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Isolated Systolic Hypertension among Diabetes Mellitus Subjects; a national cross-sectional study in Indonesia

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Abstract

Isolated systolic hypertension (ISH) reflects atherosclerosis. Studies reported hypertension prevalence among diabetes mellitus (DM); however, limited studies provided community prevalence. The present study aimed to explore ISH prevalence among DM in Indonesia. This study obtained data from the 2018 Indonesia Basic Health Survey. The DM category was determined by fasting plasma glucose (PG) level ≥126 mg/dL or 2 hours postprandial and random PG level ≥200 mg/dL or previously diagnosed by a doctor. ISH is categorized if systolic blood pressure is≥140 mmHg and diastolic blood pressure is <90 mmHg. This study also explored the subject's determinants, i.e., compliance, demography, and lipid profile. A Chi-square and Binary logistic regression were used to determine the association. The study included 3,911 DM individuals and disclosed the prevalence of ISH at 17.5%. ≥65 years old (OR=13.61 95%CI: 3.297-19.365) and 45-64 years old OR=4.59 95%CI: 3.297-6.383)), high HDL-cholesterol (OR=0.77; 95%CI: 0.626-0.936), and longer DM duration (OR=2.89; 95%CI: 2.405-3.474), all together were related to the ISH. Subjects with the oldest age category, i.e., ≥65 years old, had the highest OR. Older DM individuals with low HDL-C and longer DM duration were related to the ISH, suggesting lipid profile treatments, mainly the HDL-C, is a pivotal effort to delay ISH.

Introduction

International Diabetes Federation reports that 463 million people globally and 10.7 million people in Indonesia live with diabetes mellitus (DM), placing Indonesia in the seventh rank among countries for the number of adults with DM (International Diabetes Federation, 2019). Hypertension is the most frequent comorbidity for DM(Colosia et al., 2013; Nguyen et al., 2015; Tesfaye et al., 2019; Farahdika et al., 2015). Both hypertension and DM are the major risk factors for cardiovascular diseases due to the vascular mechanism (Petrie et al., 2018). Hypertension is associated with 30% of death and 25% of cardiovascular events among DM subjects (Chen et al., 2011). DM subjects with hypertension have seven times more likely to experience end-stage renal disease and two to four times to get myocardial infarction and stroke (Chen et al., 2011).

Hypertension occurs due to vascular resistance and increased fluid volume (Ohishi, 2018). Vascular resistance in DM subjects is related to vascular remodeling. This remodeling caused arterial stiffness, while the increase in fluid volume is related to hyperglycemia caused by resistance-induced hyperinsulinemia (Ohishi, 2018). Isolated systolic hypertension (ISH) is the most frequent form of hypertension among the elderly (Bavishi et al., 2016) and the most frequent subtype of uncontrolled hypertension (Franklin et al., 2012). People

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with DM have a twice higher risk of getting ISH than those without DM (Os et al., 2006). ISH reflects widespread atherosclerosis and increases stroke risk by 11% and an increase in all-cause mortality risk by 16% (Os et al., 2006). Alongside the ISH, the pulse pressure (PP) values and mean arterial pressure (MAP) values are risk factors for cardiovascular events and all-cause mortality (Madan et al., 2019; Os et al., 2006; Selvaraj et al., 2016; Winston et al., 2013).

Based on the hospital-based data, a previous study Ephraim et al., (2016), reported that ISH prevalence among DM subjects was 37.4%, and age was the most related factor. Another study reported that ISH prevalence among DM subjects was 27.6%(Dagnew & Yeshaw, 2019); male, older age, obesity, and smoking were its risk factors (Dagnew & Yeshaw, 2019; Grebla et al., 2010). A study in Indonesia reported risk factors of hypertension among DM subjects such as age, mental health disorders, obesity, physical activities, duration of diabetes, dyslipidemia, and patient compliance (Sihombing, 2017). However, population-based data have limited information regarding ISH prevalence and risk factors among DM subjects. The current cross-sectional study's objective was to investigate the ISH prevalence and its determinants among DM individuals based in the Indonesian community setting. The determinants observed were demographic data, clinical characteristics, lifestyle, duration of DM, and medication status.

