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THE CORRELATION BETWEEN SERUM GLUCAGON PEPTIDE-1 LEVELS WITH INTIMA MEDIA THICKNESS OF CAROTID ARTERY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT
Type 2 Diabetes Mellitus is a group of metabolic disorders characterized by clinical hyperglycemia due to defects in insulin secretion, insulin action or both. This study was to determine the correlation between serum fasting Glucagon Like Peptide-1 (fGLP-1) levels and serum 1 hour post prandial Glucagon Like Peptide-1 (1hGLP-1) levels with IMT of carotid artery in patients with Type 2 DM. This study used a correlative analytic with a cross-sectional approach in population of Type 2 DM patients who were treated at the Interna Polyclinic at Dr. Mohammad Hoesin Palembang the IMT of carotid artery was measured with a high-resolution carotid doppler ultrasound B-mode ultrasound machine. The GLP-1 level was measured by the ELISA method. There were 40 subjects with a median age of 52 (40-59) years. A strong negative correlation was found between fGLP-1 serum levels and IMT of carotid artery with r= -0.748; p = 0.000; n=40. This study also found a strong negative correlation between serum levels of 1hGLP-1 and carotid IMT with r = -0.600; p = 0.000; n=40. There is a strong correlation between serum fGLP-1 levels and serum 1hGLP-1 levels with IMT of carotid artery in Type 2 DM patients. Measurement of serum levels of fGLP-1 and 1hGLP-1 may be an important indicator in evaluating cardiovascular risk in Type 2 DM patients. It may also provide guidance in the development of therapies for Type 2 DM patients to reduce the risk of cardiovascular disease.

Keyword: type 2 diabetes mellitus, serum glucagon like peptide-1 levels, serum fasting glucagon like-peptide 1 levels, serum 1 hour post prandial glucagon like peptide-1 levels, intima-media thickness, carotid artery.

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INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by clinical hyperglycemia due to defects in insulin secretion, insulin action, or both (Ozougwu et al., 2013). According to the International Diabetes Federation (2019) the number of DM sufferers worldwide has increased to 463 million in 2019 and the number of deaths in this case is 4.2 million, where Indonesia ranks 7th with 10.7 million sufferers (A. Rydosz, 2022). It is estimated that by 2045 cases of diabetes will increase to 700 million (Abhinav et al., 2020).

According to RISKESDAS results, DM in Indonesia from 2013-2018 was obtained in 2013 amounting to 6.9% and in 2018 amounting to 8.5%, while in South Sumatra Province, it was recorded that from 2016-2017 it had increased. According to the South Sumatra Provincial Health Office, there was an increase in type 2 DM sufferers in 2016 by 45% and in 2017 by 55% (Ismah et al., 2022). According to data from the Palembang City Service, the number of DM sufferers in 2017 was 33,676 cases of DM sufferers and in 2018 there were 49,432 DM cases.

Uncontrolled DM can caused acute complications and chronic complications including hyperglycemia, hypoglycemia, coronary heart disease, peripheral arterial disease, ischemic stroke, hemorrhagic stroke, diabetic retinopathy, nephropathy, and neuropathy (Sudarmaji et al., 2020).

In Indonesia, research, and publications on Glucagon Like Peptide 1 (GLP-1) are still very limited. Based on this, this study was submitted to determine the correlation of Glucagon Like Peptide 1 (GLP-1) levels to the Thickness of Intima Media (KIM) of the carotid artery in type 2 DM patients at Palembang Hospital. The results of this study will be useful for the selection of therapy in type 2 DM patients with cardiovascular complications in the future.

Based on the background above, the purpose of this study was to determine the relationship between fasting serum Glucagon Like Peptide-1 (fGLP-1) levels and serum Glucagon Like Peptide-1 (1hGLP-1) levels 1 hour post prandial with carotid artery BMI in patients with Type 2 DM.

METHOD

This study used a correlative analytic with a cross-sectional approach in population of Type 2 DM patients who were treated at the Interna Polyclinic at Dr. Mohammad Hoesin Palembang Hospital during August 2022- December 2022 (Gani & Abdat, 2022). The IMT of carotid artery was measured with a high-resolution carotid doppler ultrasound B-mode ultrasound machine. The GLP-1 level was measured by the ELISA method. All data were analyzed using the SPSS 26.0 for windows program. There were 40 subjects with a median age of 52 (40-59) years.

