

Comparison of renal biomarkers in obesity with early renal dysfunction

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ABSTRACT

Background: Obesity is an important risk factor of chronic kidney disease. Screening and diagnosis of the disease at the early stage are beneficial for risk control and therapeutic management.

Objectives: To assess the relationship among renal biomarkers levels and obesity parameters in obese people with early renal dysfunction.

Materials and methods: Subjects were 180 volunteers, aged 35-60 years, who participated in a health survey at the time of periodic checkup. They were divided into 3 groups using body mass index (BMI) and into 2 groups based on estimated glomerular filtration rate (eGFR); normal kidney function (NKF) and early renal disease (ERD). Serum cystatin C, urinary kidney injury molecule (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) were measured.

Results: The results show that eGFR values of NKF and ERD group were 105.02 ± 8.34 and 79.90 ± 10.76 mL/min/1.73m², respectively. The ERD group with decreased eGFR, had significantly increased serum creatinine levels ($p < 0.001$), but decreased KIM-1 in the obesity group. Serum cystatin C significantly increased in ERD ($p < 0.001$) and was negatively associated with obesity parameters but negatively correlated with eGFR. Urinary KIM-1 trended to decrease in ERD, but not significant ($p > 0.05$) compared to normal kidney function group. In addition, urinary NGAL was positively correlated with eGFR. Multivariable adjusted OR (95% confidence interval) for ERD in obese group was 3.8 (1.2-11.9) for cystatin C (p for trend=0.024). This association was more pronounced in older subjects (≥ 45 years).

Conclusion: Cystatin C could be used for monitoring normal kidney function as well as early renal injury in obese population. This could be implemented in screening, risk regulation and management of kidney diseases at the early stage.

Introduction

Overweight and obesity are considered a serious health problem worldwide. In Thailand, the prevalence of obesity increased by 10-25% during past 10 years.¹ Obesity can be assessed by using the body mass index (BMI), waist

circumference (WC) and waist to hip ratio (WHR). Previous studies have shown that obesity is high risk factor for chronic kidney disease. Obesity results in hypertension and type 2 diabetes, which is the leading cause of kidney failure and end-stage kidney disease.² Data from The Framingham Offspring Cohort and the Hypertension Detection and Follow-Up Program indicate that increased BMI is associated with progression to chronic kidney disease (CKD).³ Obesity has been reported to cause kidney failure even in people with no history of diabetes and hypertension.⁴

In obese people, high level of free fatty acids (FFAs)

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are found, which causes endothelial dysfunction.⁵ This leads to an increase in vascular permeability and albumin leakage from the glomerular endothelial cells into the urine.⁶ There is evidence that higher FFAs correlate with microalbuminuria in obese people.⁷ In addition, BMI was found to correlate with the glomerular filtration rate (GFR) and could predict early renal dysfunction (ERD) in obese individuals.⁸

Glomerular Filtration Rate (GFR) is regarded as the more precise for determining kidney function; however, it is labor-intensive and very expensive. The most commonly used method is serum creatinine for estimated GFR (eGFR). However, there are many factors affecting creatinine level such as muscle mass, protein intake, gender and age. Therefore, sensitive and early biomarkers are needed to establish for detection early renal abnormalities such as cystatin C, Kidney Injury Molecule-1 (KIM-1), and Neutrophil Gelatinase-Associated Lipocalin (NGAL).

Cystatin C is a low molecular weight protein produced in the constant level from all types of nucleated cells. It is freely filtered by the glomerular membrane and reabsorbed almost entirely in the proximal tubules.⁹ The cohort studies in type 1 and type 2 diabetes and diabetic nephropathy, it was found that a higher stage by eGFR_{cyst} than eGFR_{creat} had a significantly higher risk of end-stage renal disease (ESRD) than those with concordant staging in all three cohorts.¹⁰

Neutrophil gelatinase-associated lipocalin (NGAL) or lipocalin2 that is expressed at low levels in several human tissues. It is rapidly released from renal tubular cells in response to various insults of the kidney.¹¹ The studies in patients with CKD due to glomerulonephritis shows that the average concentration of NGAL in urine of patients with chronic renal failure is higher than in the control group. In addition, it was found that the concentration of NGAL in urine is related to the concentration of creatinine in serum.¹²

