Original Paper

Association of Visceral Fat Area with Chronic Kidney Disease and Metabolic Syndrome Risk in the General Population: Analysis Using Multi-Frequency Bioimpedance

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Key Words

Visceral fat • Bioimpedance analysis • Chronic kidney disease • Metabolic syndrome

Abstract

Background/Aims: Advances in bioimpedance analysis (BIA) technologies now enable visceral fat area (VFA) to be assessed using this method. The aim of this study was to evaluate the clinical relevance and usefulness of VFA as a predictor of chronic kidney disease (CKD) and metabolic syndrome (MS), using BIA. **Methods:** We identified 24,791 adults who underwent voluntary routine health checkups at Yeungnam University Hospital. In total 22,480 patients were recruited into our study. Participants were divided into 3 tertiles based on their VFA: low, middle, and high tertiles. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m². **Results:** The higher tertile of VFA was associated with a higher prevalence of diabetes mellitus, hypertension, and male sex. Waist-to-hip ratio, body mass index, blood pressure, lean mass, body fat %, and fasting glucose, total cholesterol, triglyceride, GGT, AST, ALT, and uric acid levels all increased as the VFA tertile increased ($P < 0.001$ for all variables). The prevalence of CKD was 6.9% in the low tertile, 13.9% in the middle tertile, and 25.2% in the high tertile ($P < 0.001$). The prevalence of MS was 2.2% in the low tertile, 12.8% in the middle tertile, and 36.7% in the high tertile ($P < 0.001$). The AUROC values for VFA were higher than those for BMI and WHR. For VFA, the sensitivity and specificity for predicting CKD were 62.66% (95% CI, 61.0–64.3) and 64.22% (95% CI, 63.5–64.9), respectively, and 77.65% (95% CI, 76.3–79.0), and 68.81% (95% CI, 68.1–69.5), respectively for predicting MS. **Conclusion:** Our results demonstrated that the VFA, measured by BIA, is a simple method for predicting the risk of CKD and MS.

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Introduction

The worldwide incidence of chronic kidney disease (CKD) has increased over the last decade, and is expected to increase further [1]. The United States Renal Data System 2013 Annual Data Report showed that the prevalence of CKD is approximately 14% in the general population [2]. End-stage renal disease (ESRD) requiring renal replacement therapy is associated with low quality of life and survival rate [3]. Early diagnosis of and proper monitoring for CKD are essential for preventing progression to ESRD. Metabolic syndrome (MS) and obesity are among the most important risk factors for CKD, and their frequency is also increasing worldwide [4-8].

Visceral fat plays a key role in the development of metabolic and cardiovascular disease, and many studies have demonstrated that anthropometric methods such as body mass index (BMI), waist circumference, or waist-to-hip ratio (WHR) are closely associated with CKD [9-15]. However, such anthropometric methods cannot distinguish between increased visceral fat and increased muscle mass. The most precise methods for measuring visceral fat are computed tomography (CT) and magnetic resonance imaging (MRI). However, these methods are impractical for screening the general population, since they require expensive and specialized equipment, and exposure to radiation.

Multi-frequency bioimpedance analysis (BIA) is a diagnostic measurement that evaluates body compositions such as lean mass, fat mass, and hydration status. Many studies have examined the accuracy of BIA, and have established it as a useful tool for evaluating body composition [16-18]. Advances in BIA technologies now enable visceral fat area (VFA) to be assessed using this method. The aim of this study was to evaluate the clinical relevance and usefulness of VFA as a predictor of CKD and MS, using BIA.

Patients and Methods

Study Population

We identified 24,791 adults (>18 years old) who underwent voluntary routine health checkups at Yeungnam University Hospital between June 2008 and April 2014. When a subject underwent multiple examinations, we analyzed the data acquired during their first visit. Among these patients, 2311 lacked information regarding their renal function or BIA, and were therefore excluded. In total 22,480 patients were recruited into our study. This study was approved by the Institutional Review Board of Yeungnam University Hospital (YUH-14-0411-045). The board waived the need for informed consent.

