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Association of Metabolic Syndrome Parameters with Kidney Stones in Indonesia

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Abstract

Kidney stone disease is common throughout the world. Elevated prevalence of kidney stones is often associated with metabolic syndrome itself. This study aimed to assess the association between kidney stones and metabolic syndrome parameters in differences gender. This was a cross-sectional study with Chi-square and multivariate logistic regression for data analysis from the secondary data Riskesdas 2013 with 26,063 respondents. Diagnosis of kidney stone based on Riskesdas 2013 interview, metabolic syndrome based on NCEP ATP-III and PERKENI. Result showed that there were 226 (0.9%) diagnosed kidney stones cases by doctors. After adjustment age, central obesity was dominant factor which associated with the risk of kidney stones in male (OR 1.9; 95% CI 1.3-2.9; p=0.003) and metabolic syndrome was dominant factor which associated with the risk of kidney stones in female (OR 6.1; 95% CI 3.4-11.3; p<0.001). The conclusion was that metabolic syndrome and central obesity were associated with risk of kidney stones.

INTRODUCTION

Kidney stone disease is common throughout the world with the lifetime risk in the United States exceeding 10.94% in men and 9.4% in women (Chen et al., 2018). This disease increased morbidity and major cause urinary tract stones deaths in the world. The study on 1999-2013 in England and Wales, kidney stones and ureter stones accounted for 91% of all urinary tract stones death (Kum et al., 2016). In addition, kidney stones contribute to chronic kidney disease (16.8%) (Vupputuri et al., 2004), stroke (4.37%) (Lin et al., 2016), and coronary heart disease (15.7%) (Ferraro et al., 2013). Kidney stones was contributed to 0.5% of all inpatient hospital stays, with the average length of inpatient stay being 2.8 days (Kum et al., 2016). The annual cost of kidney stones, inflation-adjusted for 2014, has been estimated at US$2.81 billion in USA. The cost of kidney stones is projected to increase to US$1.24 billion per year by 2030 (Antonelli et al., 2014).

The prevalence of kidney stones has increased in recent years. The recent study of The National Health and Nutrition Examination Survey (NHANES) reported that prevalence of kidney stones in the United States from 2007-2010 was 8.8% (Scales et al., 2012). The prevalence rate in Italy 2011 was 7.5 % (Croppi et al., 2012). The prevalence of kidney stones in China was 3.5% in 2012, increasing

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to 7.47% in 2013 (Wang et al., 2017). Number of kidney stones incidence in Indonesia based on hospital data was 37,636 new cases in 2012, with 58,959 visits. Number of patients hospitalized was 19,018 people and 378 people were deaths. The prevalence of kidney stones increased in 2013. Based on survey data of *Riset Kesehatan Dasar* (*Riskesdas* or Indonesian Basic Health Research) 2013, the prevalence of kidney stones diagnosed by doctors was 0.6%. The prevalence of kidney stone disease based on increases with age and decline at age 65 years (Indonesia Health Ministry, 2013).

In Northwest Russia prevalence rates of the metabolic syndrome among men were 11,5% and women were 11,5% by the National Cholesterol Education Program (NCEP), increasing at ages >60 years to 24,2% in men and 44,8% in women (Sidorenkov et al., 2010). In Malaysia, 54.7% of men and 45.3% of women meet the metabolic syndrome criteria established by the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) (Moy & Bulgiba, 2010). Prevalence of metabolic syndrome in Indonesia is still not clear. Nevertheless, *Riskesdas* 2013 results show that the prevalence related to metabolic syndrome parameters such as central obesity (26.6%), overweight (13.5%), obesity (15.4%), hypertension (25.8%), high total cholesterol (39.5%), low high density lipoprotein (22.9%), high low-density lipoprotein (l15.9%), high triglyceride (11.9%) and elevated fasting blood glucose (6.9%) (Indonesia Health Ministry, 2013).

