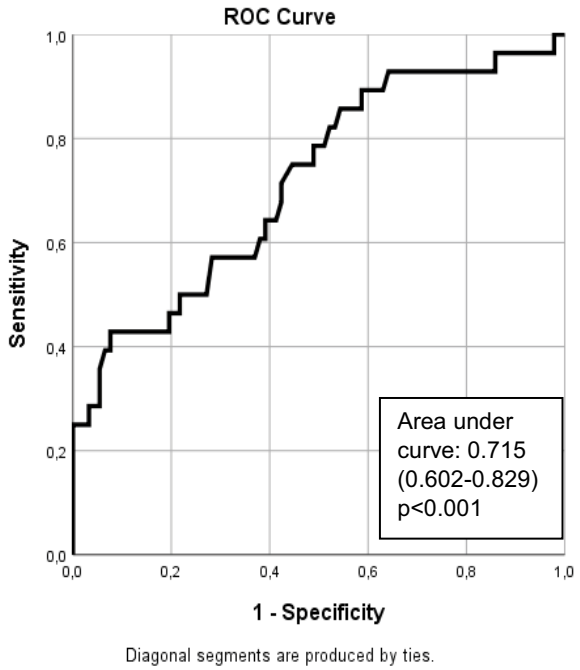

Fig. 1. ROC curve for aBSI in estimating CVD in stage 3-4 CKD patients.

Abbreviations: *aBSI: A body shape index **CVD: cardiovascular disease.

Discussion. There was no significant correlation between aBSI and inflammatory parameters such as IL-6, CRP in our study. The multivariate regression analysis assessing the effect of aBSI on IL-6 and CRP after adjustment for age, gender, eGFR, the presence of DM and HT, showed that aBSI had no effect on log IL-6 or rank CRP. The relationship between aBSI and CVD was still present after adjustment. aBSI demonstrated a predictive power for CVD based on the ROC curve.

Adipose tissue can be divided into two parts: visceral and subcutaneous adipose tissue. Visceral adipose tissue (VAT) produces markers such as adipokines, causing inflammation and this is associated with increased cardiovascular risk.

Obesity can be defined by different anthropometric measures. There has been a debate about which measure of obesity predicts CVD better [15]. BMI is not a specific indicator of visceral fat deposition. WC has been suggested as an indicator of central adiposity due to its relevance with fat distribution [16]. WC is strongly associated with metabolic diseases [17]. However, WC does not take height into account and thus may underestimate visceral fat in a short population. WHtR is developed to correct this limitation by dividing WC by height. Zhang et al. [18] found that WHtR can predict MetS better than the other anthropometric measures.

Krakauer et al. [8] developed aBSI and suggested that aBSI is related to VAT and associated with mortality risk than BMI and WC. In the NHANES (1999-2004) population, aBSI showed a better association with mortality compared with BMI and WC [8]. Afsar et al. [19] found no correlation between mortality and aBSI in dialysis patients. Zhao et al. [20] found that aBSI was better than BMI in predicting DM. But Fujita et al. [21] showed that aBSI was not a better predictor of DM, HT, or dyslipidemia than BMI or WC in Japanese adults. Li et al. [22] also found that aBSI is not suitable for determining the prevalence of MetS and IR.

Biolo et al. [23] showed that, aBSI was correlated positively with CRP ($R = 0.30$; $P < 0.05$) especially in males. We did not show any relationship between aBSI and inflammation. It can be related to our small sample size. As we know women and men have different fat distributions, visceral fat tissue is metabolically more active. If we could analyze them separately we could reach different results. But we could not divide our patients according to sex because of our small sample size. But we found that high aBSI is associated with increased CVD in CKD patients. To our knowledge, this is the first study investigating a relationship between aBSI and CVD in patients with CKD. Although some of the researchers showed a relationship between aBSI and CVD in their population study, some others could not. Anchuelo et al. [24] found that aBSI was directly and linearly related to high CVD risk in the Spanish Caucasian population. Contrary Maessen et al. [25] reported that aBSI was not a suitable index to identify either CVD or CVD risk factors in Dutch adults. There is still ongoing debate regarding the usefulness of aBSI in routine clinical practice.

Limitations. There are some limitations in this study. Our sample size was relatively small. We could not compare aBSI with more reliable methods such as magnetic resonance imaging and CT for evaluation.

Conclusions. In conclusion, it is clear that obesity plays a major role in many of the causes of preventable deaths worldwide. Therefore, prevention and treatment of obesity are very important. Accurate, reliable, and cost-effective methods are needed to diagnose obesity, especially central obesity. In our study, the use of aBSI for the diagnosis of obesity was found to be significant, especially in terms of CVD in CKD patients. To recommend the routine clinical use of aBSI as a CVD marker in pre-dialysis CKD patients, further studies are needed to determine aBSI value as a risk factor for cardiovascular mortality.

Conflict of interest. The authors declare no competing interest.

Authors' Contributions

Gulsah Sasak: The work conception, data collection, data analysis and interpretation, drafting and critical revision of the manuscript, final approval of the version to be published;

Banu Isbilen Basok: The work design, data collection, critical revision of the manuscript, final approval of the version to be published;

Semih Basci: The work conception, data collection, analysis and interpretation, drafting and critical revision of the manuscript, final approval of the version to be published;

Abdulkadir Kocanoglu: Data analysis and interpretation, drafting the article, final approval of the version to be published

Ali Bakan: Data collection, analysis and interpretation, final approval of the version to be published;

Ferruh Kemal Isman: The work conception, critical revision and final approval of the manuscript.

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