Data collection

The subjects arrived at the hospital after an overnight fast. Clinical and laboratory data collected during the health examination included age, sex, systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), BMI (kg/m^2), WHR, and fasting glucose (mg/dL), serum creatinine (mg/dL), total cholesterol (mg/dL), triglyceride (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), gamma-glutamyl transferase (GGT, U/L), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), and uric acid (mg/dL) levels. Anthropometric measurements and blood pressure were measured by two trained nurses. Serum creatinine level was measured by an Olympus AU5400 automatic chemical analyzer (alkaline picrate, Jaffé kinetic). The estimated glomerular filtration rate (eGFR) was calculated using The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19]. VFA (cm^2), lean mass (kg), and body fat % were measured using multi-frequency BIA (In-Body 720; Biospace, Seoul, Korea). VFA measured by BIA correlated significantly with that acquired by CT ($r = 0.922$ for VFA, using data from the Biospace of 332 patients) (Figure 1).

Definitions

Participants were divided into 3 tertiles based on their VFA: low ($<81.8 \text{ cm}^2$), middle ($81.8\text{--}105.6 \text{ cm}^2$), and high tertiles ($>105.6 \text{ cm}^2$). CKD was defined as an eGFR $<60 \text{ mL}/\text{min}/1.73\text{m}^2$. Diabetes mellitus (DM) was defined as a self-reported history of a diagnosis of DM or a fasting glucose level of $\geq 126 \text{ mg}/\text{dL}$. Hypertension (HTN) was defined as an SBP of $\geq 140 \text{ mmHg}$, DBP $\geq 90 \text{ mmHg}$, a self-reported history of HTN, or use of anti-HTN drugs. BMI was calculated based on body weight and height [body weight (kg)/height (m^2)]. MS was defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines [20].

Statistical analyses

The data were analyzed using SPSS version 19 (SPSS, Chicago, IL, USA). The variables were expressed as mean $\pm$ standard deviation and compared using *t*-tests or one-way analysis of variance (ANOVA). Categorical variables were expressed as counts and percentages. Pearson's χ^2 test or Fisher's exact test were used to analyze categorical variables. We analyzed any correlations present assess the strength of the relationship between continuous variables. Multivariate logistic regression was used to estimate the odds ratio (OR), and the 95% confidence interval (CI) was used for determining the relationship between VFA tertiles and CKD, or MS. Covariates considered potential confounders (age, sex, DM, and HTN) were included in multivariate models. Model 1 was unadjusted, model 2 included age and sex, model 3 included age, sex, DM, and HTN. Discrimination—the model's ability to differentiate between participants who had MS or CKD, and those who did not—was examined using the area under the receiver operating characteristic curve (AUROC). AUROC analysis was also performed to calculate cutoff values, sensitivity, and specificity. The cutoff risk point was defined from the highest sensitivity (100 - specificity) value in the AUROC. The AUROC was calculated using MedCalc version 11.6.1.0 (Medcalc, Mariakerke, Belgium). The level of statistical significance was set at $P < 0.05$.

Fig. 1. Correlation between VFA using BIA and VFA calculated using abdominal CT at the level of the umbilicus (data from the Biospace of 162 males and 170 females). Abbreviations: VFA, visceral fat area; BIA, bioimpedance analysis; CT, computed tomography.

Results

Baseline characteristics of subjects

The low, middle, and high VFA tertiles included 7506, 7491, and 7483 subjects, respectively (Table 1). The mean VFA in the low, middle, and high tertiles was 63.2 ± 14.2 , 94.0 ± 6.9 , and 123.6 ± 15.4 cm², respectively. The higher tertile of VFA was associated with a higher prevalence of DM, HTN, and male sex. WHR, BMI, SBP, DBP, lean mass, body fat %, and fasting glucose, total cholesterol, triglyceride, GGT, AST, ALT, and uric acid levels all increased as the VFA tertile increased ($P < 0.001$ for all variables). HDL cholesterol level and eGFR decreased as the VFA tertile increased ($P < 0.001$). Table 2 shows the correlation between VFA and variable findings. VFA was positively correlated with SBP, DBP, total cholesterol, triglyceride, GGT, AST, and ALT. An inverse correlation was observed between HDL cholesterol and eGFR.