The increased prevalence of kidney stones is often associated with metabolic syndrome, in epidemiological studies (Cho et al., 2013; Farahdika & Azam, 2015) Several studies have suggested that metabolic syndrome, which is a condition clinically defined by a clustering of central obesity, elevated body mass index (BMI), elevated blood pressure (BP), elevated total cholesterol, elevated low-density lipoprotein (LDL), elevated triglyceride, low high density lipoprotein (HDL) and elevated fasting plasma glucose (FPG), was linked directly to the formation of kidney stones (Jeong et al., 2011; Torricelli et al., 2014; Yoshimura et al., 2016). A recent Korean study reported that metabolic syndrome had a significant relation with the presence of kidney stones (OR 1.1; CI 95% 1.02-1.20; p=0.01) (Kim et al., 2013). In Indonesia, there has not been studied yet the relationship between metabolic syndrome parameters and the incidence of kidney stones. Therefore, we investigated the association between kidney stones and metabolic syndrome parameters in large sample size and community-based studies which data obtained from secondary data of *Riskesdas* 2013 to assess the association between kidney stones and metabolic syndrome parameters in differences gender.

METHODS

This cross-sectional study was used secondary data of *Riskesdas* 2013. *Riskesdas* was a community-based health research covering all regions of Indonesia to be implemented every 5-6 years and the latest is *Riskesdas* 2013. *Riskesdas* is a research that collects baseline data and health indicators that represent the national, provincial and district/city description. *Riskesdas* 2013 was used cross sectional design, where the number of respondents from 33 provinces and 497 provinces in Indonesia are 1,027,763 respondents. *Riskesdas* 2013 was approved by Health Research Ethics Committee (KEPK) National Institute of Health Research and Development (NIHRD), Ministry of Health Indonesia with the number protocol was 01.1206.207. Detailed information on the design and method of data collection can be accessed in report of *Riskesdas* 2013(Kementerian Kesehatan RI, 2013).

The population in this study were respondents at the *Riskesdas* 2013 ± 15 years old who taken measurement anthropometric (height, body weight, waist circumference (WC) and BP (systolic and diastolic)) and biomedical such as total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, and fasting plasma glucose.

The survey included questions about respondents' characteristics such as age, sex, employed status, the level of education. In addition, parameters of syndrome metabolic such as central obesity, BMI, hypertension, total cholesterol, HDL, LDL, triglyceride, and fasting plasma glucose were taken measurements.

A total of 49,931 respondents were taken biomedical measurements. In subsequent analysis after biomedical data is combined with interview data, the number of patients who were excluded was 11.532. We also excluded another 12,335 respondents with missing data for central obesity, BMI, hypertension, total cholesterol, HDL, LDL, triglyceride, and fasting plasma glucose. A total of 26,063 patients were included in the final analyses (Fig.1).

Central obesity was defined waist circumference >90 cm in men and >80 cm in women. Measurement of waist circumference was starting from the midpoint and then parallel/horizontal circle around the waist and the abdomen back to the midpoint at the beginning of measurement. For measuring the body weight and height of each subject, subjects wore indoor clothing and no shoes**.** Blood pressure was measured using automatic blood pressure monitors (Omron IA1), which blood pressure is measured after the respondent had been sitting upright for at least 10 minutes. BMI was calculated as weight in kilograms divided by square of height in meters, categorized as obese if BMI >25 kg/m (Perkumpulan

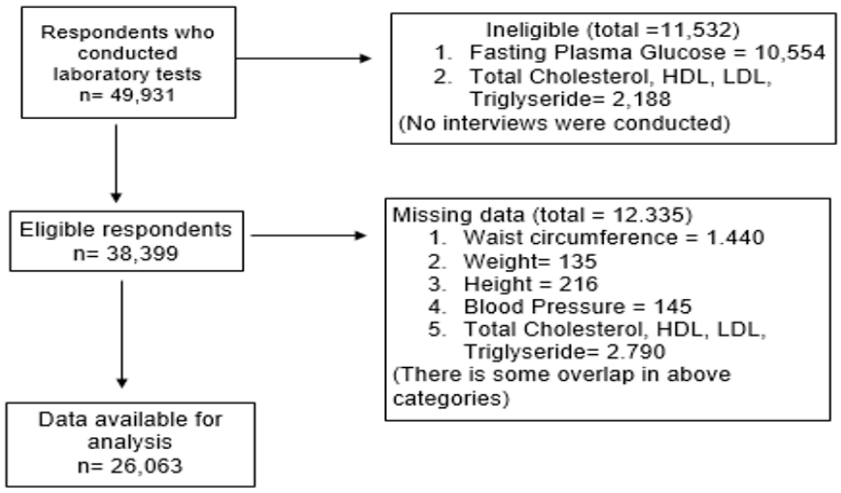

Figure 1. Flowchart of Research

Endokrinologi Indonesia, 2015; Kum et al., 2016). Measurement of fasting blood was taken after the respondent fast for at least 8 hours and maximum 14 hours and only allowed to drink fresh water. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride were measured by the electrochemical method using the TRX 7010 autoanalyzer.

