



# The Role Vascular Endothelial Growth Factor, Control Glycemic, Lipid Profile, and Hypoxia-inducible Factor 1-Alpha at Type 2 Diabetic Patients in North Sumatera, Indonesia

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## Abstract

**BACKGROUND:** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder whose prevalence continues to increase worldwide. Chronic hyperglycemia increases the area of hypoxia that can be measured by markers of hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) and endothelial cell damage by vascular endothelial growth factor (VEGF) secretion and the association of the course of diabetes mellitus, dyslipidemia is also a risk factor that can aggravate the condition. diabetes mellitus.

**AIM:** The aim of this study was to correlate VEGF with HIF-1 $\alpha$  and other metabolic markers in T2DM.

**METHODS:** Examination such as blood pressure, height, and body mass index, and duration of diabetes were recorded. Laboratory examination like blood sugar levels and glycated hemoglobin (HbA1C) levels, lipid profile such as cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were evaluated by Paramitha Laboratory Clinic and VEGF and HIF-1 $\alpha$  we examined by ELISA methods in the Integrated laboratory of Medical Faculty, Universitas Sumatera Utara. The study was done by cross-sectional analytic methods, among 135 patients with T2DM who were admitted from the various primary health-care centers in Medan city and surrounding areas in North Sumatera. The inclusion criteria of the samples were all the patients diagnosed with T2DM, both the sexes, and the exclusion criteria of the samples with T1DM and severe disease. The data of the samples were processed using a computer with the SPSS program.

**RESULTS:** There was a positive significant correlation between VEGF with HIF-1 $\alpha$ , with a strong correlation, and found a negative correlation between VEGF with fasting blood sugar and HDL ( $p < 0.005$ ).

**CONCLUSION:** By finding a strong and positive correlation between VEGF and HIF-1 $\alpha$ , the sample shows that the increase in VEGF concentration increases in line with the increase in the concentration of HIF-1 $\alpha$  and this indicates that the process of angiogenesis in the sample is taking place as a compensatory mechanism of vascular defense.

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## Introduction

Type 2 diabetes mellitus (T2DM) is responsible for increasing associated vascular complications, leading to considerable morbidity and mortality [1]. These complications of diabetes, such as nephropathy, retinopathy, neuropathy, impaired wound healing, and accelerated atherosclerosis, are implicated in a large number of cellular and subcellular changes in vessels [2]. The previous study found that vascular endothelial growth factor (VEGF) was involved in diabetic complications of pathogenesis [3]. VEGF is a growth factor that induces angiogenesis in vascular endothelial cells [4]. Many studies have found that serum VEGF levels were elevated in patients with diabetes complications [5]. The synthesis and secretion of VEGF are affected by several factors, including gender, hypoxia, hyperglycemia, smoking, blood lipids,

inflammatory reaction, and activated stress axes [6]. And therefore, our aim study was to evaluate the relation of VEGF with hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ), control glycemic, and lipid profile at T2DM who attended primer health-care center in and around Medan city.

## Materials and Methods

This study used 135 samples with T2DM; we recruited them from the primary health care in Medan city and primary health care in Binjai and Stabat city, North Sumatera, Indonesia. Our study was conducted from Mei to August 2020. Patients with known diabetics taking oral hypoglycemic agents or managed with diet

or using insulin for the glycemic control were included in the study. Permission from the Institutional Review Committee was obtained. Patients were informed of the study's detail, and written consent was obtained from the patients before they participated in the study. Because of the pandemic coronavirus disease 2019 (COVID-19) in our country, we used personal protective equipment to prevent transmission of the viral COVID-19, and all the samples used the mask when attending 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 ( $\text{kg}/\text{m}^2$ ). 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 (FBS), glycosylated hemoglobin (HbA1c), and lipid profile. Blood sugar levels were examined using hexokinase methods, glycosylated hemoglobin using high-performance liquid chromatography methods, lipid profile using direct CHOD PAP, and GPO PAP. We examined the glycosylated hemoglobin test for patients because this examination is the gold standard for T2DM patients. We used ELISA methods for examining VEGF and HIF-1 $\alpha$ . The process underwent in the laboratory medical faculty of Sumatera Utara.