Association between VFA and CKD or MS

The prevalence of CKD was 6.9% in the low tertile, 13.9% in the middle tertile, and 25.2% in the high tertile ($P < 0.001$). The prevalence of MS was 2.2% in the low tertile, 12.8% in the middle tertile, and 36.7% in the high tertile ($P < 0.001$, Figure 2). The AUROCs for CKD and MS were analyzed in all participants. The AUROC values for CKD were 0.673 for VFA, 0.616 for BMI, and 0.613 for WHR (Figure 3A and Table 3). Those for MS were 0.802 for VFA, 0.787 for BMI, and 0.778 for WHR (Figure 3B and Table 3). The AUROC values for VFA were higher than those for BMI and WHR. For VFA, the sensitivity and specificity for predicting CKD were 62.66% (95% CI, 61.0–64.3) and 64.22% (95% CI, 63.5–64.9), respectively, and 77.65% (95% CI, 76.3–79.0), and 68.81% (95% CI, 68.1–69.5), respectively for predicting MS.

Presence of CKD or MS according to VFA tertiles

In the models adjusted for variables, we examined the association of CKD or MS and VFA tertiles (Table 4). Increasing VFA tertiles showed a positive correlation with the development

Table 1. Clinical characteristics of participants

Characteristics	Low tertile (n=7506)	Middle tertile (n=7491)	High tertile (n=7483)	P-value
Age	42.7 ± 9.3	51.2 ± 9.5	58.1 ± 11.4	<0.001
Sex (male, %)	2878 (38.3%)	4368 (58.3%)	5022 (67.1%)	<0.001
Hypertension (%)	463 (6.2%)	1181 (15.8%)	2177 (29.1%)	<0.001
Diabetes mellitus (%)	161 (2.1%)	520 (6.9%)	1177 (15.7%)	<0.001
CKD (%)	518 (6.9%)	1041 (13.9%)	1882 (25.2%)	<0.001
WHR	0.86 ± 0.03	0.91 ± 0.03	0.95 ± 0.04	<0.001
BMI (kg/m ²)	21.3 ± 2.1	23.9 ± 2.0	26.4 ± 2.8	<0.001
SBP (mmHg)	112.4 ± 12.6	118.8 ± 13.4	124.9 ± 13.7	<0.001
DBP (mmHg)	70.7 ± 9.6	75.5 ± 9.9	79.5 ± 9.8	<0.001
Fasting glucose (mg/dL)	88.1 ± 15.6	93.6 ± 20.5	100.1 ± 26.0	<0.001
Total cholesterol (mg/dL)	186.4 ± 33.0	202.7 ± 35.8	206.8 ± 38.2	<0.001
Triglyceride (mg/dL)	91.5 ± 64.2	133.1 ± 98.5	158.1 ± 110.3	<0.001
HDL cholesterol (mg/dL)	62.1 ± 15.2	55.3 ± 14.4	51.8 ± 13.4	<0.001
GGT (U/L)	25.5 ± 59.1	38.5 ± 59.1	48.4 ± 66.0	<0.001
AST (U/L)	22.5 ± 14.7	25.8 ± 19.3	28.4 ± 18.1	<0.001
ALT (U/L)	19.9 ± 20.0	27.1 ± 28.3	32.4 ± 25.0	<0.001
Uric acid (mg/dL)	4.7 ± 1.3	5.2 ± 1.4	5.6 ± 1.5	<0.001
VFA (cm ²)	63.2 ± 14.2	94.0 ± 6.9	123.6 ± 15.4	<0.001
eGFR (mL/min/1.73m ²)	90.9 ± 26.2	79.8 ± 23.9	73.5 ± 25.0	<0.001
Body fat %	13.7 ± 3.6	17.2 ± 3.9	22.0 ± 5.8	<0.001
Lean mass (kg)	41.8 ± 8.3	45.6 ± 8.8	47.6 ± 9.4	<0.001