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and *Perhimpunan Endokrinologi Indonesia* (*PERKENI*, The Indonesian Society of Endocrinology) criteria that have been adapted for Indonesian people. Metabolic syndrome in our study were defined as those who satisfied at least three of the following five parameters: waist circumference >90 cm for men and >80 cm for women according to *PERKENI* criteria for central obesity, hypertension is defined BP>140/90 mmHg, hyperglycemia or fasting blood glucose ≥126 mg / dL) (Perkumpulan Endokrinologi Indonesia,2015), low HDL-cholesterol (male <40 mg/dL and women <50 mg/dL), and hyper triglyceride (triglyceride ≥150 mg/dL)(NCEP-ATP III,2003). Elevated total cholesterol (≥200 mg/dL) and LDL-cholesterol (≥150 mg/dL) were categorized as risk of kidney stones**.** Respondents are categorized as obese if they have BMI> 25kg/m (Perkumpulan Endokrinologi Indonesia, 2015; Kum et al., 2016).

The diagnosis of kidney stones was determined who respondents had been diagnosed with kidney stone disease by a doctor based on *Riskesdas* 2013 interview, with the question: "Have you ever diagnosed kidney stones by a doctor?". Kidney stones were defined as the respondent's answer "Yes" to this question.

We compared the demographic and clinical characteristics in entire respondents, male, and female. These variables were expressed as absolute values and percent and compared between the kidney stones group and non-kidney stones group by using a chi-square test. We estimated the odds ratios (OR) and 95% confidence intervals (CI) between kidney stones and parameters of kidney stones based on both univariate and multivariate logistic regression analysis. Multivariate analysis was used to find dominant factor associated with the risk kidney stones after adjustment confounding variables such as age. Statistical analyses were carried out using SPSS version 16.0, which p values less than 0.05 was considered significant.

RESULTS AND DISCUSSION

The number of respondents analyzed were 26,063 with the number of kidney stones was 226 (0.9%) respondents. The number of male respondents was 10,565 and female was 15,598 respondents. Male respondents had a higher prevalence of metabolic syndrome and kidney stones than females. The prevalence of metabolic syndrome in respondents with kidney stones was higher than respondents without kidney stones (27.9% vs.15.9%, p<0,001). The prevalence of age, sex, central obesity, employment status, BMI, blood pressure, total cholesterol, LDL cholesterol, triglycerides, fasting blood glucose, and metabolic syndrome was significantly different between the two groups in entire respondents. Kidney stones were significantly higher in the respondents with metabolic syndrome than those without metabolic syndrome (p<0,001). Respondent distribution by demographic characteristics presented in Table 1.

Table 1. Sociodemographic Characteristics of Kidney Stones and Healthy Subjects

Variable	**Total**			**Male**			**Female**		
	Kidney Stone (%)	No (%)	p	Kidney Stone (%)	No (%)	p	Kidney Stone (%)	No (%)	p
Age (>43 y)	167 (73.9)	12.396 (47.9)	<0,001	107 (73.3)	5.376 (51.6)		60 (75.0)	7.020 (45.5)	<0,001
Education level (Illiterate, primary school, secondary school)	169 (74.8)	19.515 (75.5)	0,854	97 (66.4)	7.519 (72.1)	0,150	72 (90.0)	11.996 (77.8)	0,013
Employment Status (Unemployed)	163 (72.1)	16.874 (65.3)	0,038	128 (87.7)	9.200 (88.3)	0,916	35 (43.7)	7.674 (49.8)	0,336
Central Obesity (WC>90 cm for men and WC>80 cm for women)	86 (38.1)	7.513 (29.1)	0,004	32 (21.9)	1.072 (10.3)		54 (67.5)	6.441 (41.8)	<0,001
BMI (≥25 kg/m^2)	81 (35.8)	7.178 (27.8)	0,009	40 (27.4)	1.876 (18.0)	0,005	41 (51.3)	5.302 (34.4)	0,002
Hypertension (BP≥140/90 mmHg)	108 (47.8)	8.952 (34.6)	<0,001	69 (47.3)	3.170 (30.4)		39 (48.8)	5.742 (37.2)	0,049
Total Cholesterol (≥200 mg/dL)	101 (44.7)	9.069 (35.1)	0,003	58 (39.7)	3.090 (29.6)	0,011	43 (53.8)	5.979 (38.3)	0,009
HDL-Cholesterol (<40 mg/dL for male, <50 mg/dL for female)	98 (43.4)	10.380 (40.2)	0,165	58 (39.7)	3.326 (31.9)	0,045	40 (40.0)	7.054 (45.8)	0,52
LDL-Cholesterol (≥100 mg/dL)	188 (83.2)	19.776 (76.5)	0,023	120 (82.1)	7.664 (73.6)	0,024	68 (85.0)	12.112 (78.6)	0,20
Triglyceride (≥150 mg/dL)	78 (34.5)	5.439 (21.1)	<0,001	57 (39.0)	2.644 (25.4)		21 (26.3)	2.795 (18.1)	0,083
FPG (≥126 mg/dL)	25 (11.1)	1.829 (7.1)	0,029	11 (7.5)	687 (6.6)	0,774	14 (17.5)	1.142 (7.4)	0,001
Metabolic Syndrome	63 (27.9)	4.117 (15.9)	<0,001	35 (23.9)	1.061 (10.2)		28 (35.0)	3.056 (19.8)	<0,001
Total (%)	226 (0.9)	25.837 (99.1)		146 (1.4)	10.419 (98.6)		80 (0.5)	15.418 (99.5)	