ISH is a subtype of hypertension that commonly occurs in young people and adults, and it is categorized when systolic blood pressure is≥140 mmHg and diastolic blood pressure is <90 mmHg. Yano Y. e., (2017). Hypertension is a condition that has no visible symptoms (Lilies, 2015), where high blood pressure in the arteries causes an increased risk of cardiovascular-related diseases such as stroke, heart failure, heart attack, and kidney damage. Hypertension is called the silent killer because it often does not show any symptoms for ten to twenty years and is usually only known when complications have occurred in target organs such as the heart, kidneys, brain, and eyes so that treatment is delayed and reduces life expectancy due to weakness in organ function. Resulting in disability and even death (Oktaviarini, 2019). Table 1 and Table 2 describe the classification of hypertension and ISH.

Table 1. Classification of hypertension based on the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VIII

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-90
Hypertension Stage 1	140-159	90-99
Hypertension Stage 2	>60	>100
Isolated Systolic Hypertension	≥140	<90

Source: Primary data, 2018

Table 2. ISH Itself Categorized

Grade	Systolic (mmHg)	Diastolic (mmHg)
ISH Grade 1	<160	<90
ISH Grade 2	<180	<90
ISH Grade 3	≥180	<90

Source: Primary data, 2018

ISH develops from the presence of diastolic hypertension in patients with long-term essential (primary) hypertension or increased systolic pressure in hypertension secondary to increased arterial stiffness in previously normal blood pressures. (Franklin S., 2012). Secondary causes of systolic hypertension include type 1 diabetes, osteoporosis with vascular calcification, accelerated atherosclerosis from chronic kidney disease, peripheral vascular disease, altered elastin formation during intrauterine fetal growth retardation, thyrotoxicosis, repair of coarctation of the aorta, and proximal aortic aging. Pathophysiological changes due to aging of the arterial wall that predispose elderly individuals to the occurrence of isolated systolic hypertension include endothelial dysfunction, hardening of the arteries, proinflammatory release, insensitivity to vasodilators, and elastin calcification (AlGhatrif, 2015).

In line with age and the progression of atherosclerosis, there is an increase in arterial calcium and collagen deposition associated

with the rupture of arterial elastin. The resulting decrease in arterial elasticity and compliance leads to a decrease in the lumen-to-wall ratio and increased arterial stiffness (Chobanian, 2007). These changes typically involve the predominantly large arteries and aorta. A translational study has shown that an increase in systolic blood pressure causes an increase in enzyme levels or a proinflammatory action, leading to endothelial dysfunction.

For example, matrix metalloproteinase enzymes inhibit vasodilation through endothelial nitric oxide degradation and increase vasoconstriction through cleavage of the vasoconstrictase enzyme (Fontana, 2012). Furthermore, matrix metalloproteinases play a role in the development of atherosclerosis, leading to intima and media thickening (Ma, 2012). Rigidity causes an increase in systolic pressure and a further decrease in diastolic pressure, creating an increase in pulse pressure and, thus, a reduced Windkessel effect (Bavishi, 2016). Pulse wave velocity used to measure arterial stiffness increases as arterial compliance decreases. High velocity will trigger the reflected wave pressure more quickly, causing ventricular-vascular mismatch, resulting in increased left ventricular pressure and systolic pressure.

Chronic diseases often co-occur in elderly patients with hypertension, such as diabetes mellitus, chronic kidney disease, hyperlipidemia, and smoking contribute to the pathological process of isolated systolic hypertension. It accelerates the occurrence of atherosclerosis and hardening of the arteries resulting in increased pressure and decreased arterial compliance. Decreased diastolic pressure and impaired diastolic relaxation, together with hardening of the arteries and reduced Windkessel function of the aorta, will cause an increase in systolic blood pressure reactivity due to volume fluctuations. Thus, increased pulse pressure and unstable systolic pressure across microvascular organs can lead to vessel damage and "ischemic outflow" of end organs.

