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Original Article

The Correlation of Vitamin D Levels and Ghrelin, Adiponectin, and Resistin Levels Among Post-Ischemic Stroke Patients

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Abstract

Background : Dyslipidemia is one of the modifiable risk factors for stroke. The pathogenesis of dyslipidemia is through several mechanisms including adipose tissue-mediated adiponectin, resistin, and leptin secretion. Vitamin D is correlated with lipid profiles, but there is no evidence of the role of vitamin D in ghrelin, adiponectin, and resistin secretion, which may contribute to the mechanisms of the impairment of lipid profile among post-ischemic stroke. The aims of this study was to determine the correlation between vitamin D and ghrelin, adiponectin, and resistin among post-ischemic stroke.

Methods : An observational analytic study with a cross-sectional approach was conducted among forty post-ischemic stroke patients which was obtained consecutively. The serum vitamin D, ghrelin, adiponectin, and resistin levels were measured using the venous blood obtained from the median cubital vein. Data analysis was performed using the Spearman correlation test to determine the correlation between the serum vitamin D levels, ghrelin, adiponectin, and resistin levels.

Results : The age of our subjects is approximate 57 years old with the proportion of males being more than female subjects. There is a significant association between serum vitamin D levels and gender, total energy as well carbohydrate diet but no significant association between hormonal status and the characteristics of subjects was revealed. Furthermore, there is no significant correlation between serum vitamin D levels with the hormonal status of ghrelin, adiponectin, or resistin levels (p=0.994; 0.395; 0.858, respectively).

Conclusion : There is no significant correlation between serum vitamin D levels and serum ghrelin, adiponectin, or resistin levels among post-ischemic stroke patients

Keywords : Dyslipidemia, Vitamin D, Ghrelin, Adiponectin, Resistin

INTRODUCTION

Stroke is the second rank of neurological disorders leading to a high annual mortality index and morbidity with the consequences of disability among 50% of survivors with the consequences on social and economic aspects.[1]

Dyslipidemia is one of the modifiable risk factors for stroke and also a predictor for the outcome of stroke.[2,3] Previous studies revealed that high levels of serum triglyceride and LDL cholesterol and low levels of serum HDL cholesterol cause atherosclerosis, resulting in several vascular diseases.[3]

Dyslipidemia is one of the consequences of several mechanisms including the role of adipose tissue-mediated process.[5,6] Mature adipocytes can perform many functions, including synthesis of lipids, traffic of fatty acids across the membrane, and response to insulin signaling and adipokine secretion such as adiponectin, resistin, and leptin.[7] Adiponectin is a serum protein produced specifically by differentiated adipocytes. It affects the regulation of energy metabolism including lipid metabolism. Adiponectin has multidirectional biological action. It inhibits hepatic gluconeogenesis, reduces hepatic glucose output, and decreases the level of free fatty acids due to their oxidation.[8] Resistin is an adipokine that has been linked to the development of T2DM in rodent models. The overexpression of resistin from adipocytes induced the development of insulin resistance and dyslipidemia in healthy mice.[9]

Another hormone that can affect lipid metabolism is ghrelin. Ghrelin is a peptide hormone secreted by the stomach and duodenum and is involved in the short-term regulation of appetite as well as in the storage processes of lipids within white adipose tissue (WAT).[10] Ghrelin also affects the lipid metabolisms in the liver and promotes lipogenesis through receptor-mediated direct activation in hepatocytes.[11] Previous studies demonstrated that there was a correlation between ghrelin and LDL-cholesterol, as well as HDL-cholesterol.[12]

Vitamin D3 is one of the cholesterol derivates synthesized from 7-dehydrocholesterol in the skin upon ultraviolet irradiation. Its metabolism and function are still in debate. The classical function of 1a,25(OH)2-D3 is the regulation of calcium homeostasis. However, vitamin D receptor (VDR) is expressed in tissues not involved in calcium metabolism indicating that vitamin D may be implicated in the regulation of many non-calcemic functions including lipid metabolisms.[5,6]