Another very well characterized urinary biomarker is kidney injury molecule (KIM-1). It is a transmembrane type 1 glycoprotein expressed at very low levels in the normal kidney. It is markedly upregulated in proximal tubules following renal ischemic or toxic injury.¹³ The results of experimental and clinical studies show that increased urinary KIM-1 levels are related to KIM-1 expression, indicating that KIM-1 is a biomarker for tubular interstitial pathology.¹⁴

Most of these renal biomarkers were studied in diabetic nephropathy but there is no information in obese people with ERD. Considering these important gaps, the aim of the present study was to assess the relationship of Cystatin C, NGAL and KIM-1 levels among obese people with early renal dysfunction (ERD) and those with normal kidney function (NKF). In addition, obesity parameters (BMI, WC, and WHR) were also determined the correlation with renal biomarkers (serum creatinine, cystatin C, eGFR (CKD-EPI), urine albumin/creatinine ratio (UACR), NGAL and KIM-1) in order to identify ERD in people with obesity

Materials and methods

Study population

This study protocol was approved by the Human Ethics Committee of Thammasat University, Thailand (COA No.019/2559). The participants were selected from volunteers in Thailand between March 2018 and September 2018. All participants fulfilled the following inclusion criteria: between 35 and 60 years of age and do not use of drugs that affect the function of the liver and kidneys such as acetaminophen, ascorbic acid, cefazolin, chlorothiazide, cimetidine, dexamethasone, nitrofurantoin, ibuprofen, and furosemide. Participants who had hypertension, diabetes, liver and kidney disease were excluded from the current analyses. We included 180 participants and divided into 6 subgroups according to body mass index (BMI) and kidney function. The participants were classified as: (1) normal weight with normal kidney function (NKF) (2) normal weight with ERD (3) overweight with NKF (4) overweight with ERD (5) obesity with NKF, and (6) obesity with ERD. BMI was calculated as weight in kilograms divided by the square of height in meters (normal weight; 18-22.9 kg/m², overweight; 23.0-24.9 kg/m², obesity; 25 kg/m²) and ERD subgroups were classified as eGFR; 30-89 or urine albumin to creatinine ratio (UACR); 30-300 mg/gm.

Anthropometric and biochemical measurement

Anthropometric measurements were performed, including weight (Wt), height (Ht) and waist (WC) and hip (HC) circumferences. Wt was measured to the nearest 0.1 kg using a digital scale, and Ht was measured to the nearest centimeter in the standing position. WC was measured midway between the bottom of the rib cage and iliac crest, and HC was measured as the maximum circumference of the buttocks. The waist-to-hip ratio (WHR) was calculated as the WC divided by the HC.

Systolic and diastolic blood pressure (BP) were measured with an automated sphygmomanometer (BP103iil, Omron Health Care Co. Ltd., Kyoto, Japan). Venous blood was drawn into a vacuum tube and centrifuged to separate the serum. Creatinine was measured by enzymatic method using a Beckman Coulter UniCel DXC 800 Synchron automated chemistry analyzer (Beckman Coulter, Inc., Atlanta, USA). This assay maintains a range from 0.2 to 25.0 mg/dL and intra-assay and interassay coefficients of variation of 0.6% to 1.5% and 1.8% to 3.0%, respectively. Albumin was measured by automated analyzer using Bromocresol green (BCG) method with a range from 1.5 to 6.0 gm/dL and intra-assay and interassay coefficients of variation less than 3.0%. Microalbumin was measured by turbidimetry immunoassay with linearity from 0.5-30 mg/dL. Serum cystatin C level was analyzed by immunoassay using an ARCHITECT c8000 automated (Abbott, Abbott Park, Illinois, USA). eGFR were calculated by using the CKD-EPI formula, the most widely-used equations for estimating GFR in adults. The CKD-EPI equation, expressed as a single equation, is: $GFR = 141 * \min(Scr/\kappa, 1)^\alpha * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018 [if\ female] * 1.159 [if\ black]$

(Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.)¹⁵

Renal biomarkers measurements

Renal biomarkers including urinary KIM-1 and NGAL were measured by ELISA assays using a Human TIM/KIM-1 ELISA kit (Cat.No. DKM 100, R&D systems, Minneapolis, MN, USA). NGAL was measured with a Human NGAL ELISA kit (Cat.No. DLCN 20, R&D systems, Minneapolis, MN, USA) according to the manufacture's protocols. All biomarkers concentration was performed in duplicate and adjusted for urinary creatinine concentration.

Statistical analysis

All analyses and calculations were performed using SPSS statistical ver.18.0 (IBM Co., Armonk, New York, USA). Data are expressed as numbers and percentages. Continuous variables were expressed as mean±standard deviation (SD). The Kruskal-Wallis test was used to compare continuous variables between groups. Differences variables among the six groups were determined using a generalized linear model (Duncan's test of multiple comparisons). Multivari-

able-adjusted logistic regression analysis was conducted to determine odds ratios (ORs) and 95% confidence interval (CIs) for the evaluation risk of ERD. The *p* values of <0.05 were considered statistically significant.

Results

Characteristic of participants

Characteristics of study participants according to renal function are shown in Table 1. Participants were assigned to two groups according to the renal function. Ninety people were assigned to normal kidney function group (NKF; eGFR >90 or UACR <30 mg/gm) and another ninety people were designated to early renal dysfunction (ERD; eGFR 30-89 or UACR 30-300 mg/gm). ERD group had the statistically significant higher mean age, systolic BP, and diastolic BP, creatinine. On the other hand, ERD group showed the statistically significant lower eGFR level than the NKF group (*p*<0.001). Other characteristics including BMI, WC, WHR, and UACR were not different among the two groups.

Table 1 Baseline characteristics of study population in NKF and ERD groups.

Variables	NKF Group (n=90)	ERD Group (n=90)	<i>p</i> value
Male/Female (%)	15.6/84.4	26.7/73.3	0.069
Age (years)	43.52±5.93	49.99±6.51	<0.001*
BMI (kg/m ²)	24.70±3.88	24.36±3.19	0.971
Systolic BP (mmHg)	116.28±12.46	124.49±13.61	<0.001*
Diastolic BP (mmHg)	75.89±9.34	81.32±11.40	<0.001*
WC (cm)	82.56±10.14	84.37±9.00	0.162
WHR	0.83±0.08	0.86±0.06	0.046*
Creatinine (mg/dL)	0.71±0.11	0.93±0.17	<0.001*
eGFR (mL/min/1.73m ²)	105.02±8.34	79.90±10.76	<0.001*
UACR (mg/gm)	6.72±4.28	13.97±32.96	0.209
KIM-1 (µg/gCr)	0.81±0.51	0.57±0.53	0.003*
NGAL (µg/gCr)	16.95±22.08	15.08±18.12	0.121
Cystatin C (mg/L)	0.82±0.11	0.93±0.13	<0.001*
eGFRcys (mL/min/1.73m ²)	100.69±12.87	85.88±13.98	<0.001*

Note: NKF: Normal kidney function, ERD: Early renal dysfunction, Data are presented as mean±standard deviation. Asterisks indicate significant differences between groups using student t-test at *p* value <0.05.

Level of renal biomarkers and factors associated with obesity parameter and renal function

Comparison of study parameters in NKF and ERD groups showed in Table 2. Participants were categorized to six subgroups according to the renal function and obesity parameters. The mean difference in diastolic BP and WC were statistically significant among the six groups using Kruskal-Wallis test ($p=0.003$ and 0.001). Renal biomarkers; KIM-1, NGAL and cystatin C were compared among the six groups. In NKF groups, it was found that the BMI was different among the study population. Systolic BP ($p=0.001$), diastolic BP ($p=0.005$), WC ($p<0.001$), WHR ($p=0.029$), KIM-1 ($p=0.011$), cystatin C ($p=0.013$) and eGFRcys ($p=0.021$) were statistical significantly different. The post-hoc comparison showed the BMI was significantly different in all three groups ($p<0.001$). Systolic BP and diastolic BP in obesity were higher than in the overweight group and normal weight group respectively. It indicated that obesity was a significant factor contributed to elevate of systolic and diastolic BP. WC was significantly different in all three groups ($p<0.001$). WC of obesity group was higher than the overweight and normal weight group, respectively. WHR of obesity group was increased significantly from the normal weight group ($p=0.011$), but there was no difference between the normal weight and the overweight

