CEOG Clinical and Experimental Obstetrics & Gynecology

The association between cystatin C and metabolic syndrome according to menopausal status in healthy Korean women

Y.J. Lee, K.Y. Yun, S.C. Kim, J.K. Joo, K.S. Lee

Department of Obstetrics and Gynecology, Medical Research Institute, Pusan National University School of Medicine, Busan (Korea)

Summary

Objective: Cystatin C (Cys-C) is used as a marker for the measurement of the glomerular filtration rate (GFR) in chronic kidney disease and as a predictive marker of cardiovascular disease. The authors investigated the relationship between serum Cys-C level and metabolic syndrome (MetS). *Materials and Methods:* A total of 3,670 women who visited the health promotion center were included in the cross-sectional study. Single logistic regression analysis was used to analyze the relationship between Cys-C and MetS in premenopausal and postmenopausal women. One-way analysis with linear trends was performed to determine the association between serum Cys-C level and MetS components. *Results:* The authors divided the subjects into four groups (premenopausal women with or without MetS, postmenopausal women with or without MetS) and compared the interquartile range (IQR) of the basic characteristics in each group. The level of Cys-C was increased only in postmenopausal women with MetS. The mean value of Cys-C increased progressively as the number of MetS components increased and the *p value* for the trend ($p < 0.0001$) was lower in postmenopausal women with MetS. Logistic regression analysis showed that the mean value of Cys-C was higher in MetS women and that the odds ratio was higher in postmenopausal women with MetS than in premenopausal women with MetS. These results indicated that the interaction between Cys-C and MetS was higher in postmenopausal women with MetS. *Conclusions:* Higher Cys-C level was found to have a positive correlation with MetS in Korean premenopausal and postmenopausal women. These interactions were more significant in postmenopausal women.

Key words: Cystatin C; Menopause; Metabolic syndrome.

Introduction

Cystatin C (Cys-C) is a member of the human cysteine superfamily and is an extracellular inhibitor of cysteine proteases. This low molecular protein (13.4kDa) can be freely filtered by glomerulus but is not secreted and reabsorbed at the renal tubule. It can be used to represent the changes in the glomerular filtration rate (GFR), similar to serum creatinine. Several studies were performed to evaluate the usefulness of serum Cys-C level as a marker of GFR. Serum Cys-C level was found to be a better marker than serum creatinine level and also a better representative of GFR than the serum level of beta 2-microglobulin [1-3].

Renal function is an important prognostic factor for cardiovascular disease (CVD). Hence, Cys-C has also been studied as a biomarker for risk prediction of CVD. Shlipak *et al.* reported that elderly patients with higher Cys-C levels had a higher risk of mortality and cardiovascular events [4]. Taglieri *et al.* reported that increased Cys-C was related to a higher risk of developing both CVD and chronic kidney disease (CKD) and it was also strongly associated with CVD [5]. However, the pathophysiologic mechanisms of Cys-C in cardiorenal metabolic syndrome are not totally understood [6].

Metabolic syndrome (MetS) has at least three of the following clinical characteristics: abdominal obesity, increased blood pressure (BP), impaired glucose tolerance or diabetes, dyslipidemia (elevated levels of triglycerides and low concentration of high-density proteins) [7]. These characteristics are relevant for the development of CKD and CVD. Additionally, MetS is known as an important risk factor for cardiovascular disease incidence and mortality [8-10]. Due to this intimate relationship between MetS and renal disease, as well as CVD, several studies have been conducted to explore the relationship between MetS and Cys-C. Magnusson *et al.* demonstrated that Cys-C affected metabolic factors, particularly abdominal obesity, thus contributing to the development of MetS [11]. As described above, there were several reports on the relationship between Cys-C and MetS in patients with underlying diseases but studies involving healthy people are scarce.

Many clinical findings on MetS have emerged in postmenopausal women. Menopause may be a predictor and an independent risk factor for MetS [12-14]. Therefore, the present authors studied the correlation between Cys-C and MetS, as well as the differences in the interaction between Cys-C and MetS in healthy women according to menopausal status.