Data are expressed as numbers (percentages) for categorical variables and mean ± standard deviation for continuous variables. Abbreviations: CKD, chronic kidney disease; WHR, waist to hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; VFA, visceral fat area; eGFR, estimated glomerular filtration rate

Fig. 2. Prevalence of MS according to VFA tertiles (2.2% in the low tertile, 12.8% in the middle tertile, and 36.7% in the high tertile; $P < 0.001$). Abbreviations: MS, metabolic syndrome; VFA, visceral fat area.

of CKD and MS compared with low VFA tertiles. In model 2, patients in the middle and high tertiles had a 6.283, and 25.312-fold increased risk for MS compared with patients in the low tertile (95% CIs: 6.283–7.434 for the middle tertile and

21.477–29.832 for the high tertile). In model 3, patients in the middle and high tertiles had a 4.983, and 17.660-fold increased risk for MS, respectively, compared with those in the low tertile (95% CIs: 4.197–5.917 for the middle tertile and 14.993–20.885 for the high tertile).

Table 2. Correlation between VFA and other variables

	Correlation coefficient
Age	0.569
SBP	0.386
DBP	0.364
Fasting glucose	0.242
Total cholesterol	0.244
Triglyceride	0.287
HDL cholesterol	-0.299
GGT	0.150
AST	0.145
ALT	0.216
Uric acid	0.275
eGFR	-0.287

Abbreviations: VFA, visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate. Values are the correlation coefficients and $P < 0.001$ for all analyses

Fig. 3. Receiver operating characteristic curve of VFA, BMI, and WHR for prediction of CKD (A) or MS (B). Abbreviations: VFA, visceral fat area; BMI, body mass index; WHR, waist-to-hip ratio.

Table 3. Comparison of AUROC according to the variables

	AUC	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	P-value
AUROC for CKD					
VFA	0.673	>101.1	62.7% (61.0-64.3)	64.2% (63.5-64.9)	<0.001
BMI	0.616	>23.3	71.5% (69.9-73.0)	47.8% (47.1-48.5)	<0.001
WHR	0.613	>0.89	82.7% (81.4-84.0)	37.9% (37.2-38.6)	<0.001
AUROC for MS					
VFA	0.802	>101.6	77.7% (76.3-79.0)	68.8% (68.1-69.5)	<0.001
BMI	0.787	>24.9	70.5% (69.1-72.0)	73.2% (72.6-73.8)	<0.001
WHR	0.778	>0.91	75.9% (74.5-77.2)	66.7% (66.0-67.4)	<0.001

Abbreviations: AUROC, area under receiver operating characteristics; AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; VFA, visceral fat area; BMI, body mass index; WHR, waist to hip ratio

In model 2, patients in the middle and high tertiles had a 1.389, and 2.105-fold increased risk for developing CKD, respectively, compared with those in the low tertile (95% CIs: 1.235–1.563 for the middle tertile and 1.878–2.359 for the high tertile). In model 3, patients in the middle and high tertiles had a 1.368, and 2.027-fold increased risk of developing CKD, respectively, compared with those in the low tertile (95% CIs: 1.216–1.540 for the middle tertile and 1.805–2.277 for the high tertile).

Discussion

The results of the present study show that VFA measured using BIA is related to CKD, MS, and other metabolic parameters. The univariate and multivariate analyses revealed that VFA tertiles were associated with CKD in the general population.

MS was first described in 1988 [21]. The components of MS include waist circumference (WC), blood pressure, and fasting glucose, HDL cholesterol, and triglyceride levels. Many studies demonstrated that MS is associated with cardiovascular disease and mortality in the general population [9-11, 20]. Recent studies have demonstrated that MS is associated with the development of CKD [6-8, 22]. MS induces abnormalities such as inflammation, insulin resistance, HTN, and dyslipidemia that increase the expression of adipokines, angiotensin, and inflammatory cytokines, which result in renal injury [8].

