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The Correlation between Serum Vascular Endothelial Growth Factor and Lipid Profile in Type 2 Diabetes Mellitus

Rusdiana Rusdiana[1]*, Sry Suryani Widjaja[1], Rina Amelia[2]

[1]Department of Biochemistry, Medical Faculty, Universitas Sumatera Utara, Medan, Indonesia; [2]Department of Public Health, Medical Faculty, Universitas Sumatera Utara, Medan, Indonesia

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***Correspondence:** Rusdiana Rusdiana, Department of Biochemistry, Medical Faculty, Universitas Sumatera Utara, Jl. Dr. Mansur Kampus USU Medan 20155, Indonesia. E-mail: rusdiana7165@yahoo.com
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Abstract

BACKGROUND: Diabetes mellitus is a chronic metabolic disease characterized by increased blood sugar levels (BSLs). Elevated BSL was to be reliably measured by measuring the concentration of hemoglobin glycosylate (HbA1C). Chronic hyperglycemia can result in damage to endothelial cells resulting in disruption of vascular hemostasis leading to complications in the form of vascular disorders. Endothelial damage or dysfunction will increase cytokines, one of which is vascular endothelial growth factor (VEGF), which induces angiogenesis.

AIM: In our study we wanted to investigate the correlation between serums VEGF with lipid profile at type 2 diabetes mellitus patients in primary health care in Medan city of North Sumatera, Indonesia.

MATERIALS AND METHODS: This study conducted at type 2 diabetes mellitus with the cross-sectional analytic method. The inclusion criteria of the samples were all the patients diagnosed with type 2 diabetes mellitus, both the sexes. Body mass index (BMI), blood pressure, duration of disease, and family history were recorded. The laboratory parameters, including fasting blood sugar, HbA1c, high-density lipoprotein, low-density lipoprotein, triglycerides (TG), and cholesterol, were examined by Paramita Laboratory Clinic and VEGF and hypoxia-inducible factor (HIF)-1α, we examined by ELISA methods in the laboratory Medical Faculty, Universitas Sumatera Utara. The data of the samples were processed using a computer with the SPSS program.

RESULTS: There was a significant correlation between VEGF and BMI, TG, and HIF-1α. The statistical analysis using correlation test found that there was a significant correlation between VEGF and BMI, TG, HIF-1α type 2 diabetes mellitus patients ($p < 0.005$).

CONCLUSION: Therefore, our study showed that the correlation between VEGF and lipid profile (TG), BMI, and HIF-1α was a positive correlation, which showed a directional relationship, if the VEGF level is high then the BMI, TG and HIF-1α values are also high.

Introduction

Type 2 diabetes mellitus was a metabolic disorder characterized by hyperglycemia and associated with deficiency insulin activity or secretion with absolute and relative [1]. Because of chronic hyperglycemic and insulin resistance caused increasing permeability of blood vessel and disorder endothelial cell (EC). Type 2 diabetes patients have early development of abnormal endothelial function, it caused vasoconstriction, inflammation cell accumulated, migration of smooth muscle cell, and increased cytokine production, which results in plaque development [2]. One of the cytokines secretions is the vascular endothelial growth factor (VEGF) which is a growth factor that induces angiogenesis in vascular ECs [3] and is a significant regulator of angiogenesis in both physiological and pathological conditions. VEGF is a growth factor that can induce angiogenesis in vascular ECs and is a significant regulator of angiogenesis in both physiological and pathological conditions [4].

In the angiogenesis process, the most potent mitogens acting on ECs are the VEGF and basic fibroblast growth factor. The expression of VEGF, which occurs under the influence of hypoxia-inducible factor-1 (HIF-1), starts and maintains a neovascularization process [5].

Processes occurring in diabetes such as hyperglycemia, insulin resistance, hypertension, dyslipidemia, central obesity, and impaired NO synthesis affect blood flow in the vessels and cause tissue hypoxia. Hypoxia is a signal for the induction of angiogenesis and the expression of many genes, including VEGF and VEGFR2, which, due to their functions, may have an impact on the development of diabetic complications [6]. Research has shown that increased angiogenesis is closely associated with the HIF-1α pathway and the HIF-1α/VEGF axis plays a pivotal role in tumor angiogenesis [7]. Several types of research that demonstrated that serum VEGF levels were increased in type 2 diabetes mellitus patients with complications [8]. Therefore, VEGF is associated with the development of type 2 diabetes mellitus and is influenced by various factors. In our study we wanted to investigate the correlation between serums VEGF with lipid profile at type 2 diabetes mellitus patients in primary health care in Medan city of North Sumatera, Indonesia.