Table 2. Univariate Analysis of Kidney Stone Incidence According to Parameters of Metabolic Syndrome

Parameters	Male		Female	
	OR (CI 95%)	p	OR (CI 95%)	p
Central Obesity (WC >90 cm for men and >80 cm for women)	2,4 (1,6-3,5)	<0,001	2,9 (1,8-4,6)	<0,001
BMI (≥25 kg/m^2)	1,7 (1,2-2,4)	0,005	1,9 (1,3-3,1)	0,002
Hypertension (BP≥140/90 mmHg)	2,0 (1,6-2,8)	<0,001	1,6 (1,02-2,5)	0,049
Total Cholesterol (≥200 mg/dL)	1,6 (1,1-2,2)	0,011	1,8 (1,2-2,8)	0,009
HDL-Cholesterol (<40 mg/dL for men, <50 mg/dL for women)	1,4 (1,01-1,9)	0,045	1,2 (0,7-1,8)	0,520
LDL-Cholesterol (≥100 mg/dL)	1,6 (1,1-2,5)	0,024	1,5 (0,8-2,8)	0,206
Triglyceride (≥150 mg/dL)	1,9 (1,3-2,6)	<0,001	1,6 (0,9-2,6)	0083
FPG (≥126 mg/dL)	1,2 (0,6-2,1)	0,774	2,6 (1,5-4,7)	0,001
Metabolic Syndrome	2,7 (1,9-3,9)	<0,001	2,2 (1,4-3,4)	<0,001

Note: Criteria for metabolic syndrome were used as defined by the National Cholesterol Education Program Adult Treatment Panel III, and *PERKENI*.

Abbreviations: WC=waist circumference; BMI=body mass index; HDL=high-density lipoprotein; LDL=low-density lipoprotein; FPG=fasting plasma glucose; CI=confidence interval; OR=odds ratio.

Characteristics kidney stones by metabolic syndrome parameters are listed in Table 2.

Note: Criteria for metabolic syndrome were used as defined by the National Cholesterol Education Program Adult Treatment Panel III, and *Persatuan Endokrinologi Indonesia*.

Abbreviations: BMI=body mass index; BP=blood pressure; HDL=high-density lipoprotein; LDL=low- density lipoprotein; FPG=fasting plasma glucose; CI=confidence interval; OR=odds ratio.

Central obesity, BMI, hypertension, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides were significantly associated with kidney stones in male respondents (p<0.05). FPG was not associated with kidney stones in male respondents (p=0,774). In male respondents, the OR were as high as 2.0 (95% CI, 1.5 to 2.8) for blood pressure >140/90 mmHg and 1.9 (95% CI, 1.3 to 2,6) for respondents with triglyceride ≥150 mg/dL. Central obesity (OR 2.9; 95% CI 1.8-4.6; p<0.001), BMI (OR 1.9; 95% CI 1.3-3.1; p=0.002), hypertension (OR 1.6; 95% CI 1.02-4.5; p=0.049), total cholesterol (OR 1.8; 95% CI 1.2-2.8; p = 0.009), and fasting blood glucose (OR 2.6, 95% CI 1.5-4.7; p<0,001) were associated with kidney stones in female respondents. HDL-cholesterol, LDL-Cholesterol and triglycerides were not associated with kidney stones in female respondents. Respondents with metabolic syndrome are at higher risk for kidney stones (OR 2.7; 95% CI 1.9-3.9; p<0.001 in male respondents and OR 2.2; 95% CI 1.4-3.4; p=0.001).