BMI is as an important obesity index. However, the negative effect of obesity is increasingly attributed to excess adiposity, particularly central and visceral adiposity, and BMI cannot differentiate between fat mass and other body compositions such as lean mass or bone mass. Various studies have reported a U-shaped relationship between BMI and mortality [23-26].

Table 4. Odds ratios for CKD or MS according to VFA tertiles

	Low tertile	Middle tertile	High tertile
MS			
Model 1: unadjusted			
Odds ratio	1	6.397	25.378
95% CI	reference	5.412-7.562	21.626-29.782
P-value	-	<0.001	<0.001
Model 2: adjusted for age, sex			
Odds ratio	1	6.283	25.312
95% CI	reference	5.310-7.434	21.477-29.832
P-value	-	<0.001	<0.001
Model 3: adjusted for age, sex, DM, HTN			
Odds ratio	1	4.983	17.660
95% CI	reference	4.197-5.917	14.933-20.855
P-value	-	<0.001	<0.001
CKD			
Model 1: unadjusted			
Odds ratio	1	2.177	4.533
95% CI	reference	1.949-2.432	4.088-5.027
P-value	-	<0.001	<0.001
Model 2: adjusted for age, sex			
Odds ratio	1	1.389	2.105
95% CI	reference	1.235-1.563	1.878-2.359
P-value	-	<0.001	<0.001
Model 3: adjusted for age, sex, DM, HTN			
Odds ratio	1	1.368	2.027
95% CI	reference	1.216-1.540	1.805-2.277
P-value	-	<0.001	<0.001
Abbreviations: MS, metabolic syndrome; CKD, chronic kidney disease; VFA, visceral fat area; DM, diabetes mellitus; HTN, hypertension			

This discrepancy has been termed the obesity paradox or reverse epidemiology. WC and WHR are the most frequently used indicators of visceral obesity [20, 27]. These can be used to evaluate visceral obesity, but are inadequate for monitoring changes in visceral fat over time, and they are difficult to apply to peritoneal dialysis patients [28]. CT and MRI are the most accurate methods for evaluating visceral fat mass, but are expensive for routine use in the general population [29]. Normally they are used only in clinical research, or to validate other methods.

VFA is an important component and cause of the MS. Measurement of VFA is important to predict MS and CKD. BIA measures impedance of the arms, trunk, and legs using multi-frequencies from eight polar tactile electrode impedance meters [18]. Fat tissue in the trunk distributes to subcutaneous and visceral areas. Subcutaneous fat is connected in parallel for alternating current, and an increase in this has no significant effects on the impedance of the trunk. Visceral fat and visceral lean tissue however, are serially connected for alternating current, and therefore an increase in visceral fat dose result in a significant increase in impedance. VFA measured by BIA is calculated by a regression equation taking into account the differences of impedance in variable frequencies. Two validation studies demonstrated significant correlation between VFA measured by BIA and CT as a reference method [30, 31]. To our knowledge, the present study is the first study to evaluate the association between VFA and CKD or MS, using BIA. The present study showed that VFA tertiles measured by BIA are associated with the prevalence of CKD and MS, as well as other metabolic parameters such GGT level, uric acid level, and body fat %. In addition, the results obtained using correlation analysis were similar. Some reviews have described the limitations and contraindications of BIA measurements [32, 33]. Pregnant women, children, subjects wearing a pacemaker, patients with skin lesions that do not permit the use of electrodes, or patients with limited contact should be considered as contraindications for BIA measurements.

Conclusion

This study has several limitations. First, it is limited by its cross-sectional and single-center nature. Second, habitual parameters such as alcohol consumption and smoking were not evaluated in the present study. Third, eGFR was calculated using the CKD-EPI equation, but the validity of this equation has not been fully evaluated in the Korean population. We did not measure more precise parameters such as cystatin C or inulin clearance. However, the impact of these limitations will be reduced by the large sample size in this study.

In summary, our results demonstrated that the VFA, measured by BIA, is a simple method for predicting the risk of CKD and MS.

Disclosure Statement

The authors have declared that no competing interests exist, neither financial nor others.

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