The renin angiotensin aldosterone system (RAAS) is involved to some extent in the pathogenesis of isolated systolic hypertension through mechanisms that increase vascular thickness, stiffness, and loss of contractility, such as altering the elastin-collagen content of the arterial wall, thickening and fibrotic remodeling of the vascular intima, and inducing proliferation. Arterial smooth muscle cells (Chrysant, 1998). However, there is a gradual progressive decrease in plasma renin activity with increasing age. The renin-angiotensin-aldosterone system is modulated by several other factors, such as sodium intake and comorbidities (Bavishi, 2016).

Data from the Baltimore Longitudinal Study of Aging (BLSA) show that arterial stiffness causes an increase in systolic blood pressure in the elderly (Najjar SS., 2008), whereas an earlier increase in systolic blood pressure was associated with a tremendous increase in arterial stiffness. The organ closest to the aorta that experiences stiffness is the heart; therefore, the heart is the organ that is directly affected by isolated systolic hypertension. Increased pulse pressure is a sign of cardiac abnormalities caused by increased central arterial stiffness and wave reflection. Increased pressure in the aorta is a significant factor in developing left ventricular hypertrophy, with increased demand for coronary blood flow (Giannattasio C., 2020). In addition, increased turbulent flow causes endothelial dysfunction with a greater propensity for coronary atherosclerosis and rupture of unstable atherosclerotic plaques.

Elevated systolic blood pressure and failure of diastolic blood pressure in the elderly with isolated systolic hypertension can cause an imbalance in coronary blood supply and myocardial ischemia. Decreased diastolic blood pressure very rarely falls to critical levels (<60 mmHg), which can result in impaired coronary flow auto-regulation (Somes, 1999). The outflow of cardiac output into the rigid arterial system results in greater coronary perfusion during the systolic period, making the heart more susceptible to changes in systolic blood pressure and impaired cardiac function. In addition to arterial stiffness, the left ventricle also plays a role in developing systolic stiffness as an adaptive change in facilitating cardiac ejection and maintaining the connection of the heart to the arteries. The combination of increased cardiac flow and compromised left ventricle will eventually lead to heart failure

Methods

The present study took out secondary data from the 2018 Indonesia Basic Health Survey (Riset Kesehatan Dasar; RISKESDAS), the latest five-annual national scope cross-sectional study conducted by the National Institute of Research and Development, Ministry of Health, the Republic of Indonesia. The survey was conducted and delivered to households systematic-randomly selected from 514 districts/cities in 34 provinces. For each province and district/city, the number of proportional census blocks was determined systematically. Three hundred households, or 30.000 census blocks, were then determined to be involved in the survey. Of them, 94.2 % or 282,654 households completed the questionnaire, consisting of 1,017,290 individual subjects (Badan Penelitian dan Pengembangan Kesehatan, 2018). The study population involved subjects with DM in the RISKESDAS 2018 data. Subjects with DM were defined by fasting plasma glucose level ≥ 126 mg/dL or 2 hours postprandial and random plasma glucose level ≥ 200 mg/dL or had been confirmed by a doctor diagnosis previously. To minimize the potential of bias regarding the question of "previously had been diagnosed DM by a doctor," delivering questions about the DM medication as well as plasma glucose test was conducted.