Table 3 shows the results of crude and multivariable-adjusted OR for kidney stones according metabolic syndrome parameter. Compared to the non-metabolic syndrome group in female respondents, metabolic syndrome had a significantly higher prevalence of kidney stones after adjustment for age (OR 7.1; CI 95% 2.9-17.0; p<0,001). After adjustment for age, triglyceride was associated with risk of kidney stones (OR 2.4; 95% CI 1,2-4.5; p=0,009) in female respondents. Central obesity, BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol, and fasting plasma glucose were not associated with kidney stones in female respondents. After adjustment for age, central obesity was associated with risk of kidney stones (OR 2.0; 95% CI 1,1-3.6; p=0,020) in male respondents. BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and fasting plasma glucose were not associated with kidney stones in male respondents. Of the eight parameters, only hypertension was a factor significantly related with the presence kidney stones in both male and female respondents after adjustment for age (in male: OR 1.6; 95% CI 1,1-2.3; p=0,014, in female: OR 2.0; 95% CI 1.1-3.5; p=0.012).

Note: Criteria for metabolic syndrome were used as defined by the National Cholesterol Education Program Adult Treatment Panel III, and *Persatuan Endokrinologi Indonesia*.

Abbreviations: WC=waist circumference; BMI=body mass index; HDL=high-density lipoprotein; LDL=low-density lipoprotein; FPG=fasting plasma glucose; CI=confidence interval; OR=odds ratio.

Table 4 shows the variables associated with

Table 3. Crude and multivariate-adjusted OR (95%) for Kidney Stones and Metabolic Syndrome Parameters

Variable	Male				Female			
	Crude PR (CI 95%)	**p**	**Adjusted PR (CI 95%)**	**p**	**Crude PR (CI 95%)**	**p value**	**Adjusted PR (CI 95%)**	**P**
Central Obesity (WC >90 cm for men and >80 cm for women)	2,1 (1,1-3,7)	0,015	2,0 (1,1-3,6)	0,02	1,5 (0,8-2,9)	0,184	1,4 (0,7-2,6)	0,296
BMI (≥25 kg/m^2)	0,9 (0,5-1,5)	0,642	0,9 (0,6-1,6)	0,800	1,1 (0,6-1,9)	0,733	1,2 (0,7-2,1)	0,472
Hypertension (BP≥140/90 mmHg)	1,9 (1,3-2,7)	<0,001	1,1 (0,7-1,6)	0,600	1,6 (0,9-2,8)	0,093	2,0 (1,2-3,5)	0,012
Total Cholesterol (≥200 mg/dL)	1,2 (0,8-1,7)	0,460	1,1 (0,7-1,6)	0,635	1,5 (0,9-2,5)	0,124	1,3 (0,7-2,1)	0,353
HDL-C (<40 mg/dL for men, <50 mg/dL for women)	1,27 (0,9-1,9)	0,245	1,3 (0,9-1,9)	0,197	1,8 (1,02-3,1)	0,043	1,7 (0,9-2,9)	0,083
LDL-C (≥100 mg/dL)	1,3 (0,8-2,1)	0,257	1,2 (0,7-1,9)	0,384	0,9 (0,4-1,8)	0,859	0,8 (0,4-1,7)	0,626
Triglyceride (≥150 mg/dL)	0,5 (0,9-2,2)	0,556	1,5 (0,9-2,3)	0,062	2,1 (1,1-3,9)	0,024	2,4 (1,2-4,5)	0,009
FPG (≥126 mg/dL)	0,8 (0,4-1,6)	0,646	0,8 (0,4-1,5)	0,453	1,1 (0,5-2,1)	0,873	0,9 (0,4-1,7)	0,713
Metabolic Syndrome	0,8 (0,4-1,6)	0,637	0,9 (0,4-1,7)	0,676	6,9 (2,9-16,5)	<0,001	7,1 (2,9-17,0)	<0,001

kidney stones in a multivariate analysis after adjustment for age.