Materials and Methods

In this study, we used 89 of the samples with type 2 diabetes mellitus, we recruited them from the Primary Health Care in Medan city and Primary Health Care in Binjai and Stabat city, North Sumatera, Indonesia. This was conducted from May to July 2020. Patients with known diabetics taking oral hypoglycemic agents or managed with diet or using insulin for glycemic control were included in the study. Permission from the institutional review committee was obtained. Patients were informed with the detail of the study and written consent was obtained from the patients before they participated in the study. Because of the pandemic COVID 19 in our country, we used personal protective equipment for prevention of transmission of the viral COVID 19 and all the samples used the mask when attending to the clinic.

We measured height and weight with the subjects standing in light clothes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Blood pressure values were taken as the mean of two measurements after the subjects had been seated for at least 5 min. Subjects fasted overnight to provide a blood specimen. Blood samples were collected (using syringe) and transferred to Paramitha Clinical Laboratory immediately to be conducted fasting blood sugar, glycosylated hemoglobin, and lipid profile. In the Paramitha Clinical Laboratory the examination of fasting blood sugar using hexokinase methods, the examination of glycosylated hemoglobin using HPLC methods, examination of lipid profile using direct CHOD PAP, and GPO PAP methods. We examined the glycosylated hemoglobin test for patients because of this examination as a gold standard for diabetes mellitus patients. VEGF levels were measured with an ELISA assay in laboratories in Medical Faculty, Universitas Sumatera Utara.

The examination VEGF levels in the serum which allows samples to clot for 10–20 min at room temperature. Sample concentrations should be predicted before being used in the assay and samples to be used within 5 days should be stored at 2–8°C. Samples should be aliquoted or must be stored at −20°C within 1 month or −80°C within 6 months. The samples was centrifuged 2000–3000 RPM for 20 min. All reagents should be brought to room temperature before use. Reconstitute the 120 μl of the standard (6400 ng/L) with 120 μl of standard diluent to generate a 3200 ng/L standard stock solution. Allow the standard to sit for 15 min with gentle agitation before making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (3200 ng/L) 1:2 with standard diluent to produce 1600 ng/L, 800 ng/L, 400 ng/L, and 200 ng/L solutions. Standard diluent serves as the zero standards (0 ng/L). Any remaining solution should be frozen at −20°C and used within 1 month. Dilution of standard solutions suggested is as follows:

3200 ng/L	Standard No.5	120 μl Original Standard + 120 μl Standard diluent
1600 ng/L	Standard No.4	120 μl Standard No.5 + 120 μl Standard diluent
800 ng/L	Standard No.3	120 μl Standard No.4 + 120 μl Standard diluent
400 ng/L	Standard No.2	120 μl Standard No.3 + 120 μl Standard diluent
200 ng/L	Standard No.1	120 μl Standard No.2 + 120 μl Standard diluent

Dilute 20 ml of wash buffer concentrate 25× into deionized or distilled water to yield 500 ml of 1× Wash Buffer. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

Assay procedure

1. Add 40 μl sample to sample wells and then add 10 μl anti-VEGF antibody to sample wells, then add 50 μl streptavidin-HRP to sample wells and standard wells (not blank control well). Mix well. Cover the plate with a sealer. Incubate 60 min at 37°C
2. Remove the sealer and wash the plate 5 times with a wash buffer. Soak wells with at least 0.35 ml wash buffer for 30 s to 1 min for each wash. For automated washing, aspirate all wells and wash 5 times with wash buffer, overfilling wells with wash buffer. Blot the plate onto paper towels or other absorbent material
3. Add 50 μl substrate solution A to each well and then add 50 μl substrate solution B to each well. Incubate plate covered with a new sealer for 10 min at 37°C in the dark
4. Add 50 μl stop solution to each well, the blue color will change into yellow immediately
5. Determine the optical density (OD value) of each well immediately using a microplate reader set to 450 nm within 10 min after adding the stop solution.

Calculation of result

Construct a standard curve by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and draw a best fit curve through the points on the graph. These calculations can be best performed with computer-based curve-fitting software and the best fit line can be determined by regression analysis.

Typical data

This standard curve is only for demonstration purposes. A standard curve should be generated with each assay.

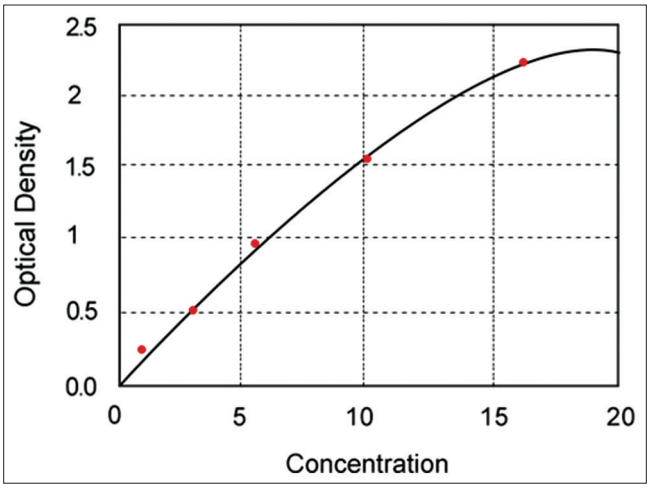

Figure 1: Standard curve

Statistical analysis

The continuous data were expressed as mean ± standard deviation (SD). Pearson correlation test was used for checking the normality of distribution. If the data were normally distributed, the correlation test was used. $p < 0.05$ was considered as statistically significant.