Ethical clearance for the RISKESDAS 2018 study was obtained from the Ethics Committee, the National Institute of Health Research and Development (NIHRD), and the Ministry of Health, Republic of Indonesia. Subject with ISH was defined as those with systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg (Members et al., 2013). We categorized the individuals as non-hypertensive when meeting the criteria of optimal (<120 mmHg and <80 mmHg), normal (120 mmHg-129 mmHg and/or 80-84 mmHg), or high normal (130-139 mmHg and/or 85-89 mmHg). While non-ISH hypertension was categorized as grade 1-3 hypertension; grade 1 hypertension: 140-159 mmHg and/or 90-99 mmHg; grade 2 hypertension: 160-179 mmHg and/or 100-109 mmHg; grade 3 hypertension >180 mmHg and or ≥110 mmHg (Members et al., 2013). Based on blood pressure measurement, we also calculated pulse pressure (PP) and mean arterial pressure (MAP). PP was calculated as a result of the formula (PP = SBP –DBP), while the MAP was calculated as the formula of (MAP=((SBP+2*DBP))/3) (Members et al., 2013).

The data obtained from RISKESDAS 2018 were gender, age, urban-rural residence status, educational level, marital status, employment status, total cholesterol level, HDL-cholesterol level, triglycerides level, history of hypertension, smoking, physical activity status, alcohol consumption, body mass index (BMI), duration of DM, type of medication, and medication compliance. Characteristics of the subjects were presented as proportions since they are categorical types of data. We categorized age as ≥75, 65-74, 55-64, 45-54, and 35-44, and BMI category as overweight/obesity and normal/underweight, under the cut-off point of 27. The association between the subject's characteristics and ISH status was analyzed using the Chi-square test. The p-values <0.05 were appraised as statistically significant. The binary logistic regression was then performed to determine the relationship between determinants and ISH and find the best regression model. Parameters with a p-value <0.25 were involved in Binary logistic regression analysis. Analyses of statistics were conducted using the Statistical Package for the Social Sciences (SPSS) software (version 23.0 for Windows, IBM SPSS Inc., Chicago, IL).

Results and Discussion

Table 3. Characteristics of Subjects Based on ISH Status

Parameters	ISH								95%CI	
	Yes		No		Total		p value	OR	Lower	Lower
	n	(%)	n	(%)	n	(%)				
Age (years old)										
≥65	244	(36.5)	425	(63.5)	669	(17.1)	0.001	12.75	9..042	17.981
45-64	398	(17.7)	1846	(82.3)	2244	(57.4)	0.001	4.79	3.464	6.625
15-44	43	(4.3)	955	(95.7)	998	(25.5)	Reference	1		
Gender										
Female	451	(17.2)	2171	(82.8)	2622		0.489	0.95	0.821	1.093
Male	234	(18.2)	1055	(81.8)	1289					
Residence status										
Urban	370	(18)	1687	(82)	2057		0.437	1.06	0.924	1.214
Rural	315	(17)	1539	(83)	1854					
Marital status										
Un-married	23	(15.6)	124	(84.4)	147		0.619	0.89	0.607	1.303
Married	662	(17.6)	3102	(82.4)	3764					
Education level										
Low	553	(18.4)	2453	(81.6)	3006		0.009	1.26	1.059	1.502
High	132	(14.6)	773	(85.4)	905					
Employment status										
Un-employed	308	(18.8)	1331	(81.2)	1639		0.081	1.13	0.988	1.298
Employed	377	(16.6)	1895	(83.4)	2272					
Total Cholesterol level										
≥200 mg/dL	345	(18.8)	1487	(81.2)	1832		0.046	1.15	1.005	1.319
<200 mg/dL	340	(16.4)	1739	(83.6)	2079					
HDL level										
≥40 mg/dL	169	(14.8)	971	(85.2)	1140		0.005	0.80	0.679	0.934
<40 mg/dL	516	(18.6)	2255	(81.4)	2771					
LDL level										
≥100 mg/dL	591	(17.9)	2705	(2.1)	3296		0.127	1.17	0.961	1.433
<100 mg/dL	94	(15.3)	521	(84.7)	615					
Triglyceride										
≥150 mg/dL	261	(16.2)	1351	(83.8)	1612		0.075	0.88	0.763	1.010
<150 mg/dL	424	(18.4)	1875	(81.6)	2299					
History of hypertension										
Yes	250	(18.5)	1100	(81.5)	1350		0.248	1.09	0.947	1.255
No	435	(17)	2126	(83)	2561					
Smoking										
Yes	182	(18.2)	820	(81.8)	1002		0.563	1.05	0.901	1.225
No	503	(17.3)	2406	(82.7)	2909					
Physical activity status										
Sedentary	131	(21.7)	474	(78.3)	605		0.004	1.29	1.091	1.531
Active	554	(16.8)	2752	(83.2)	3306					
Alcohol consumption										
Yes	2	(5.4)	35	(94.6)	37		0.084	0.31	0.080	1.182
No	683	(17.6)	3191	(82.4)	3874					
BMI category										
Overweight/Obese	377	(18.3)	1681	(81.7)	2058		0.088	0.88	0.753	1.049
Normal/underweight	308	(16.6)	1545	(83.4)	1853					
Duration of DM										
>5 years	469	(25.1)	1398	(74.9)	1867		0.001	2.38	2.049	2.758
<5 years	216	(10.6)	1828	(89.4)	2044					