Previous studies demonstrated that there is an association between Vitamin D and lipid profiles. Vitamin D deficiency is one of the risk factors for the occurrence of dyslipidemia.[5] Level of 25(OH)D3 negatively correlates with total cholesterol, LDL cholesterol, and triglyceride levels, and has a positive correlation with HDL cholesterol levels.[6] Furthermore, vitamin D supplementation resulted in a decrease of triglycerides, LDL cholesterol, and total cholesterol levels and an increase of HDL cholesterol level.[7]

The mechanisms of vitamin D affect metabolisms of lipids and cholesterol are still unknown. One of its mechanical hypotheses through the adipose mediated mechanisms resulted in the changes of lipid profile.[6] Furthermore, vitamin D3 also contributes to the absorption of calcium and inhibits lipid deposition.[5,6] through its interaction with membrane receptors, adaptor molecules, phosphatases, and nuclear coregulator proteins which contribute to the control of gene expression as well as cell signaling.[5,6]

Even though there is some evidence of the role of vitamin D in adipokine secretion especially for the pathogenesis of obesity, there is little evidence showing the relationship between vitamin D and ghrelin, adiponectin, and resistin, which may contribute to the mechanisms of the impairment of lipid profile among post-ischemic stroke, so herewith we determine their correlation to get a better understanding of the role of vitamin D on the lipid metabolism.

METHODS

This is an observational analytic study with a cross-sectional approach conducted in forty post-ischemic stroke patients in the outpatient Department of Neurology RSUP Dr. Kariadi Semarang from July to September 2022 obtained consecutively with the inclusion criterion 1) diagnosed with a post-ischemic stroke, 2) aged between 18–60 years old and consented to be involved in this study, and exclusion criterion of 1) history of vitamin D supplementation, 2) history of parathyroid hormone disorders, 3) history of dyslipidemic or cholesterol-lowering drugs consumption. Sample size estimation was measured based on the formula for the minimum sample for correlation study.

Demographic characteristics such as age, gender, and history of prior diseases including diabetes mellitus (DM), hypertension, and cardiovascular disorders were recorded from medical records, and the intake of energy, carbohydrate, protein, lipids, and cholesterol was assessed using 24-hour diet recall methods.

Vitamin D and serum ghrelin, adiponectin, and resistin levels were measured using the venous blood obtained from the median cubital vein. The measurement was performed in the *Gangguan Akibat Kekurangan Yodium* (GAKY) Laboratory Faculty of Medicine Universitas Diponegoro Semarang Indonesia employing ELISA methods. The protocol of examination was performed according to the manufacturer's sheet.

Data analysis was performed with *SPSS for Windows version 23*, which is divided into two phases. First, descriptive analyses was done to describe the

characteristics of the subjects. Categorical data was presented in frequency with percentage and numerical data was presented in the median, minimal, and maximal values because of abnormal data distribution. Then, analysis was continued using the Spearman correlation test to determine the correlation between the characteristics of subjects, serum vitamin D levels, and ghrelin, adiponectin, and resistin levels.

Study protocols were approved by The Local Research Ethics Committee and the ethical clearance was obtained from the Health Research Ethical Committee RSUP Dr. Kariadi Semarang Indonesia with the number of ethical clearance No 993-1/EC/KEPK-RSDK/2022.

RESULTS

Characteristics of Subjects

The demographic, recall of diets, and laboratory findings data of the subjects are demonstrated in Table 1.

Table 1 reveals that the age of our subjects is approximately 57 years old with 32 being the youngest and 71 being the oldest age with the proportion of male being more than female subjects. Regarding the vascular risks of stroke, hypertension is the most often with or without diabetes Mellitus and cardiac problems.

TABLE 1
Demographic Characteristics of Subjects

Variable	n	%	Median (min – max)
Age			57.5 (32 – 71)
Gender			
Male	23	57.5	
Female	17	42.5	
History of hypertension			
No	8	20.0	
Yes	32	80.0	
History of diabetes mellitus			
No	26	65.0	
Yes	14	35.0	
History of cardiac abnormality			
No	25	62.5	
Yes	15	37.5	
Energy recall diet (Kcal/day)			1482.3 (869.7 – 1921.3)
Protein recall diet (Kcal/day)			62.35 (33.20 – 156.80)
Lipid recall diet (Kcal/day)			41.75 (16.90 – 62.10)
Carbohydrate recall diet (Kcal/day)			221.6 (115.5 – 347.9)
Cholesterol recall diet (Kcal/day)			175.9 (66.1 – 400.1)
Total Cholesterol (mg/dL)			207.70 ± 40.81
LDL Cholesterol (mg/dL)			145.35 ± 46.47
Triglycerides (mg/dL)			159.50 ± 85.43
HDL Cholesterol (mg/dL)			47.47 ± 15.272
Vitamin D (ng/dL)			21.72 ± 9.54
Ghrelin (ng/dL)			223.83 ± 85.00
Adiponectin (ng/dL)			4366.33 ± 548.36
Resitin (ng/dL)			14.17 ± 1.12