group. Renal biomarkers, including KIM-1, cystatin C and eGFRcys are different in normal weight compared to obesity ($p=0.002$, 0.004 and 0.005 respectively). However, the values did not differ between normal weight and overweight group. The result demonstrated that obese people with normal kidney function had KIM-1, cystatin C and eGFRcys levels higher than those with normal weight. For ERD group, it was found that the BMI was different among the study population. Diastolic BP, WC, cystatin C and eGFRcys were statistically significant different. So, this showed that BMI in ERD group was determined according to the criteria. The obesity group has a higher significantly diastolic BP than the overweight group ($p=0.008$) and in the normal weight group ($p=0.002$). The WC in normal weight was lower significantly than the overweight ($p<0.001$) and obesity ($p<0.001$). But there was no difference of WC between the overweight and obesity groups. The mean differences in cystatin C were statistically significant; 1.01 ± 0.16 mg/L in obesity, 0.88 ± 0.11 mg/L in overweight, and 0.91 ± 0.07 mg/L in normal weight with ERD. The eGFRcys in obesity was lower significantly than overweight ($p<0.001$) and normal weight ($p=0.001$). The value in other renal biomarker parameters were also evaluated but did not show significantly difference according to group.

Table 2 Comparative study in NKF and ERD groups.

Variables	NKF Groups (n=90)				ERD Groups (n=90)			
	Normal weight (n=30)	Overweight (n=30)	Obesity (n=30)	p value	Normal weight (n=30)	Overweight (n=30)	Obesity (n=30)	p value
Age (years)	42.6±6.38	45.07±6.30	43.50±4.73	0.053	49.51±6.81	49.43±7.07	51.03±5.64	0.673
BMI (kg/m ²)	21.21±1.05	23.93±0.57	28.96±3.57	<0.001 [†]	21.01±1.34	24.11±0.56	27.95±2.01	<0.001 [†]
Systolic BP (mmHg)	111.47±14.60	114.87±10.33	122.50±9.53	0.0015 [§]	120.57±15.01	124.10±11.56	128.80±13.21	0.094
Diastolic BP (mmHg)	74.07±10.45	74.03±8.55	79.57±8.01	0.0055 [§]	79.20±9.08	77.70±9.31	87.07±13.33	0.0035 [§]
WC (cm)	73.93±7.08	82.33±5.51	91.40±8.79	<0.001 [†]	77.28±7.49	85.90±6.55	89.93±7.95	<0.001 [§]
WHR	0.80±0.08	0.85±0.08	0.85±0.06	0.029 [§]	0.84±0.08	0.87±0.05	0.87±0.06	0.077
Creatinine (mg/dL)	0.70±0.08	0.69±0.10	0.73±0.15	0.477	0.89±0.11	0.91±0.17	0.98±0.22	0.292
eGFR (mL/min/1.73m ²)	106.00±8.59	104.93±7.57	104.13±8.97	0.604	81.37±5.77	82.33±10.33	76.00±13.82	0.060
UACR (mg/gm)	6.12±2.83	6.19±3.06	7.83±6.07	0.816	0.53±0.48	13.65±25.15	20.83±50.79	0.099
KIM-1 (µg/gCr)	0.61±0.40	0.74±0.49	0.95±0.53	0.011 [§]	0.43±0.36	0.56±0.53	0.69±0.62	0.413
NGAL (µg/gCr)	20.08±34.87	17.43±12.88	13.35±9.49	0.436	18.44±17.29	12.58±10.21	14.22±24.19	0.153
Cystatin C (mg/L)	0.77±0.11	0.82±0.10	0.85±0.10	0.013 [§]	0.91±0.07	0.88±0.11	1.01±0.16	<0.0015 [§]
eGFRcys (mL/min/1.73m ²)	105.63±12.80	99.57±12.65	96.87±11.94	0.021 [§]	87.33±9.98	92.30±12.85	78.00±15.04	<0.0015 [§]