### Statistical analysis

We used SPSS version 24.0 (SPSS Inc., Chicago, Illinois) statistical software for statistical analysis. Shapiro–Wilk tested all the variables in this sample of the study, the standard distribution variables ( $p > 0.005$ ) were tested by parametric correlation test, but the abnormal distribution variables ( $p < 0.005$ ) were tested by Pearson correlation.

## Results

We evaluated clinical and laboratory findings in 135 patients with T2DM. Of the total number of subjects, 32.6% (44) were male, and 67.4% (91) of the subjects were female. Controlled T2DM found 58 samples (43%) and 77 samples (57 %) with uncontrolled T2DM. The age median was 57 years old by the interval 35–79 years old. The minimum BMI of the samples were  $17.63 \text{ kg}/\text{m}^2$  and a maximum of  $46.44 \text{ kg}/\text{m}^2$  with a mean of BMI  $26.01 \text{ kg}/\text{m}^2$  and SD  $5.3 \text{ kg}/\text{m}^2$ . The minimum abdominal circumference was 64 cm and the maximum 121 cm, and the mean 91.35 cm and SD 10.89 cm. The minimal blood pressure of the samples

were 98/60 mmHg and the maximal 216/113 mmHg, and the mean blood pressure 145.43/86.22 mm Hg. The samples' illness lasted until 30 years, with the median duration of illness 5 years. The minimum FBS of the sample was 73 mg/dL, and the maximum of BSL levels was 610 mg/dL and the median 222 mg/dL. The minimum HbA1C value is 4.7%, and the maximum value is 15.2%, with a median of 8.6%. The median of cholesterol levels of the samples 212(111–342) mg/dL, the median high-density lipoprotein (HDL) levels 46 (24–77) mg/dL, the median low-density lipoprotein (LDL) 124 (50 – 259) and the median triglycerides (TG) level 205 (49–1157) mg/dL. The median of HIF-1 $\alpha$  level was 1.04 (0.02–13.96) mg/dL and the median of VEGF levels 428.89 (111.64–75421.89) mg/dL. Furthermore, in our study, we found a significant correlation between VEGF with FBS, HDL, and HIF-1 $\alpha$  in T2DM patients ( $p < 0.005$ ). There was no significant correlation between VEGF with age, BMI, abdominal circumference, blood pressure, duration of illness, HbA1c, cholesterol, LDL, and TG ( $p > 0.005$ ). We can see in Tables 1 and 2.

**Table 1: Characteristic samples**

Characteristics	Median	Mean	SD	R	p
Age (years)	57 (35–79)	–	–	0.035	0.688
Gender					0.442
BMI ( $\text{kg}/\text{m}^2$ )	24.44 (17.63–46.44)	26.01	5.3	–0.030	0.726
Abdominal circumference (cm)	90 (64–121)	91.35	10.89	–0.10	0.911
TDS (mmHg)	144 (98–216)	145.43	23.35	–0.46	0.592
TDD (mmHg)	84 (60–113)	86.22	10.40	–0.56	0.521
Duration of diabetes (years)	5 (1–30)	–	6.2	0.023	0.794

BMI: Body mass index.

In our study using the Spearman correlation test, we found that there was not a significant correlation between VEGF with age, BMI, abdominal circumference, duration of illness, and blood pressure ( $p > 0.05$ ). We can see in Table 1.

**Table 2: Data marker metabolic sample and Pearson correlation test of VEGF with the metabolic marker**

Metabolic markers	Median	Mean	SD	R	p
FBS	222 (73–610)	247.56	131.59	–0.199*	0.02
HbA1c	8.6 (4.7–15.20)	8.93	2.58	–0.123	0.154
Cholesterol	212 (111–342)	212.26	45.34	0.052	0.551
LDL	124 (50–259)	126.18	37.33	0.107	0.217
HDL	46 (24–77)	46.87	11.45	–0.180*	0.037
TG	205 (49–1157)	231.07	139.11	0.125	0.150
HIF-1 $\alpha$	1.04 (0.02–13.96)	1.99	2.65	0.707**	0.000
VEGF	428.89 (111.64–75421.89)	1468.13	6839.20	–	–

VEGF: Vascular endothelial growth factor, HIF-1 $\alpha$ : Hypoxia-inducible factor 1-alpha, FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein. VEGF was correlated with the previous metabolic markers and shod be labeled with - -