Results

We evaluated clinical and laboratory findings in 89 patients with type 2 diabetes mellitus. Of the total number of subjects, 22.5% (20) were male, and 77.5% (69) of the subjects were female. The minimum age of the samples 35 years old and the maximum age was 79 years old and the median of age 54 years old. The minimum of the BMI of the samples was 17.63 kg/m^2 and the maximum 46.44 kg/m^2 and the mean 26.29 kg/m^2. The minimum of abdominal circumference was 98 cm and the maximum 216 cm and the mean 92.69 cm and SD 10.47 cm. The minimum of blood pressure of systole and diastole 98 mmHg and 60 mmHg and maximum 216 mmHg and 113 mmHg with means value 150.96 mmHg and 87.75 mmHg and SD 22.048 and 10.444 mmHg. The minimum of blood sugar level (BSL) of the sample 73 mg/dL and the maximum of BSL levels was 610 mg/dL and the mean of value 283.55 mg/dL and SD 137.428 mg/dL. The minimal glycated hemoglobin (HbA1C) value 4.7% and maximum value 14.7% with the mean value of 9.1% and SD value 2.72%. The minimum HIF-1α levels were 0.52 ul/dL and the maximum was 13.45 ul/dL and the mean was 1.93 ul/dL and SD 2.46 ul/dL. The minimum VEGF levels of the samples were 111.64 ul/dL and the maximum was 22052.61 ug/dL and the mean was 931.4882 ug/dL and SD 2405.95 ug/dL (Tables 1 and 2).

Table 1: Characteristics of the sample

Characteristic	Mean	Median	Minimum	Maximum	SD
Age (years)	55.20	54	35	79	8.92
BMI (kg/m^2)	26.2972	24.5600	17.63	46.44	5.61078
Abdominal circumference (cm)	92.69	91.00	68	121	10.470
Blood pressure (systole) mmHg	150.96	150	98	216	22.048
Blood pressure (diastole) mmHg	87.75	86	60	113	10.444

BMI: Body mass index.

Correlations between VEGF and other variables

In our study, using statistic we assessed the core relationships between serum VEGF levels and other variables in all the type 2 diabetes mellitus patients and found that the serum VEGF level was positively associated with the triglyceride (TG) value ($r = 0.255$, $p < 0.05$), cardiac risk index ($r = 0.238$, $p \leq 0.005$), HIF-1α ($r = 0.659$, $p < 0.005$), and BMI ($r = 0.271$, $p < 0.05$).

Table 2: Metabolic markers

Marker	n	Minimum	Maximum	Mean	Std. deviation
BMI	89	17.63	46.44	26.2972	5.61
LP	89	68	121	92.69	10.47
TDS	89	98	216	150.96	22.05
TDD	89	60	113	87.75	10.44
BSL	89	73	610	283.55	137.43
Hba1c	89	4.70	14.70	9.1011	2.72
Cholesterol	89	136	335	220.55	42.06
LDL	89	51	249	126.43	34.7
HDL	89	24	77	46.69	11.68
TG	89	77	708	244.37	124.04
Durasi	89	1	18	4.44	4.25
VEGF	89	111.64	22052.61	931.4882	2405.95

VEGF: Vascular endothelial growth factor, BSL: Blood sugar level, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerides, BMI: Body mass index.

However, we found no significant correlation ships between VEGF and any of the following factors: Sex, age, HbA1c, BSL, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C). We can see in the bellow Table 3.

Table 3: Correlation between VEGF and other variables

Variable	P	R
Age	0.36	0.098
Gender	0.417	0.087
BMI	0.041	0.217*
Abdominal circumference (cm)	0.166	0.148
Blood pressure (systole) mmHg	0.702	0.041
Blood pressure (diastole) mmHg	0.384	0.093
BSL	0.983	0.002
Hba1c	0.849	−0.020
Cholesterol	0.897	−0.14
LDL-C	0.591	−0.058
HDL-C	0.048	−0.211
TG	0.016	0.255*
Cardiac risk index	0.024	0.238*
Durasi	0.464	−0.079
HIF-1α	0.00	0.659**

VEGF: Vascular endothelial growth factor, BSL: Blood sugar level, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, TG: Triglycerides, BMI: Body mass index.