Note: NKF: Normal kidney function, ERD: Early renal dysfunction, Data are presented as mean±standard deviation, [†]The difference in Normal weight, overweight and obesity, [‡]The difference is between normal weight and overweight, [§]The difference is between normal weight and obesity, ^{||}The difference is between overweight and obesity.

Association between renal biomarkers and obesity parameters

Table 3 displays the correlations of obesity parameters and eGFR with renal biomarkers. It was found that BMI were positively correlated with KIM-1 and Cystatin C ($r=0.227$ and 0.211 respectively). Cystatin C concentration showed a positive correlation with obesity parameters (BMI, WC, WHR). A weak negative correlation between NGAL concentrations, WC ($r=-0.237$), and WHR ($r=-0.253$) were observed in this study.

Multiple logistic regression analysis was also used to investigate the independent factors for predicting ERD

adjusting for BMI, WC, and other factors related to ERD in obesity, such as age; systolic BP; diastolic BP; cystatin C; and eGFRcys (Table 4). As shown in Table 4, the probability of ERD in obesity were higher in the study population with older and increased cystatin C level. The OR and 95%CI for risk of ERD in obesity significantly increased with increasing age (OR=6.5; 95%CI=2.0-21.0; p for trend=0.002) and increasing cystatin C greater than 0.875 mg/L (OR=3.8; 95%CI=1.2-11.9; P for trend=0.024). There were no interactions between blood pressure, eGFRcys, and the other independent factors.

Table 3 Correlations of obesity parameter and eGFR with renal biomarkers.

Characteristics	BMI		WC		WHR		eGFR	
	r	p value	r	p value	r	p-value	r	p value
Creatinine (mg/dl)	0.036	0.633	0.279	<0.001*	0.346	<0.001*	-0.856	<0.001*
eGFRcre(mL/min/1.73m ²)	-0.039	0.607	-0.191	0.010*	-0.216	0.004*	-	-
UACR (mg/gm)	0.065	0.384	-0.040	0.597	-0.098	0.192	-0.045	0.552
KIM-1 (μg/gCr)	0.227	0.004*	0.142	0.072	-0.101	0.200	0.222	0.004*
NGAL (μg/gCr)	-0.098	0.191	-0.237	0.001*	-0.253	0.001*	0.173	0.020*
Cystatin C (mg/L)	0.211	0.004*	0.317	<0.001*	0.223	0.003*	-0.612	<0.001*
eGFRcys (mL/min/1.73m ²)	-0.200	0.007	-0.270	<0.001*	-0.167	0.025	0.650	<0.001*

r: Correlation Coefficient

Table 4 Adjusted odds ratio from multiple logistic regression analysis for evaluating risk of ERD.

Variables	B	S.E.	Wald	Adjusted odds ratio (95%CI)	p value
Age					
35-45 years				1	
46-55 years	1.126	0.386	8.491	3.1 (1.4-6.5)	0.004*
>55 years	1.881	0.594	10.016	6.5 (2.0-21.0)	0.002*
Systolic BP					
<130 mmHg				1	
≥130 mmHg	0.156	0.516	0.091	1.2 (0.4-3.2)	0.763
Diastolic BP					
<85 mmHg				1	
≥85 mmHg	0.443	0.489	0.821	1.6 (0.6-4.0)	0.365
Cystatin C					
<0.875 mg/L				1	
>0.875 mg/L	1.327	0.586	5.131	3.8 (1.2-11.9)	0.024*
eGFRcys					
<90 mL/min/1.73m ²				1	
<90 mL/min/1.73m ²	0.399	0.604	0.437	1.5 (0.5-4.8)	0.509