## Discussion

In our study the samples were more females (67.4%) than males (32.6%) with T2DM. 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 in favor of having more free time because most of them were housewives. Our study aimed to evaluate the correlation between VEGF levels with HIF-1 $\alpha$ ,

glycemic control, and other metabolic markers in T2DM patients. In our study, we found that there was a significant correlation between VEGF with FBS, HDL, and HIF-1 $\alpha$ ,  $p < 0.05$ . Moreover, there was no significant correlation between VEGF with age, gender, BMI, abdominal circumference, blood pressure, HbA1c, and other metabolic markers (cholesterol, LDL, and TG),  $p > 0.05$ . The detailed other research found no significant relationships between VEGF and sex, age, BMI, HbA1c, FBG, TG, TC, HDL-C, LDL-C, UA, or HCY [7]. Nevertheless, our study found a significant correlation between VEGF with FBS, HDL, and HIF-1 $\alpha$ . The other study found that VEGF levels in plasma were positively correlated with glycemic control indicators (FBG and HbA1c) and demonstrated a close association between hyperglycemia and VEGF in T2DM patients [8]. This study found a significant negative correlation between VEGF with FBS, and there was a positive and enormously significant correlation between VEGF with HIF-1 $\alpha$ . International Diabetes Federation estimated that the number of diabetes cases globally was approximately 366 million, constitutes approximately 90–95% and up to 80% of mortality associated with micro- or macro-vascular complication [9], [10]. Many factors cause complications, but the most crucial factor was that chronic hyperglycemia causes the pathological change of hypoxia [11]. The other researchers demonstrated that the expression of HIF-1 $\alpha$  and VEGF was positively correlated with diabetic retinopathy severity. HIF-1 $\alpha$  and VEGF play an essential role in the process of retinopathy induction and vascularization [12]. Hyperglycemia and hypoxia are suggested to play essential pathophysiological roles in the complications of diabetes, which may result from an inadequate response of the tissues to low oxygen tension [13]. VEGF includes a family of growth factors that act on endothelial cells regulated by hypoxia and promote angiogenesis, increases permeability in the vasculature, and is also known as a significant regulator of endothelial proliferation, migration, and survival [14].

VEGF and HIF-1 $\alpha$  are the body's defense mechanisms against compensating cells in a hypoxic state, induced by a chronic hyperglycemic state that causes hypoxic tissue, with the secretion of VEGF protein causing vasodilation and an angiogenesis process [15]. Increased VEGF concentration indicates the progression of various complications in DM and is related to the severity of a complication and a compensatory reaction to damage to endothelial cells [16]. However likely, retinal VEGF levels are initially elevated due to a reaction against retinal hypoxia or ischemia in diabetes to maintain endothelial function and circulation due to pericytes loss and acellular capillaries. This increase in VEGF is probably a tissue response to increase survival [17].

There was a negative correlation negative between VEGF with FBS in this study, which means increased VEGF levels and decreased FBS levels. It was likely with other research that showed acute

hypoglycemia is associated with an increase in serum VEGF in humans and increasing VEGF secretion during hypoglycemic conditions correlated positively with the maintenance of cognitive performance during hypoglycemia where they found that acute hyperglycemia is significantly associated with an elevation in serum VEGF in human [18]. Moreover, the research suggested that VEGF release during hypoglycemia is positively correlated to neurocognitive function keeping, too [18]. This study found a negative correlation between VEGF with HDL, the same as the previous studies [19].

Many studies have found that VEGF is involved in the pathogenesis of diabetic complications [20], [21]. As we know that hyperglycemia-induced diacylglycerol, a lipid molecule, activates protein kinase C in the vascular tissues, and then turn promotes VEGF signaling, resulting in diabetic microvascular complications [22]. But still, the other factors, including hypoxia, gender, smoking, elevated levels of blood lipids, inflammatory status, and activated stress axes, may affect the synthesis and secretion of VEGF; among them, the significant physiological stimulus for VEGF expression is the cellular hypoxia [23], [24].

## Conclusion

We conclude that in the study of diabetic patients, the relationship between VEGF levels was positive and firmly with the HIF-1 $\alpha$  and negatively correlated with FBS and HDL.

VEGF and HIF-1 $\alpha$  were a positive and strong correlation, but the correlation between VEGF and FBS can be negative.

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