Discussion

There were more females (77.5%) than males (22.5%) with type 2 DM in this study. The high proportion of females in this study may be due to the nature of the population admitting to primary health care in that more of them seek medical attention than men under the

favor of having more free time because most of them were housewives. This aim of the study to evaluate the correlation between VEGF with lipid profile (cholesterol, LDL, HDL and Triglyceride) and other marer metabolic at type 2 diabetes mellitus patients.

An important risk factor for type 2 diabetes is obesity and strongly related disorders of lipid parameters. It is estimated that dyslipidemia occurs in 60–80% of diabetic patients [9]. Angiogenesis is a key factor in adipogenesis [10]. The previous study reports the positive correlation between serum TG levels and VEGF, which is consistent with the study by Peczyńska *et al*. (2004), which reported patients with incipient diabetic angiopathy [11]. Mahdy *et al*. (2010) also noted a positive correlation between lipid parameters (total cholesterol and LDL-C) in patients with type 2 diabetes [12]. Besides, Wada *et al*. (2011) also noted a positive correlation between serum TG and VEGF-A levels [13].

In my study, we found that there was a significant and positive correlation between VEGF with TG, the high TG concentration, so the high VEGF concentration too in my study, we found that there was no significant correlation between VEGF and cholesterol total, LDL, and HDL. Like research by Martynova *et al*. reported that high TGs were associated with high serum VEGF [14]. However, different research by Sun *et al*. that there were no significant relationships between VEGF and any of the following factors such as sex, age, BMI, HbA1c, FBG, TG, TC, HDL-C, and LDL-C at type 2 DM [15]. In this study, we found that there was a significant and positive correlation between VEGF and BMI over a large range of BMI 17.63 kg/m^2 and 46.44 kg/m^2. Previous studies indicate that overweight and obese individuals display elevated serum VEGF levels and a statistical BMI dependence of VEGF levels in normal-weight subjects within a wide variance of male and female participants at different metabolic states [16]. The other research reported a positive correlation between plasma VEGF concentrations and BMI over a large range of BMI between 17.6 kg/m^2 and 43.6 kg/m^2 [17]. The same with our study the samples with the lowest BMI 17.63 kg/m^2 which was the low weight and 46.44 kg/m^2 was the obese category. And there was positive correlation BMI with VEGF. Although the research has stated that there was a positive correlation between VEGF and BMI, how the role of VEGF in the pathogenesis of obesity was unclear, Type 2 diabetes mellitus whose pathogenesis is tightly linked to increased BMI [18], it has been shown that the insulin sensitivity is decreased [19] suggesting a direct negative relationship between VEGF concentrations and insulin sensitivity.

Research by Zehetner showed at the retinopathy diabetic patients that HbA1c levels revealed a significant correlation with plasma VEGF concentrations [20] and the other research showed that VEGF levels in plasma were positively correlated with glycemic control indicators (FBG and HbA1c) [21] as we know that the fundamental regulator most widely known to be involved in angiogenesis is VEGF. VEGF is also associated with tumor progression and poor outcomes in various human cancers [22]. In cultured ECs, VEGF has been proven to be induced by elevated levels of glucose and advanced glycation end-products [23]. However, in my study, we found that there was no significant correlation VEGF with Hba1c and BSL, the same with research by Sun X reported that there were no significant relationships between VEGF with glycemic control (HbA1c, FBG). There are other reasons because VEGF is affected by several factors, including gender, smoking, hyper- and hypoglycemia, elevated blood lipids, hypoxia, and activated stress axes, but the major stimulant is cellular hypoxia [24].

The expression of VEGF, which occurs under the influence of HIF1, starts and maintains a neovascularization process [5]. It has become evident that hypoxia plays an important role in all diabetic vascular complications [25]. This research found that that there was a significant and positive correlation between VEGF and HIF-1α that mean the high HIF-1α concentration and expressed the high VEGF concentration. Research by Jiang *et al*. showed that the serum levels of VEGF, HIF-1α, and IGF-I were significantly higher in diabetic patients than in the controls and there were positive correlations existed between VEGF and HIF-1α [26].

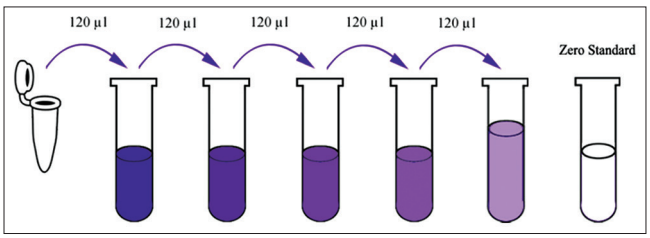

Figure 2: Dilution of the samples

Conclusion

In our study showed that there was a significant and positive correlation between VEGF and lipid profile (TG), BMI, and HIF-1α.

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