Revised manuscript accepted for publication January 11, 2016

Table 1. — *The basic characteristics of premenopausal women with or without MetS and postmenopausal women with or without MetS.*

Variables	Premenopausal women without MetS (n=1290)	Premenopausal women with MetS (n=116)	Postmenopausal women without MetS (n=1777)	Postmenopausal women with MetS (n=487)
Age, median (IQR), years	44.0 (38.0 - 48.0)	47.0 (42.5 - 50.5)	57.0 (54.0 - 62.0)	61.0 (56.0 - 66.0)
Body weight, median (IQR), kg	55.1 (50.8 - 60.1)	63.2 (59.0 - 71.2)	55.9 (51.5 - 59.9)	60.9 (56.1 - 66.4)
Waist circumference, median (IQR), cm	75.5 (71.0 - 80.0)	86.0 (82.5 - 90.0)	79.0 (74.0 - 84.0)	86.0 (82.0 - 91.0)
BMI, median (IQR), kg/m^2	21.7 (20.2 - 23.6)	25.6 (23.9 - 27.9)	22.7 (21.1 - 24.5)	25.3 (23.6 - 27.4)
SBP, median (IQR), mmHg	111.0 (102.0 - 120.0)	131.0 (121.5 - 140.5)	117.0 (107.0 - 128.0)	132.0 (119.0 - 143.5)
DBP, median (IQR), mmHg	68.0 (63.0 - 74.0)	79.0 (73.5 - 86.0)	72.0 (65.0 - 78.0)	79.0 (71.5 - 86.0)
Total bilirubin, median (IQR), mg/dl	0.9 (0.7 - 1.1)	0.9 (0.7 - 1.0)	0.9 (0.7 - 1.1)	0.8 (0.7 - 1.1)
Direct bilirubin, median (IQR), mg/dl	0.2 (0.2 - 0.2)	0.2 (0.1 - 0.2)	0.2 (0.2 - 0.2)	0.2 (0.1 - 0.2)
Total protein, median (IQR), g/dl	7.2 (6.9 - 7.5)	7.3 (7.0 - 7.5)	7.2 (6.9 - 7.4)	7.3 (7.0 - 7.6)
Albumin, median (IQR), g/dl	4.3 (4.2 - 4.5)	4.4 (4.2 - 4.5)	4.4 (4.2 - 4.5)	4.4 (4.2 - 4.5)
BUN, median (IQR), mg/dl	12.6 (10.7 - 15.1)	13.0 (10.2 - 14.4)	14.6 (12.5 - 17.3)	14.6 (12.2 - 17.4)
Creatinine, median (IQR), mg/dl	0.7 (0.7 - 0.8)	0.7 (0.7 - 0.8)	0.7 (0.7 - 0.8)	0.7 (0.6 - 0.8)
Estimated GFR, median (IQR), ml/min/1.73m^2	94.9 (85.6 - 105.9)	93.6 (81.5 - 101.8)	89.3 (78.8 - 100.1)	89.1 (78.3 - 100.9)
Phosphate, median (IQR), mg/dl	3.7 (3.4 - 4.0)	3.7 (3.4 - 4.1)	3.9 (3.5 - 4.2)	3.9 (3.5 - 4.3)
Calcium, median (IQR), mg/dl	9.3 (9.1 - 9.6)	9.4 (9.3 - 9.6)	9.5 (9.2 - 9.7)	9.6 (9.3 - 9.8)
Cystatin C, median (IQR), mg/l	0.7 (0.7 - 0.8)	0.7 (0.7 - 0.8)	0.8 (0.7 - 0.9)	0.9 (0.8 - 1.0)
Total cholesterol, median (IQR), mg/dl	186.0 (166.0 - 209.0)	202.0 (174.5 - 235.0)	209.0 (183.0 - 234.0)	209.0 (182.0 - 238.0)
Triglyceride, median (IQR), mg/dl	69.5 (53.0 - 94.0)	156.0 (116.0 - 195.0)	79.0 (58.0 - 107.0)	151.0 (103.0 - 190.0)
HDL-cholesterol, median (IQR), mg/dl	60.0 (52.0 - 70.0)	43.0 (38.0 - 48.0)	60.0 (52.0 - 71.0)	44.0 (39.0 - 49.0)
LDL-cholesterol, median (IQR), mg/dl	111.0 (92.0 - 133.0)	127.0 (103.5 - 155.0)	132.0 (108.0 - 155.0)	138.0 (112.0 - 163.0)
Glucose, median (IQR), mg/dl	85.0 (79.0 - 90.0)	93.5 (87.0 - 101.0)	87.0 (82.0 - 94.0)	98.0 (89.0 - 117.0)
Insulin, median (IQR), uIU/ml	3.6 (2.6 - 4.6)	5.3 (4.1 - 7.1)	4.0 (3.1 - 5.2)	5.4 (4.1 - 7.8)
Free T4, median (IQR), ng/dl	1.3 (1.2 - 1.4)	1.3 (1.2 - 1.5)	1.3 (1.2 - 1.4)	1.3 (1.2 - 1.4)
TSH, median (IQR), uIU/ml	1.6 (1.1 - 2.5)	1.7 (1.2 - 2.7)	1.7 (1.1 - 2.6)	1.7 (1.2 - 2.7)