Type of DM medication							
No medication	235 (28.3)	595 (71.7)	830	0.001	2.09	1.766	2.471
OHD+insulin	158 (19.1)	670 (80.9)	828	0.001	1.41	1.164	1.703
Insulin	91 (11.8)	679 (88.2)	770	0.261	0.87	0.692	1.099
OHD	201 (13.6)	1282 (86.4)	1483	Reference	1		
Medication compliance							
No	307 (18.9)	1318 (81.1)	1625	0.062	1.14	0.997	1.310
Yes	378 (16.5)	1908 (83.5)	2286				

*Chi-square test
HDL: high density lipoprotein; LDL: low density lipoprotein; OHD: oral hypoglicaemic drugs; OR: odds ratio
Source: Primary data, 2018

Table 4. Binary Logistic Regression of ISH Risk Factors Among DM Subjects

Variables	p	OR	95% CI.	
Age 45-64	0.001	4.59	3.297	6.383
Age ≥65	0.001	13.61	9.565	19.365
High HDL cholesterol	0.009	0.77	0.626	0.936
History of hypertension	0.454	0.93	0.775	1.121
Overweight/Obese	0.12	1.26	0..091	1.499
Longer duration of DM	0.001	2.89	2.405	3.474

BMI: body mass index; HDL: high density lipoprotein; OR: odds ratio
Pseudo-R-square=0.67 (Nagelkerke)
Source: Primary data, 2018

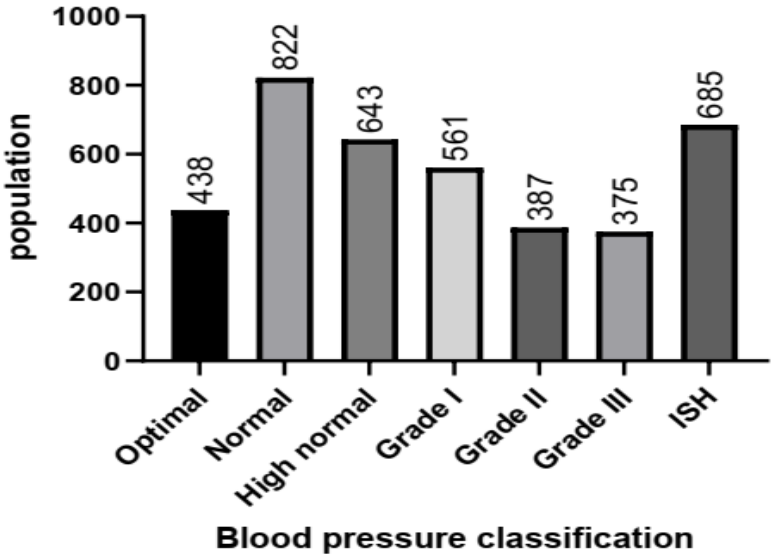

Figure 1. Frequency of Blood Pressure Classification Among DM Subjects
Optimal: <120 and <80; Normal: 120-129 and/or 80-84; High normal: 130-139 and/or 85-89; Grade I hypertension: 140-159 and/or 90-99; Grade II hypertension: 160-179 and or 100-109; Grade III hypertension: ≥180 and or ≥110; Isolated systolic hypertension (ISH): ≥140 and <90