Inclusion Criteria were Type 2 DM patients are currently between 40-50 years old that want to participate in the research by signing an informed consent form. The exclusion Criteria were the pregnant patient, patients with severe liver disease, severe kidney disease, patients with pancreatic malignancy or severe pancreatic disease, and patients who use GLP-RA class drugs, α-glucosidase inhibitors and DPP4i.

All data from anamnesis, physical examination, and laboratory were processed using SPSS 26.0 for Windows (Giménez et al., 2013). The data is presented in the form of tables and graphs. The data is tested whether the distribution is normal or not, if the distribution is normal then the Pearson correlation test is performed, if the data is not normally distributed the Spearman test is used. The significance level used was $p<0.05$.

RESULTS AND DISCUSSION

A total of 40 subjects were taken, that were include study inclusion and exclusion criteria from August-December 2022. Characteristics of the subjects, including age, gender, education, occupation, clinical, comorbid, body mass index, and duration of DM, are shown in table 1.

This study grouped subjects based on the age of 40-50 years as many as 14 people (35%), and 50-60 years as many as 26 people (65%). In this study, the median age of the research subjects was 52 (40-59) years. Women as many as 20 subjects (50%) and men 20 subjects (50%),

Based on education, the research subjects were grouped into 2 subjects (5%) elementary school, 2 junior high school subjects (5%), 7 high school subjects (17.5%), and 29 subjects (72.5%) undergraduate. Based on occupation, research subjects were grouped into private as many as 23 subjects (57.5%), nurses as many as 11 subjects (27.5%), soldiers as many as 1 subject (2.5%), lecturers as many as 1 subject (2.5%), did not work as much as 4 subjects (10%).

Based on the comorbid characteristics of hypertension, the study subjects were grouped into no hypertension as many as 18 subjects (45%), while subjects who suffered from hypertension were 22 subjects (55%). In this study, 11 subjects (27.5%) had comorbid dyslipidemia, while 29 subjects (72.5%) did not suffer from dyslipidemia.

Subjects were grouped into 2 groups based on the duration of DM 1-5 years in 31 subjects (77.5%) and 9 subjects (22.5%) suffering from DM 5-10 years. The median duration of suffering from DM is 5 years, with a minimum duration of DM of 1 year and a maximum of 10 years.

The body mass index of research subjects was distinguished based on the distribution of 0 subjects (0%) underweight BMI, 21 subjects (52.5%) of normal or normoweight BMI, and 19 subjects (47.5%) of overweight BMI. The median body mass index was 24.97 kg/m2 where the lowest result was 20.57 kg/m2 and the highest result was 33.2 kg/m2.

The HbA1C of the study subjects was differentiated based on the distribution of <7.5%, in 10 subjects (25%), >7.5% in 30 subjects (75%). Examination of hbA1c in this study obtained a median result of 9.25, where the lowest result was 6.8 and the highest result was 18.3.

Based on the fGLP-1 levels, the study subjects were grouped into normal fGLP-1 levels of 2 subjects (5%), while subjects with low fGLP-1 levels were 38 subjects (95%). Examination of serum fGLP-1 levels in this study obtained a median result of 0.909 pg/mL where the lowest result was 0.57 pg/mL and the highest result was 4.389 pg/mL.

Based on the 1hGLP-1 levels, the study subjects were grouped into normal 1hGLP-1 levels, 3 subjects (7.5%), while subjects with low fGLP-1 levels were 37 subjects (92.5%). Examination of serum 1hGLP-1 levels in this study obtained a median result of 1.15 pg/mL where the lowest result was 0.698 pg/mL and the highest result was 4.623 pg/mL.