All data are presented as the interquartile range (IQR). *P*-value of all data < 0.05. MetS: metabolic syndrome; IQR: interquartile range; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TSH: thyroid stimulating hormone.

Materials and Methods

A total of 3,670 women who visited the health promotion center at Pusan National University hospital from January 2011 to December 2014 were included in the cross-sectional study. Information on gynecological history including menstrual history, operative history, and gynecological disease history, in addition to medical history, medication use, and lifestyle were obtained using self-report questionnaires and interviews with healthcare providers. Using a standing stadiometer, body weight and height were measured with light clothing while the subjects were barefoot. The values were rounded to the nearest 0.1 kg and 0.1 cm. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. BP was measured with an automatic machine in a sitting position after a ten-minute rest.

The authors included all patients who completed their self-report questionnaires without exception. In order to apply this study to the normal population group, the authors set the exclusion criteria as follows: (1) to minimize the effect of renal or liver dysfunction, patients with renal disease or liver disease were excluded. Patients whose blood test results raised the suspicion of renal disease and liver disease were also excluded (alanine aminotransferase level higher than 60 U/L, a total bilirubin level higher than 1.5 mg/L, an eGFR less than 60 ml/minute/1.73 m^2); (2) patients that received hormone therapy within the last 12 months; (3) those currently undergoing chemotherapy or radiation therapy; (4) patients who had amenorrhea within the last year.

Blood was drawn from the antecubital vein for all subjects between 8:30 and 10:00 am following at least eight hours of fasting. Cys-C was analyzed using the turbidimetric immunoassay method. Liver and renal function tests included alanine aminotransferase, aspartate aminotransferase, lipid profiles, blood urea nitrogen (BUN), serum creatinine, and total bilirubin were measured.

The authors defined menopause according to the International Menopause Society terminology. Menopause was recognized to have occurred after 12 consecutive months of amenorrhea with no other obvious pathological or physiological causes [15]. If the patient had a hysterectomy, menopause was diagnosed as serum FSH above 40 IU/ml.

As the National Cholesterol Education Program reported in the Adult Treatment Panel III, metabolic syndrome can be defined by applying one of three or more out of five diagnostic criteria. The diagnostic criteria are as follows: 1) abdominal circumference over 80 cm (Asian); 2) triglyceride level over 150 mg/dl; 3) HDL cholesterol less than 50 mg/dl; 4) FBG over 110 mg/dl or DM; 5) BP over 130/85 or hypertension medication [7].