TABLE 2
Correlation of Serum Vitamin D Levels and Characteristics of Subjects

Variable	Mean ± SD	*p*
Age		0.638
Gender		0.002*
Male	24.49 ± 8.56	
Female	17.97 ± 9.76	
History of hypertension		0.624
No	22.05 ± 7.56	
Yes	21.63 ± 10.08	
History of diabetes mellitus		0.288
No	23.32 ± 10.90	
Yes	18.74 ± 5.50	
History of cardiac abnormality		0.759
No	21.30 ± 7.67	
Yes	22.42 ± 12.32	
Energy recall diet (Kcal/day)		0.001*
Protein recall diet (Kcal/day)		0.076
Lipid recall diet (Kcal/day)		0.397
Carbohydrate recall diet (Kcal/day)		<0.001*
Cholesterol recall diet (Kcal/day)		0.444

*Significant (p<0.005)

TABLE 3
Correlation of Serum Ghrelin Levels and Characteristics of Subjects

Variable	Mean ± SD	*p*
Age		0.650
Gender		0.494
Male	226.22 ± 86.44	
Female	220.59 ± 85.54	
History of hypertension		0.735
No	224.13 ± 90.62	
Yes	223.75 ± 85.06	
History of diabetes mellitus		0.387
No	208.19 ± 72.58	
Yes	252.86 ± 100.74	
History of cardiac abnormality		0.944
No	219.08 ± 81.80	
Yes	231.73 ± 92.46	

TABLE 3. Continued.

Variable	Mean ± SD	*p*
Energy recall diet (Kcal/day)		0.815
Protein recall diet (Kcal/day)		0.323
Lipid recall diet (Kcal/day)		0.574
Carbohydrate recall diet (Kcal/day)		0.883
Cholesterol recall diet (Kcal/day)		0.634

TABLE 4
Correlation of Serum Adiponectin Levels and Characteristics of Subjects

Variable	Mean ± SD	*p*
Age		0.288
Gender		0.397
Male	4302.26 ± 492.00	
Female	4453.00 ± 621.48	
History of hypertension		0.204
No	4143.88 ± 729.54	
Yes	4421.94 ± 492.10	
History of diabetes mellitus		0.843
No	4363.69 ± 461.87	
Yes	4371.21 ± 701.31	
History of cardiac abnormality		0.706
No	4313.16 ± 511.31	
Yes	4454.93 ± 613.22	
Energy recall diet (Kcal/day)		0.955
Protein recall diet (Kcal/day)		0.980
Lipid recall diet (Kcal/day)		0.780
Carbohydrate recall diet (Kcal/day)		0.930
Cholesterol recall diet (Kcal/day)		0.653

Correlation of Serum Vitamin D Levels and Characteristics of Subjects

Initially, we determined the correlation between serum vitamin D levels and the characteristics of subjects. The results of its data analysis are depicted in Table 2.

Table 2. revealed that there is a significant association between serum vitamin D levels and gender, total energy as well carbohydrate diet, but none for other characteristics including age.

Correlation of Serum Hormonal Levels and the Characteristics of Subjects

The data analysis was continued for the hormonal status including ghrelin, adiponectin, and resistin levels and characteristics of subjects which are displayed in Table 3, 4, and 5.

Tables 3, 4, and 5 demonstrated that there is no significant association of hormonal status including the ghrelin, adiponectin, and resistin levels, and the characteristics of subjects including age.