Based on the carotid artery intima media, study subjects were grouped into carotid artery intima media which was thickened by 23 subjects (57.5%), carotid artery which was thickened with plaque and sclerotic by 3 subjects (7.5%), carotid artery which was thickened with plaque 11 subjects (27.5%), thickened carotid arteries with sclerotic 2 subjects (5%), thickened carotid arteries without plaque and sclerotic 7 subjects (17.5%), and normal carotid arteries 17 subjects (42.5%). Carotid artery intima media examination in this study obtained a median result of 0.85 where the lowest result was 0.5 and the highest result was 1.5

Table 1. Characteristics of Subjects

Characteristics	Total (n=40)
Age (years) median (min-maks)	52(40-59)
40-50, n (%)	14 (35)
50-60, n (%)	26 (65)
Education	
Elementary school, n (%)	2 (5)
Junior high school, n (%)	2 (5)
Senior high school, n (%)	7 (17,5)
Bachelor degree, n (%)	29 (72,5)
Occupation	
Entrepreneur, n (%)	23 (57,5)
Nurse, n (%)	11 (27,5)
Military, n (%)	1 (2,5)
Lecturer, n (%)	1 (2,5)
Unemployed, n (%)	4 (10)

Characteristics	Total (n=40)
Hypertension	
Yes, n (%)	18(45)
No, n (%)	22 (55)
Dyslipidemia	
Yes, n (%)	11 (27,5)
No, n (%)	29 (72,5)
Duration of DM, median(min-maks)	5(1-10)
1-5 years, n (%)	31 (77,5)
5-10 years, n (%)	9 (22,5)
Body mass index, median(min-maks)	24,97(20,57-33,2)
Underweight, n (%)	0(0)
Normoweight, n (%)	21 (52,5)
Overweight, n (%)	19 (47,5)
HbA1c, median(min-maks)	9,25(6,8-18,3)
<7.5%, n (%)	10 (25)
>7.5%, n (%)	30 (75)
fGLP-1 levels	0,909(0,57-4,389)
Normal, n (%)	2 (5)
Low <2.21pg/L, n (%)	38 (95)
1hGLP-1 levels	1,15(0,698-4,623)
Normal, n (%)	3 (7,5)
Low <2.57pg/L, n (%)	37 (92,5)
Intima Media A. Carotid	0,85(0,5-1,5)
Thickened, n (%)	23 (57,5)
Thickened + Plaque + sclerotic, n (%)	3 (7,5)
Thickened + Plaque, n (%)	11 (27,5)
Thickened + sclerotic, n (%)	2 (5)
Thickened without Plaque and sclerotic, n (%)	7 (17,5)
Normal, n (%)	17 (42,5)

Correlation of Carotid Artery Intima Media (KIM) Thickness with Fasting Glucagon Like Peptide 1 (fGLP-1) Serum Levels

The correlation between A. carotid KIM values and fGLP-1 serum levels in this study was analyzed using the Spearman correlation test (Phi Thi Nguyen et al., 2022). From the results of the analysis, it was found that the KIM A. carotid value and fGLP-1 serum levels had a negative correlation, with a strong correlation strength, which was expressed by the value of r = -0.748 and the degree of significance of p = 0.000. Based on this analytical test, the correlation between carotid artery KIM values and serum fGLP-1 levels is clinically and statistically significant. In this study it can be concluded that the higher the KIM value of the carotid artery, the lower the fGLP-1 serum levels.

The results of this study are similar to the research conducted by Le et al. (2020) in Vietnam who stated that serum fGLP-1 was significantly reduced in patients with thickened KIM, in other words a negative correlation (Le et al., 2020). In this study, the results of the correlation test for KIM A. femoralis and fGLP-1 serum levels yielded a significant p = 0.000 with a value of r = -0.433. This study showed that serum GLP-1 values decreased significantly in patients with thick KIM. Endothelial dysfunction plays an important role in the development of diabetic microvascular complications in patients with type 2 diabetes mellitus. Previous studies have proven that serum GLP-1 levels make a major contribution to not only preventing arterial walls from inflammatory responses, atherosclerosis, oxidative stress, but also promote relaxation. endothelium. Serum GLP-1 benefits endothelial function through various mechanisms. GLP-1 inhibited the formation of foam