The Statistical Analysis System (SAS) 9.3 program was used for statistical analysis. All data were entered into a database and were verified by a second independent person. The authors divided the study population into four groups: premenopause without MetS, premenopause with MetS, postmenopause without MetS, and postmenopause with MetS. The basic characteristics of the groups were investigated by single logistic regression analysis with a significance level of 5% or less and each median level was determined by interquartile range (IQR). The authors compared the mean value of Cys-C and the number of MetS compo-

Table 2. — *Relationship between mean value of Cys-C and number of MetS components.*

Total (n=3670)	N (%)	Cystatin C level, mean (SD)
0 components	1143 (31.1%)	0.75 (0.11)
1 component	1142 (31.1%)	0.77 (0.13)
2 components	782 (21.3%)	0.81 (0.14)
3 components	404 (11.0%)	0.84 (0.17)
4 components	163 (4.44%)	0.89 (0.22)
5 components	36 (0.98%)	0.89 (0.17)
p value for trend		< 0.0001
Premenopausal women (n=1406)	1406 (38.4%)	Cystatin C level, mean (SD)
0 components	626 (44.5%)	0.72 (0.12)
1 component	455 (32.4%)	0.73 (0.12)
2 components	209 (14.9%)	0.73 (0.10)
3 components	91 (6.47%)	0.76 (0.10)
4 components	22 (1.56%)	0.73 (0.13)
5 components	3 (0.21%)	0.92 (0.16)
p value for trend		0.0017
Postmenopausal women (n=2264)	2264 (61.6%)	Cystatin C level, mean (SD)
0 components	517 (22.8%)	0.78 (0.11)
1 component	687 (30.3%)	0.80 (0.12)
2 components	573 (25.3%)	0.83 (0.14)
3 components	313 (13.8%)	0.86 (0.17)
4 components	141 (6.23%)	0.92 (0.22)
5 components	33 (1.46%)	0.89 (0.17)
p value for trend		< 0.0001

MetS: metabolic syndrome.

nents by single logistic regression analysis with a trend test. The interactions between Cys-C and MetS were evaluated to determine the predicted probabilities of MetS according to the mean level of Cys-C with the odds ratio.

Results

The basic characteristics of the study groups are presented in Table 1. Compared to women without MetS, women with MetS had higher basic characteristics as follows: age, body weight, waist circumference, BMI, systolic BP, diastolic BP, calcium, triglycerides, LDL-cholesterol, glucose, and insulin. The estimated GFR and HDL-cholesterol were lower in both premenopausal and postmenopausal women with MetS ($p < 0.05$) The level of Cys-C was increased only in postmenopausal women with MetS.

The relationship between the mean value of Cys-C and the number of MetS components are shown in Table 2. The mean level of Cys-C progressively increased as the number of MetS components increased in both premenopausal and postmenopausal women. However, this linear *p* value trend line was lower in postmenopausal women ($p < 0.0001$) than in premenopausal women ($p < 0.0017$) and both *p*-value trend lines were significant in all groups.

Table 3 shows the interactions between Cys-C and MetS with the odds ratio. The predicted probabilities of MetS according to the mean value of Cys-C are presented in Figure 1. Depending on the method used to calculate the mean value of Cys-C, the increase in the mean Cys-C level differed in all groups and in the premenopausal and postmenopausal groups according to the presence of MetS. The median IQR of Cys-C was only higher in postmenopausal women with MetS, but the mean standard deviation of Cys-C level was higher in all three groups with MetS. *P* value was statistically significant in all three groups, but that of premenopausal women groups was slightly higher. The odds ratio of the Cys-C level was higher in postmenopausal women than in premenopausal women. The predicted probabilities of MetS according to the mean value of Cys-C were also higher and had steeper slopes in postmenopausal women (Figure 1).