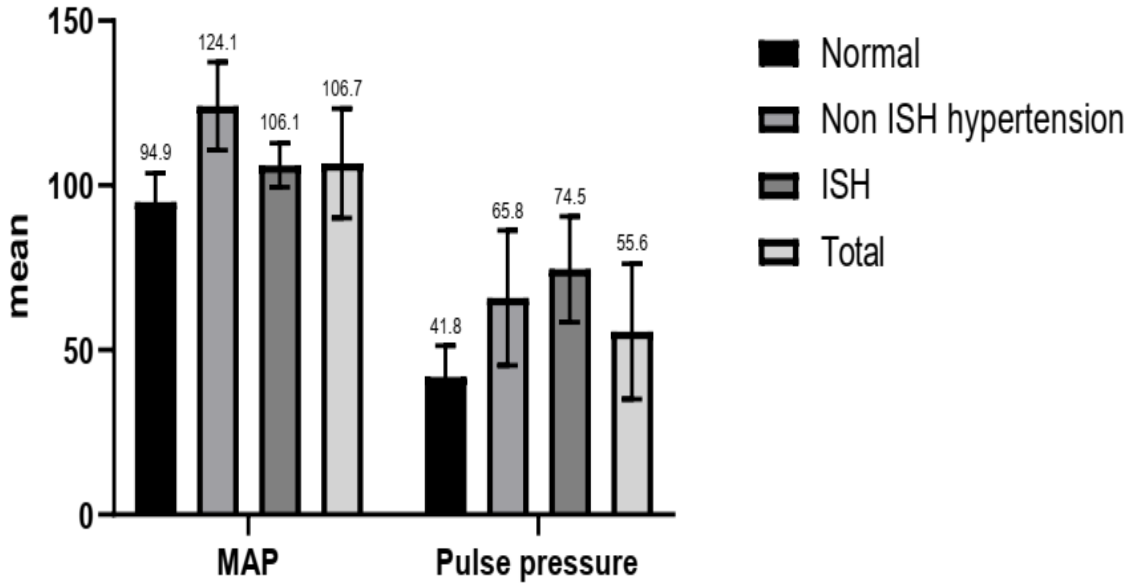

Figure 2. Mean Arterial Pressure (MAP) and Pulse Pressure Based on Hypertension Classification. ISH: Isolated Systolic Hypertension

Data from the RISKESDAS 2018 consisted of 3,911 DM subjects included in the final analysis. The subjects were 1,289 (33%) males and 2,622 (67%) females. The most frequent age category was 45-64 years old (57.4%). More than half of the subjects lived in the urban area with a low level of education and were employed in various sectors. Most of the subjects had lower total cholesterol levels, lower high-density lipoprotein (HDL) cholesterol levels, higher low-density lipoprotein (LDL) cholesterol levels, and lower triglyceride levels. Most had a history of hypertension, non-smoking, active physical activity, and fair medication compliance. The detailed subjects' characteristics are presented in Table 3.

Based on the result of blood pressure measurement, a total of 1,903 (48.7%) subjects were categorized as normal, while the rest of 2,008 (51.3%) were categorized as hypertension, whether grade 1,2,3 or ISH. ISH was the most frequent form of hypertension in the study population (Fig. 1). The highest mean MAP was in the non-ISH hypertension group, while the highest mean PP was in the ISH group (Fig. 2).