TABLE 5
Correlation of Serum Resistin Levels and Characteristics of Subjects

Variable	Mean ± SD	*p*
Age		0.315
Gender		0.554
Male	14.08 ± 1.24	
Female	14.29 ± 0.96	
History of hypertension		0.542
No	13.95 ± 1.16	
Yes	14.23 ± 1.12	
History of diabetes mellitus		0.402
No	14.28 ± 1.20	
Yes	13.96 ± 0.96	
History of cardiac abnormality		0.786
No	14.21 ± 1.20	
Yes	14.11 ± 1.02	
Energy recall diet (Kcal/day)		0.467
Protein recall diet (Kcal/day)		0.948
Lipid recall diet (Kcal/day)		0.346
Carbohydrate recall diet (Kcal/day)		0.428
Cholesterol recall diet (Kcal/day)		0.311

TABLE 6
Correlation of Serum Vitamin D, Ghrelin, Adiponectin and Resistin Levels

Variable	*p*	Median (Min–Max) (ng/dL)	r
Ghrelin	0.994	192 (114 – 445)	-0.001
Adiponectin	0.395	4426.5 (2934 – 5738)	-0.138
Resitin	0.858	14.4 (11.5 – 16)	-0.029

Correlation of Serum Vitamin D, Ghrelin, Adiponectin and Resistin Levels

As our main outcome, the result of data analysis of correlation of correlation of serum vitamin D, ghrelin, adiponectin, and resistin Levels was provided in Table 6.

Table 6 provides the information that there is no significant correlation between serum vitamin D levels with the hormonal status of ghrelin, adiponectin, or resistin levels.

DISCUSSION

Dyslipidemia is one of the modifiable risk factors for cardiovascular events including stroke and also a predictor for the outcome of stroke.[2,4,13] Dyslipidemia is one of the consequences of several mechanisms such as the fatty tissue-mediated processes including synthesis of lipids, traffic of fatty acids across the membrane, and response to insulin signaling and adipokine secretion such as adiponectin, resistin, leptin, and ghrelin.[5,6]

Previous studies demonstrated that there is an association between Vitamin D and lipid metabolisms

resulting in the impairment of lipid profiles.[5] Level of 25(OH)D3 negatively correlates with total cholesterol, LDL cholesterol, and triglyceride levels, and has a positive correlation with HDL cholesterol levels.[6,14]

Several factors influence the photosynthesis and bioavailability of vitamin D and contribute to the risk of impaired vitamin D status starting from factors that impact the exposure to ultraviolet radiation, absorption of vitamin D, and metabolism of vitamin D.[15,16] Furthermore, several diseases affect vitamin D statuses such as kidney disease, liver disease, and malignancies.[15] Our results provide the evidence that there is a significant association between serum vitamin D levels and gender, total energy as well carbohydrate diet. These results align with a previous study that revealed higher intake of carbohydrates might reduce vitamin D levels and also the level of vitamin D is affected by gender.[17,18]

The relationship between serum vitamin D levels with the hormonal status of ghrelin, adiponectin, or resistin levels is still in debate. Some evidence provides that vitamin D modulates the secretion of many adipokines.[19] On the other hand, some studies showed that there is no effect of vitamin D on the hormonal status related to lipid metabolism.[20] Our results show that there is no significant correlation between serum vitamin D levels with the hormonal status of ghrelin, adiponectin, or resistin levels. These results are different from previous studies that demonstrated vitamin D is associated with resistin or adiponectin.[21–23] There is no evidence among post-stroke patients, previous studies using different comorbidities such as patients with inflammatory bowel diseases, post-menopause women, and patients with type II diabetes mellitus. Our findings also suggest that dyslipidemia among post-stroke patients has resulted from different mechanisms compared with other diseases that need to be studied further.[24]

Several factors contribute to vitamin D availability in the human body such as age, gender, or maybe genetics.[15–17] Even though our results provide evidence that there are several confounding factors associated with the particular vitamin D levels in the bivariate analysis such as gender, total energy, and carbohydrate diet, we did not continue the analysis to the multivariate. Furthermore, from our findings we did not classify the level of vitamin D according to the clinical approach, which may be useful in the management of patient related to vitamin D status. Thus our study only presents the statistical importance of these findings.

CONCLUSION

There is no significant correlation between serum vitamin D levels and serum ghrelin, adiponectin, or resistin levels among post-ischemic stroke patients.

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CONFLICT OF INTEREST

There is no conflict of interest.

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