Table 3. — *The interactions between Cys-C and MetS with odds ratio.*

	Total 3670 (100.0%)	Patients without MetS 3067 (83.6%)	Patients with MetS 603 (16.4%)	*p*-value	Odds ratio	95% CI
Cystatin C (all)						
Mean ± Std	0.79 ± 0.14	0.77 ± 0.13	0.86 ± 0.18	< 0.001	45.078	(24.457 - 83.087)
Median (IQR)	0.8 (0.7 - 0.9)	0.8 (0.7 - 0.8)	0.8 (0.7 - 0.9)			
Range	0.4 - 2.7	0.4 - 1.9	0.4 - 2.7			
Cystatin C (premenopausal)						
Mean ± Std	0.73 ± 0.12	0.73 ± 0.12	0.76 ± 0.11	0.008	5.626	(1.574 - 20.106)
Median (IQR)	0.7 (0.7 - 0.8)	0.7 (0.7 - 0.8)	0.7 (0.7 - 0.8)			
Range	0.4 - 1.9	0.4 - 1.9	0.5 - 1.1			
Cystatin C (postmenopausal)						
Mean ± Std	0.82 ± 0.15	0.80 ± 0.13	0.88 ± 0.19	< 0.001	33.240	(16.293 - 67.812)
Median (IQR)	0.8 (0.7 - 0.9)	0.8 (0.7 - 0.9)	0.9 (0.8 - 1.0)			
Range	0.4 - 2.7	0.5 - 1.7	0.4 - 2.7			

MetS: metabolic syndrome.

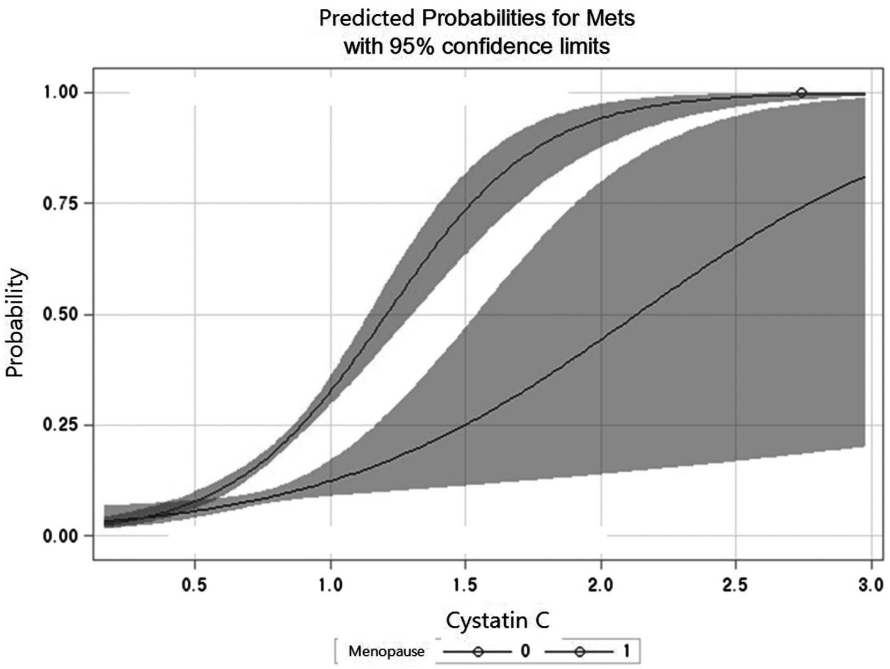

Figure 1. — The predicted probabilities for metabolic syndrome according to the mean level of cystatin-C. Menopause 0 (blue line); premenopause, menopause 1 (red line); postmenopause.