Note: Criteria for metabolic syndrome were used as defined by the National Cholesterol Education Program Adult Treatment Panel III and *Persatuan Endokrinologi Indonesia.*

Abbreviations: WC:waist circumference; BP: blood pressure; CI:confidence interval; OR:odds ratio.

Central obesity, hypertension, and triglyceride were known to be significant risk factors associated with kidney stones in male respondents (OR 1.9; 95% CI 1.3-2.9; p=0.003, OR 1.5; 95% CI 1.1-2.2; p=0.014, OR 1.6; 95% CI 1.1-2.2; p=0.008, respectively). Hypertension (OR 1.8; 95% CI 1.1-3.1; p=0.029), triglyceride (OR 2.2; 95% CI 1.2-4.1; p=0.009), and metabolic syndrome (OR 6.1; 95% CI 3.4-11.3; p<0.001) were known to be significant risk factors associated with kidney stones in female respondents. Central obesity was dominant factor which associated with the risk of kidney stones in male respondents. Metabolic syndrome was dominant factor which associated with the risk of kidney stones in female respondents.

This study uses a cross-sectional design with the large sample and community-based study covering all regions in Indonesia. We found that age was confounding factors included for the associated metabolic syndrome parameters with kidney stones. This results was consistent with study in a screened population between January 2006 and December 2006 (34,895 respondents) at the Asan Medical Center, Korea which reported that age also to be confounding factors included for the relationship between metabolic syndrome and kidney stones (Jeong et al., 2011). Kidney stones are more common in middle-aged adults, with the highest prevalence rates occurring in adults aged 45 to 59 years (Chen et al., 2018)

The results of the study show that kidney

Table 4. Variables Associated with Kidney Stones in a Multivariate Analysis

Variable	Male		Variable	Female	
	OR (95% CI)	***p value***		**OR (95% CI)**	***p value***
Central Obesity		0.003	Hypertension		0.029
WC>90 cm for men	1.9 (1.2-2.9)		BP ≥140/90 mmHg	1.8 (1.1-3.1)	
WC≤90 cm for men	Reference		BP <140/90 mmHg		
Hypertension		0.014	Triglyceride		0.009
BP ≥140/90 mmHg	1.5 (1.1-2.2)		≥150 mg/dL	2.2 (1.2-4.1)	
BP <140/90 mmHg	Reference		<150 mg/dL	Reference	
Triglyceride		0.008	Metabolic Syndrome		<0.001
≥150 mg/dL	1.6 (1.1-2.2)		Yes	3.5 (2.0-5.9)	
<150 mg/dL	Reference		No		

stone is more prevalent among male than among female. Mini review reported that male was significantly associated with risk of kidney stone (Chen et al., 2018). Previous study report that male-to-female ratios generally vary 3:1 (Ferrari, 2007). Kirejczyk & Porowski (2014) have found higher urinary excretion of stone promoters such as calcium, oxalate, urine acid, and sodium among men than women. On the contrary, women presented higher urinary excretion of citrate which inhibits stone formations.

The results showed central obesity was associated with risk of kidney stone in male respondents. Central obesity is determined by waist circumference. This results are consistent with those of an earlier study, that found a significant association between central obesity and kidney stones (Rendina et al., 2009; Cho et al., 2013) . Study at three hospitals in South Korea reported that elevated waist circumference was identified as significant risk factors associated with kidney stones (p<0,001) (Cho et al., 2013). Study in Spinelli Hospital, southern Italy also reported that central obesity was significantly associated with nephrolithiasis (OR adjusted 2.8; 95% CI 1.2–6.4) (Rendina et al., 2009). Central obesity is a predisposing factor of insulin resistance (Otsuki et al., 2011). Insulin resistance in the kidneys will cause ammonia genesis process in the kidneys decreases, causing a decrease in ammonium excretion. This decrease in ammonium excretion causes an increase in H^+ ions in the tubular lumens. This increase in H^+ ions causes a decrease in urinary pH resulting in the formation of uric acid stones (Hess, 2012).