Of the total 3,911 DM subjects, 685 were identified as ISH, which indicated that the prevalence of ISH was 17.5%. Table 3 identified variables associated with the ISH. Older subjects, low educational level, high total cholesterol level, low HDL level, active physical activity, obesity, longer duration of DM, and type of medication were associated with the ISH status among DM subjects. These variables, combined with other variables that $p \leq 0.25$, i.e., employment status, LDL level, triglyceride, history of hypertension, alcohol consumption, and medication compliance, continued to be included in the logistic regression, and the ending model of regression showed in Table 4. We found that age (OR= 13.61 95% CI: 3.297-19.365) for age category ≥65 years old and OR = 4.59 95% CI: 3.297-6.383 for age category 45-64 years old)), high HDL-cholesterol (OR=0.77; 95% CI: 0.626-0.936), and longer DM duration (OR=2.89; 95% CI: 2.405-3.474), all together were related to the ISH (Table 4). Subjects with the oldest age category, i.e., ≥65 years old, had the highest OR.

The present study reported a national scope, population based cross sectional study that involved 3,911 DM individuals in Indonesia. Of them, 685 had ISH, which showed that the ISH prevalence among DM individuals in this study was 17.5%. Based on this study population, the prevalence of ISH among DM subjects in Indonesia was lower than the prevalence of ISH among DM subjects in Ghana, i.e., 37.4% based on the out-

patient diabetes clinic in the teaching hospital of Tamale (Ephraim et al., 2016) — different study populations may contribute to different prevalence. Similarly, a hospital-based study, study in Jimma, Ethiopia, found that ISH prevalence among DM patients was 27.6% (Dagnew & Yeshaw, 2019). A population-based study in the district of Chiem Hoa, Vietnam, observed the general elderly population aged >60 years old and found a prevalence of 22.9 % (Bui Van et al., 2019). Another national population-based study in the USA revealed that the prevalence of ISH in the general population was 9.4% (Liu et al., 2015). A similar result to the current study reported by a hospital-based cohort study in Italy observed ISH among type 2 DM and found a prevalence of 20.3 % (Bo et al., 2004).

The present study also added evidence that DM subjects with older age, i.e., ≥75 years old, were the most influential ISH risk factor. This finding follows the previous cohort study in Italy, which concluded that the mean age of type 2 DM subjects who experienced ISH was 74.3 years old (Bo et al., 2004). On the other hand, a study in Ethiopia reported that DM subjects aged ≥60 years old were the protective factor for ISH, while the age category of 47-55 years old was the risk factor with the highest OR, i.e., 2.63 (Dagnew & Yeshaw, 2019). Similarly, the study in Ghana showed the most frequent ISH in DM subjects aged 50-69 years old (Ephraim et al., 2016). Regarding the study population, a study in Italy and Ethiopia compared ISH to non-ISH, including other forms of hypertension, while a study in Ghana compared ISH to normal subjects (Bo et al., 2004; Dagnew & Yeshaw, 2019; Ephraim et al., 2016). The previous review concluded that ISH affects 10-20% of the elderly; SBP increases with age, while DBP rises until the age of 50 years and then decreases after that (Thijs et al., 2004). An increase in blood pressure with age is mainly associated with arterial stiffness. Degenerative processes such as calcification and alteration of arteriosclerotic structure play a pivotal role in the formation of large artery stiffness and small vessels. Small vessel stiffness leads to the condition of peripheral vascular resistance that influences the increase of both systolic and diastolic blood pressure. The existence of large artery stiffness increases systolic blood pressure and, conversely, decreases diastolic blood pressure. The acceleration of large artery stiffness after 50 years old led to a steeper increase in systolic blood pressure that caused the ISH condition (Pinto, 2007).