Discussion

Cys-C can be used to estimate GFR and is less affected by renal factors such as inflammatory, infectious and liver diseases, and by extrarenal factors like age, gender, diet, and body composition. Therefore, it was reported to be a better marker of GFR than serum creatinine level [16, 17]. Liu *et al.* reported that serum Cys-C was closely related to MetS components and indicated that monitoring Cys-C might help to predict the development and prognosis of MetS in the elderly [18]. However, the relationship is unclear in relatively young people. In the present study, the average age was relatively young and the results showed positive relationships between serum Cys-C level and MetS component, especially in postmenopausal women. It is unclear whether these results are due to menopause or aging. Also, it is still unclear whether menopause is one of the causes of MetS and weight gain or not. However, from recently published reports, the present authors can postulate that the change in body fat distribution after menopause and the effect on insulin are responsible for these results rather than menopause itself. Postmenopausal women exhibit metabolic changes, such as central fat redistribution and elevated fasting plasma glucose levels [19]. Estrogen deficiency in menopausal women leads to decreased insulin secretion and elimination, as well as increased insulin resistance. Insulin resistance is also well known to be an important factor affecting renal dysfunction and disease [20-22]. Insulin resistance is defined as decreased cellular sensitivity to insulin and is connected to atherogenic dyslipidemia, hypertension, and prothrombotic state. Insulin resistance may be mediated through multiple metabolic pathways [23, 24]. These relationships suggest the potential of Cys-C as an indicator of MetS in postmenopausal women. In the present study, the odds ratio of Cys-C level and the probability of MetS were higher in postmenopausal women at the same Cys-C level. Therefore, Cys-C can be used to predict the likelihood of MetS and the severity of the MetS.

There are some limitations in this study. First, the basic characteristics of the groups and the mean value of Cys-C, as well as the number of MetS components were investigated by single logistic regression analysis. Since metabolic syndrome can be affected by various factors, eliminating the effects of these variables using multiple logistic regression analysis would have helped us determine a more precise correlation between Cys-C and MetS. Second, the present data showed the predicted probabilities of MetS according to the mean level of Cys-C, but the authors could not determine the exact cut-off value for Cys-C. When they performed multiple logistic regression analysis to reduce the effect between factors using the Chi-squared Automatic Interaction Detector (CHAID) algorithm, the calculated *p*-value for the cut-off level exceeded 0.05 and was not statistically significant. However, when the mean Cys-C level was 1 to 1.5, the predicted probabilities of MetS was around 50 percent. This linear relationship can be used to predict the likelihood of MetS according to the Cys-C level.

Despite these limitations, this study has value in that the authors found that the serum Cys-C level has a positive correlation with MetS in Korean premenopausal and postmenopausal women, and the probability of MetS was predicted according to the mean value of Cys-C. The au-

thors also verified the relationship between serum Cys-C level and MetS in middle aged women in this study. Further investigations with larger patient groups and well-controlled variables will be needed to establish the cut-off value for Cys-C in predicting MetS.

Acknowledgement

The authors acknowledge assistance with statistical analysis from the Pusan National University Hospital Clinical Trial Center Biostatistics Office.

References

[1] Coll E., Botey A., Alvarez L., Poch E., Quinto L., Saurina A., *et al.*: "Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment". *Am. J. Kidney Dis.*, 2000, *36*, 29.

[2] Salgado J.V., Neves F.A., Bastos M.G., Franca A.K., Brito D.J., Santos E.M., *et al.*: "Monitoring renal function: measured and estimated glomerular filtration rates - a review". *Braz. J. Med. Biol. Res.*, 2010, *43*, 528.

[3] Simonsen O., Grubb A., Thysell H.: "The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate". *Scand. J. Clin. Lab. Invest.*, 1985, *45*, 97.

[4] Shlipak M.G., Sarnak M.J., Katz R., Fried L.F., Seliger S.L., Newman A.B., *et al.*: "Cystatin C and the risk of death and cardiovascular events among elderly persons". *N. Engl. J. Med.*, 2005, *352*, 2049.

[5] Taglieri N., Koenig W., Kaski J.C.: "Cystatin C and cardiovascular risk". *Clin. Chem.*, 2009, *55*, 1932.