Chi-square (Omnibus Tests of Model Coefficients) = 60.96, $df = 6$, Sig. = 0.00 -2 Log likelihood = 188.57, Cox&Snell R² = 0.287, Nagelkerke R² = 0.383

Discussion and Conclusion

The present study constructed a model investigating the risk of ERD in obese people from three renal biomarkers; KIM-1, NGAL, and cystatin C. Due to the cystatin C is increasingly recognized as a more sensitive and therefore more useful marker for predicting ERD risk in obesity population. Recently, obesity and high blood pressure has been proposed as an independent risk factor for the leading causes of CKD and ESRD.^{16, 17} Being obese or overweight leads to elevations in serum cystatin C levels.¹⁸ Based on pathophysiology, the effects of weight elevation might be due to decrease in hyperfiltration, high filtration pressure, inflammation, and oxidative stress, as well as increase in nitric oxide and proteinuria.¹⁹

Microalbuminuria and eGFR currently used for CKD and ESRD has significant limitations. Microalbuminuria is suggested to be a sign of early glomerular damage. The occurrence of microalbuminuria in type 1 diabetes can already be associated with diabetic nephropathy lesions. On the other hand, decrease of GFR may not be an adequate indicator for early diagnosis. In addition, many studies have explored the relationship between renal biomarkers and renal failure. Creatinine, eGFR, and cystatin C are known to lead to an increase in the incidence of end-stage renal disease (ESRD).^{20, 21}

Our study revealed that ERD subjects had lower urinary KIM-1 and NGAL values compared to NKF subjects, but that there was no difference level in urinary NGAL. In addition, we found that urinary cystatin C is significantly elevated in ERD subjects without increased urinary albumin-creatinine ratio when compared to NKF. In another study, it was also demonstrated that ERD subject had increased cystatin C and highly correlated with eGFR when compared to control subjects.^{22, 23} Recent evidence supports that elevated waist circumference (WC) and body mass index (BMI) are among the most important factors leading to obesity. In addition, obesity is associated with hypertension and related to kidney dysfunction. Our results showed that cystatin C level were correlated with BMI, diastolic BP, and decrease eGFR level. Also, we found that the obese with ERD group had a higher value of cystatin C than the obese with NKF group. Some studies investigating the relationship between cystatin C and obesity parameters showed that urinary cystatin C level is related to BMI, WC, WHR,^{18, 19, 20} results which support our current work. In our study, urinary NGAL and KIM-1 were not significantly increased in obese people with ERD subjects. To the best of our knowledge, NGAL and KIM-1 have not previously been studied in obese subjects who have ERD condition.

In multiple logistic regression analysis, the present study is concordant with the majority of previously published work, the CREDIT study (Chronic Renal Disease in Turkey) demonstrated a risk of CKD among 30-year-olds-people increased from 1.45-2.18 times for increase every 10 years of age. In addition, cystatin C was significantly associated with ERD among older subjects (>45 years) ($p=0.004$).²³ The association between the risk of ERD and each parameter is shown in Table 4. We observed lower odds ratio of high blood pressure and low eGFR levels in the models.

We acknowledge that the current study has some limitations. First, this is a cross-sectional study and the sample number was low. Therefore, there is a need for larger prospective studies to confirm the results and reduce the possibility of confounding variables. Second, renal injury biomarkers should be investigated in long term perspective. Despite these limitations, this is the first study to investigate the association of kidney markers and obesity parameters in Thai population from survey study. This information could be implemented in screening, risk regulation and management of kidney diseases at the early stage.

Conclusion

Obesity has the great influence on renal function and it can cause renal alterations and kidney disease. The results of this study revealed that age, high systolic and diastolic BP, elevated creatinine and cystatin C level, and the decline in eGFR associated with the occurrence of ERD. Creatinine and cystatin C levels were significantly associated with eGFR. Cystatin-C could be a promising early biomarker of kidney disease in obese people. Further prospective studies should be conducted to explore the clinical usefulness of cystatin C in the early renal dysfunction in obese people.

Conflict of interest

The authors declare no conflicts of interest.

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