Lipid profile leads to the process of endothelial dysfunction that affects blood pressure. HDL cholesterol is inversely associated with hypertension, while non-HDL cholesterol has a positive association (Azam M et al., 2017; Zhan et al., 2019). The present study found that HDL was inversely associated with ISH, while in the bivariate analysis, total cholesterol showed a positive association with ISH. High HDL level, i.e., ≥40 mg/dL, was concluded as the protective factor for ISH in this study. This finding was per the Physician Health Study that reported the highest quartile of HDL level, i.e., >53 mg/dL had the lowest adjusted-RR (0.68) compared to the other quartile (Halperin. et al., 2006). A study in China also reported that HDL level was inversely related to the blood pressure and pulse-wave velocity of the brachial-ankle, an arterial stiffness development marker (Zhan et al., 2019). The oxidative activity of LDL cholesterol also influences the atherosclerotic formation structure of the vessels, which is also inhibited by HDL (Brites et al., 2017; Puri et al., 2016). However, a previous study in Japan reported a positive correlation between HDL and hypertension in apparently healthy people (Oda & Kawai, 2011). Another study revealed a positive association between HDL and hypertension in subjects with high-level circulation CD34-positive cells, a bone marrow-derived endothelial progenitor. The circulating CD-34 increases as a response to the endothelial damage, therefore masking the role of HDL as endothelial protective in healthy subjects (Shimizu et al., 2017).

The current study also found that a longer duration of DM, i.e., more than five years, was significantly associated with ISH, OR=1.82 (95% CI: 1.181-2.218). This finding adds to the previously reported evidence that revealed diabetes duration and insulin treatment status were independent predictors of ISH (Smulyan et al., 2016). The progression and duration of diabetes increase complications. Duration of diabetes is associated with arterial stiffness,

while arterial stiffness plays a pivotal role in ISH (Smulyan et al., 2016). The previous study also described the gradation of DM duration as a dose-response relationship with hypertension (Berraho et al., 2012). These findings strengthen the hypothesis that diabetes precedes arterial stiffness that causes ISH; however, another study found that the onset of diabetes and brachial-ankle pulse wave velocity coincided after a longitudinal observation, indicating a conversely condition (Y. Zhang et al., 2019). Indeed, multifactor roles contributed to arterial stiffness as a significant cause of ISH. Arterial stiffness results from degenerative processes in the extracellular matrix of elastic arteries caused by aging and many other risk factors (Palombo & Kozakova, 2016).

The final model of Binary logistic regression in this study involved a history of hypertension; however, the p-value did not meet to be considered significant. The previous history of hypertension describes the condition of individuals who tend to have a genetic predisposition (Arnett & Claas, 2018). Hypertension is a complex trait that involves multiple organs and pathways (Arnett & Claas, 2018; Lindsey et al., 2015). A comprehensive understanding of genomics, epigenomics, metabolomics, proteomics, and transcriptomics of blood pressure plays a pivotal role in the context of the previous history of hypertension (Arnett & Claas, 2018). A further study observing the detailed genetic role should be conducted to elucidate the novel hypertension pathophysiology and dissect and characterize the disorder's mechanism.

It is well established that obesity is associated with ISH (Asgari et al., 2016; Wildman et al., 2003; R. and E. R. Zhang, 2000). Obesity affects the process of inflammation, cell adhesion, and coagulation that impact in arterial stiffness (Delles et al., 2018; Wildman et al., 2003). Obesity is also related to insulin and leptin resistance that contributes to sodium retention with concomitant cardiac output (R. and E. R. Zhang, 2000). However, in this study, BMI did not significantly associate with ISH, although involved in the final model. It must be considered that the role of BMI measurement alone is inadequate for accurately predicting the disease progression in DM subjects (Murea et al., 2018). Other parameters such as body composition, total adipose mass, visceral adiposity–accumulation of intra-abdominal fat, and muscle mass should be analyzed to describe the current condition of DM subjects (Gullaksen et al., 2019; Murea et al., 2018; Owusu et al., 2018).

Conclusion

The prevalence of ISH among Indonesian DM subjects in the present study was 17.5 %. Elderly DM subjects with low HDL-cholesterol and longer DM duration were related to the ISH, suggesting that modifying the profile of lipid, mainly the level of HDL-cholesterol, is a needful effort to detain ISH in elderly and longer DM duration individuals.

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