[6] Salgado J.V., Souza F.L., Salgado B.J.: "How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence?" *J. Cardiol.*, 2013, *62*, 331.

[7] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report". *Circulation*, 2002, *106*, 3143.

[8] Galassi A., Reynolds K., He J.: "Metabolic syndrome and risk of cardiovascular disease: a meta-analysis". *Am. J. Med.*, 2006, *119*, 812.

[9] Gluba A., Mikhailidis D.P., Lip G.Y., Hannam S., Rysz J., Banach M.: "Metabolic syndrome and renal disease". *Int. J. Cardiol.*, 2013, *164*, 141.

[10] Nashar K., Egan B.M.: "Relationship between chronic kidney disease and metabolic syndrome: current perspectives". *Diabetes Metab. Syndr. Obes.*, 2014, *7*, 421.

[11] Magnusson M., Hedblad B., Engstrom G., Persson M., Nilsson P., Melander O.: "High levels of cystatin C predict the metabolic syndrome: the prospective Malmo Diet and Cancer Study". *J. Intern. Med.*, 2013, *274*, 192.

[12] Carr M.C.: "The emergence of the metabolic syndrome with menopause". *J. Clin. Endocrinol. Metab.*, 2003, *88*, 2404.

[13] Cho G.J., Lee J.H., Park H.T., Shin J.H., Hong S.C., Kim T., *et al.*: "Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome". *Menopause*, 2008, *15*, 524.

[14] Eshtiaghi R., Esteghamati A., Nakhjavani M.: "Menopause is an independent predictor of metabolic syndrome in Iranian women". *Maturitas*, 2010, *65*, 262.

[15] Utian W.H.: "The International Menopause Society menopause-related terminology definitions". *Climacteric*, 1999, *2*, 284.

[16] Dharnidharka V.R., Kwon C., Stevens G.: "Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis". *Am. J. Kidney Dis.*, 2002, *40*, 221.

[17] Seronie-Vivien S., Delanaye P., Pieroni L., Mariat C., Froissart M., Cristol J.P.: "Cystatin C: current position and future prospects". *Clin. Chem. Lab. Med.*, 2008, *46*, 1664.

[18] Liu P., Sui S., Xu D., Xing X., Liu C.: "Clinical analysis of the relationship between cystatin C and metabolic syndrome in the elderly". *Rev. Port. Cardiol.*, 2014, *33*, 411.

[19] Otsuki M., Kasayama S., Morita S., Asanuma N., Saito H., Mukai M., *et al.*: "Menopause, but not age, is an independent risk factor for fasting plasma glucose levels in nondiabetic women". *Menopause*, 2007, *14*, 404.

[20] Charlesworth J.A., Kriketos A.D., Jones J.E., Erlich J.H., Campbell L.V., Peake P.W.: "Insulin resistance and postprandial triglyceride levels in primary renal disease". *Metabolism*, 2005, *54*, 821.

[21] Nistala R., Whaley-Connell A.: "Resistance to insulin and kidney disease in the cardiorenal metabolic syndrome; role for angiotensin II". *Mol. Cell. Endocrinol.*, 2013, *378*, 53.

[22] Stevenson J.C.: "Metabolic effects of the menopause and oestrogen replacement". *Baillieres Clin. Obstet. Gynaecol.*, 1996, *10*, 449.

[23] Grundy S.M.: "Hypertriglyceridemia, insulin resistance, and the metabolic syndrome". *Am. J. Cardiol.*, 1999, *83*, 25f.

[24] Miranda P.J., DeFronzo R.A., Califf R.M., Guyton J.R.: "Metabolic syndrome: definition, pathophysiology, and mechanisms". *Am. Heart J.*, 2005, *149*, 33.

Corresponding Author:
J.K. JOO, M.D.
Department of Obstetrics and Gynecology
Pusan National University, School of Medicine
Gu-Deok-Ro 305, Seo-Gu
Busan (Republic of Korea)
e-mail: jkjoo@pusan.ac.kr