macrophages via cAMP and prevented the inflammatory response in the arteries (Tanaka et al., 2016). GLP-1 influences macrophage accumulation and modulates anti-inflammatory molecules such as IL-10, CD136, and CD204 (Shiraishi et al., 2012). By activating STAT3 in a GLP-1 receptor-dependent manner, GLP-1 reduces pro-inflammatory response and macrophage accumulation along the arterial wall. GLP-1 was correlated with coronary artery abnormalities in humans (diagnosed via coronary angiography) via multivariate logistic regression including age, sex, BMI, hypertension, diabetes, smoking, triglycerides, HDL-C, hsCRP and glomerular filtration rate (Xiong et al., 2020); (Piotrowski et al., 2013).

Tabel 2. Correlation of Carotid KIM with fGLP-1 serum levels

Variabel		fGLP-1
KIM Karotis	R	-0,748
	p	0,000*
	n	40

*Spearman's rho test (p is significant if <0.05), if the value is r= 0.0 to <0.2: very weak, r= 0.2 to <0.4: weak, r= 0.4 to < 0.6: moderate, r= 0.6 to <0.8: strong, r= 0.8 to 1: very strong

The correlation between A. carotid KIM values and serum 1hGLP-1 levels in this study was analyzed using the Spearman correlation test. From the results of this analysis, it was found that the KIM A. carotid value and 1hGLP-1 serum level had a negative correlation, with a strong correlation strength, which was expressed by the value of r = -0.600 and the degree of significance of p = 0.000. Based on this analytical test, the correlation between carotid artery KIM values and serum 1hGLP-1 levels was clinically and statistically significant. In this study it can be concluded that the higher the KIM value of the carotid artery, the lower the serum 1hGLP-1 level. The results of this study are similar to the research conducted by Lastya et al. in Bali, Indonesia where 1hGLP-1 levels were found to be significantly lower in subjects with type 2 DM (Lastya et al., 2014), confirmed by the study in Vietnam who studied fGLP-1 serum with KIM A Femoralis (Le et al., 2020). In this study, the serum GLP-1 value decreased significantly in patients with thick BMI. The GLP-1 reduces endothelial dysfunction, inflammatory response in patients with type 2 diabetes mellitus through its effects on nitro tyrosine, 8-iso prostaglandin F2a, SICAM-1, and interleukin-6 (Ceriello et al., 2013). In addition, GLP-1 inhibitors and dipeptidyl peptidase IV upregulate endothelial NO synthetase and increase NO production together with reduced expression of cyclooxygenase which increases endothelium relaxation. In univariate linear regression analysis, fGLP-1, age, WHR, SBP, DBP, total cholesterol, hsCRP, showed a significant correlation with KIM. Because many factors can influence arterial wall thickness, after adjusting for other related factors (DBP and eGFR), fGLP-1 showed a significant negative correlation with arterial KIM.

Tabel 3. Correlation of Carotid KIM with 1hGLP-1 serum levels

Variabel		1hGLP-1
KIM Karotis	R	-0,600
	p	0,000*
	n	40

*Spearman rho test (p means when <0.05), when value r= 0.0 sd <0.2: very weak, r= 0.2 sd <0.4: weak, r= 0.4 sd <0.6: medium, r= 0.6 sd <0.8: strong, r= 0.8 sd 1: very strong

CONCLUSION

A strong negative correlation was found between fGLP-1 serum levels and IMT of carotid artery with r= -0.748; p = 0.000; n=40. This study also found a strong negative correlation between serum levels of 1hGLP-1 and carotid IMT with r = -0.600; p = 0.000; n=40. There is a strong correlation between serum fGLP-1 levels and serum 1hGLP-1 levels with IMT of carotid artery in Type 2 DM patients. Limitation of this study that conducted did not further analyze the clinical outcomes of the patients and were only taken using a cross-sectional technique at one time. Another thing that can have an effect is on how long you have been on diet management, diabetes, and atherosclerosis treatment, where this can show an effect on carotid GLP-1 and KIM A. levels in each patient. Further studies by comparing GLP-1 levels and carotid intima media thickness in type 2 DM patients with normal controls with matching samples and removing confounding factors to provide more accurate comparative data.

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