Multivariate analysis after adjustment for confounding variable showed that no statistically significant association between BMI and the risk of kidney stones. This results was consistent with study in China (Zhao et al., 2012). However, some studies show different results. Study cohort in Japan reported that increased BMI was associated with the risk of kidney stones. The risk of kidney stone formation was much higher in people with BMI 23.8-35.6 kg/m^2 compared with people with BMI 15.9-21.6 kg/m (Kum et al., 2016; Yoshimura et al., 2016). A cohort study in the United States in postmenopausal women also suggests that increased BMI is associated with kidney stones (p<0,001) (Sorensen et al., 2014). The mechanism whereby obesity increases the risk of incident stone formation is uncertain. However, hyperinsulinemia is associated with obesity and has a significant effect on urine composition (Taylor et al., 2005). Elevated BMI is one of many markers of obesity and is associated with a systemic inflammatory state in patients with metabolic syndrome (Rendina et al., 2009). Insulin resistance, also associated with obesity, can also alter the composition of the urine. Insulin resistance may manifest in the kidney as a defect in ammonium production and the ability to excrete acid (Krivosikova et al., 1998). However, the results of this cross-sectional study in the general population and large number of samples was reported that no association between BMI and kidney stones.

Hypertension was a metabolic syndrome parameter that has been common knowledge was associated with risk of kidney stones (Rendina et al., 2009; Jung et al., 2011). Hypertension was common in many patients with kidney stones formers (Kittanamongkolchai et al., 2017). This study also showed that hypertension was associated with the risk of kidney stones in male and female respondents. This result was consistent with previous study. Screening test study at a health promotion center in Seoul, Korea (116,536 respondents) reported that hypertension was a significantly related factor to the presence of kidney stones (male; OR 1.08; 95% CI 1.01–1.15; p=0.043, female; OR 1.24; 95% CI 1.08–1.42; p=0.002) (Kim et al., 2013). A cross sectional study in Texas reported that hypertension was identified as a significant risk factor associated with kidney stones (Hazard Ratio=1.50; 95% confidence

interval, 1.18 to 1.92) (Kittanamongkolchai et al., 2017). Other studies reported that hypertension is associated with hypercalciuria (Ferraro et al., 2013). Hypercalciuria is undoubtedly an important risk factor for the formation of calcium oxalate calculi, and research has revealed the existence of calcium metabolism alterations, including increased renal excretion in hypertensive patients (Denburg et al., 2015).

HDL-cholesterol was not associated with kidney stones in this study. The results of this study are consistent with cross-sectional studies in a screened population at the Asan Medical Center, Korea with a total of 34,895 respondents. The study reported that after adjustment for age and sex, HDL-cholesterol were not associated with kidney stones (p=0,2) (Jeong et al., 2011). Although low HDL-cholesterol was not associated with the risk of kidney stones, after analyzed, low HDL-cholesterol was associated with metabolic syndrome (p value <0,001). Elevated HDL-cholesterol is a key mediator of the atherogenicity in metabolic syndrome. Metabolic syndrome was a direct factor affecting the incidence of kidney stones (Kim et al., 2013). There has been considerable interest in the relationship between HDL and insulin resistance. In the presence of insulin resistance, HDL cholesterol levels often are reduced. The reduction in HDL is widely believed to be the consequence of inflammatory cytokines (Eren et al., 2012). The reduced of HDL-cholesterol in the metabolic syndrome are believed to play a role in the predisposition to atherosclerosis since HDL normally has antiatherosclerosis properties. These have been attributed to its ability to play a role in reverse cholesterol transport, to its ability to inhibit oxidation, and to the anti-inflammatory properties of HDL (Hoofnagle et al.,2010).

Elevated total cholesterol and LDL-cholesterol as the component of dyslipidemia were associated with kidney stones (Torricelli et al., 2014; Musa & Idris, 2015) This study did not show that total cholesterol and LDL-cholesterol were significantly related factors with the presence of kidney stones. This result was consistent with cross-sectional studies in Korea (Kim et al., 2013), doesn't find the association between LDL-cholesterol and the risk of kidney stones. Reported in a cross-sectional study of 100 patients at the Khartoum Sudanese Hospital, LDL-cholesterol was associated with the risk of kidney stones (p<0,001) (Musa & Idris, 2015). Study in Italy reported that total cholesterol were not significantly with urid acid stone formation (Cai et al., 2018). Retrospectively study identified patients with kidney stones who underwent 24-hour urinalysis and lipid profile evaluation within 3 months suggesting that patients with high total cholesterol had high uric acid (p value <0,001) (Torricelli et al., 2014).

Elevated triglyceride was associated with the risk of kidney stones after adjustment for age in male and female respondents. This result was consistent with previous study in South Korea (Cho et al., 2013). Elevated triglyceride was causing sodium, oxalate, and uric acid significantly higher with a lower pH. It was associated with kidney stones (Torricelli et al., 2014).

Elevated fasting plasma glucose was a metabolic syndrome parameter was associated with risk of kidney stones (Jeong et al., 2011). Elevated fasting plasma glucose was associated with insulin resistance. It was causes low urinary pH, the risk of kidney stones (Cameron et al., 2012). This study reported different result. Elevated fasting plasma glucose was not associated with kidney stones. This results of this study was consistent with cross-sectional studies in Korea which large number of samples also reported that elevated fasting plasma glucose was not associated with kidney stones (p=0,771) (Kim et al., 2013). Screening population at the Asan Medical Centre hospital, Korea suggesting that elevated fasting plasma glucose were associated with kidney stones (Jeong et al., 2011). The results were different due to the population used in this study different from those studies.

In this study, metabolic syndrome was associated with kidney stones in male respondents. More studies displayed increasing odds of kidney stones with increasing number of metabolic syndrome traits, where patients with three or more metabolic syndrome traits tended to have higher prevalence of kidney stones (Wong et al., 2016). Studies in Japan reported that metabolic syndrome was associated with a 1.8-fold higher level of echo graphic evidence of kidney stones in 11,555 patients (Kohjimoto et al., 2013). Jeong et al. also reported that presence of metabolic syndrome had an OR of 1.25 (95% CI, 1.03-1.50) for kidney stone prevalence evaluated using computed tomography or ultrasonography in 34,895 individuals who underwent general health screening tests in Korea (Jeong et al., 2011). This study was consistent with earlier study (Cho et al., 2013; Jeong et al., 2011; Jung et al., 2011; Kim et al., 2013). In a separate study of UA stone formation in metabolic syndrome, Cho et al. showed that metabolic syndrome was an independent risk factor for UA stone (Cho et al, 2013). Insulin resistance has been known as a common pathogenic mechanism in both kidney stones and metabolic syndrome (Kim et al., 2013). Patients with insulin resistance have high levels of plasma free fatty acids, which can enter the proximal tubule cells and interfere with the utilization of glutamine; since free fatty acids constitute an

alternative metabolic substrate for the proximal tubule cells, it results in a reduction in glutamine usage and ammonia genesis (Li et al., 2014). In addition, insulin resistance may directly impair ammonia genesis as demonstrated by in vitro studies which showed that insulin is able to stimulate renal ammonium production from L-glutamine (Krivosikova et al., 1998). Insulin receptors are expressed in the renal tubular epithelium, and insulin stimulates the renal tubular sodium-hydrogen exchanger (Na+/H+ exchanger) to increase reabsorption of hydrogen. The activation and up-regulation of the Na+/H+ exchanger by insulin promotes ionic trapping of ammonia in the renal tubule; hydrogen ions become bound to ammonia, which is converted to ammonium and is unable to exit the lumen of the renal tubule. Resistance to insulin thereby results in decreased buffering capacity for urinary acidification due to decreased ammonia secretion (Li et al., 2014).

The study also was limited because did not have data about the type of kidney stone. Kidney stone classification based on the question, "Have you ever diagnosed kidney stones by a doctor?". This responsible for the relatively lower prevalence of the actual amount. Variable that was very important and associated with the risk of kidney stones such as plasma uric acid was not identification. In addition, there are also important variables associated with kidney stone but not identification in this study, such as family history of kidney stones, fluid intake, consumption of calcium supplements, and alcohol consumption. Furthermore, another limitation in our study was the methodology used in the analysis of kidney stones. Then, because our study was not a longitudinal study but a cross-sectional study, we could not determine the certainly causal relationship between kidney stones and metabolic syndrome parameters. Despite these limitations, our study is strengthened by the large sample size and community-based studies.

CONCLUSIONS

Metabolic syndrome is associated with kidney stones. Central obesity was dominant factor which associated with the risk of kidney stones in male respondents (OR 1.9; 95% CI 1.3-2.9; p=0.003). Metabolic syndrome was dominant factor which associated with the risk of kidney stones in female respondent (OR 6.1; 95% CI 3.4-11.3; p<0.001). In next studies, the diagnosis of kidney stone disease is necessary to use ultrasound or computed tomography (CT) and needs to be done with a cohort study to determine the causality association between metabolic syndrome parameters and risk of kidney stones.

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