



## CORRELATION OF BECK DEPRESSION INVENTORY II (BDI II) SCORE AND VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) LEVELS IN TYPE 2 DIABETES MELITUS PATIENTS

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### Abstract

**Introduction:** Depression defined as feelings of sadness, disappointment, hopelessness, and loss of interest in life. Depression can be assessed by Beck Depression Inventory II (BDI II) questionnaire. Type 2 Diabetes mellitus (DM) is a chronic metabolic disorder due to insulin deficiency or insulin resistance. Prevalence of depression has increased two times in type 2 diabetes mellitus patients. Vascular Endothelial Growth Factor (VEGF) was a vascular permeability and angiogenesis factor. Depression and Type 2 Diabetes Mellitus would increase VEGF.

**Method:** It was a correlative analytic cross sectional study, in November 2019 on Type 2 DM patients whose BDI II score and VEGF levels were assessed in outpatient clinic of Haji Adam Malik General Hospital Medan. Data were analyzed by SPSS.

**Results:** There was a very strong correlation of BDI II scores and VEGF levels ( $p = 0.0001$ ). There was correlation between hemoglobin and age, fasting blood glucose levels and 2 hours after eating blood glucose levels, 2 hours after eating glucose levels and HbA1C ( $p = 0.0001$ ,  $p = 0.0001$ ,  $p = 0.0001$ )

**Conclusion:** There was a very strong positive correlation of BDI II Scores and VEGF levels in Type 2 Diabetes Mellitus patients.

**Keywords:** Depression, Type 2 Diabetes Mellitus, Vascular Endothelial Growth Factor (VEGF), Beck Depression Inventory II (BDI II) Score.

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### Introduction

Depression is feeling of sadness, disappointment, hopelessness, no motivation, and loss of interest in life. When it lasts for a moment, it is called the "blues" period. But when it lasts more than two weeks and has an impact on daily activities, it is called as depressive disorder. There are several symptoms of depression including changes of appetite, weight gain, sleep and activity patterns, loss of energy, feelings of guilt, difficult to think and making decisions, and thinking about death or suicide.<sup>1</sup>

Beck Depression Inventory II (BDI II) is a screening tool that depicts depression for ages over 13 years. Respondents were asked to respond 21 questions based on their feelings over the past two weeks. Each item consists of four questions that indicate symptoms of depression such as sadness, pessimism, past failures, loss of interest, feelings of guilt and so on.<sup>2</sup>

Diabetes mellitus (DM) is a chronic metabolic disorder due to insulin deficiency or insulin resistance resulting in an increase of blood glucose concentration (hyperglycemia)<sup>3</sup>. Type 2 diabetes mellitus, formerly known as "insulin dependent diabetes" occupies 90-95% of all diabetes.<sup>4</sup>

The incidence of depression is increased in diabetes compared to non diabetes person. The prevalence of depression has increased threefold in type 1 diabetes mellitus and two times in type 2 diabetes mellitus when compared to normal blood glucose levels population. The presence of depression and anxiety in diabetic patients



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

make the prognosis of diabetes getting worse, increase disobedience to drug consumption, reduce quality of life and increase mortality.<sup>3</sup>

Vascular Endothelial Growth Factor (VEGF) is a vascular permeability factor and belongs to a group of signaling proteins involved in regulation of physiological and pathological angiogenesis. Normal value of serum VEGF is 62-707 pg / mL.<sup>5</sup>Normal VEGF levels produce normal neurogenesis. Stress will increase VEGF levels resulting in disrupted neurogenesis, resulting in depression. In relation to diabetes mellitus, VEGF has a very important role because VEGF induce angiogenesis which plays a role in the pathogenesis of diabetes mellitus complications through regulation of endothelial cell proliferation and vascular permeability.<sup>6</sup>There was controversy about changes in VEGF levels in depressed patients. Some research stated that VEGF levels increase in depression. On the other hand, there were studies stated that VEGF levels decrease in depressed patients. This prompted researchers to be interested in conducting a study of correlation of depression levels as measured by BDI II with VEGF levels in type 2 DM patients<sup>7</sup>. There was a study stated that VEGF levels do not differ between depressed or non-depressed patients in type 2 DM patients.<sup>8</sup>

The aim of this study was to find correlation of BDI II score and VEGF levels on type 2 Diabetes Mellitus patients.

### Materials and Methods

It was an analytic cross sectional study. The study began in November 2019. The study was conducted on outpatients at Endocrinology and Metabolic Disorder clinic, H. Adam Malik General Hospital Medan. Diabetes mellitus patients who met the inclusion and exclusion criteria were taken by consecutive sampling and the patient was willing to take part in the study by signing informed consent form. The number of subjects needed for this study was 50. Inclusion criteria were type 2 diabetes mellitus patients that are enforced by history, physical examination, and laboratory. The patients age were  $\geq 30$  old years. While the exclusion criterias were patients with history of depression and anti depressant consumption. We also exclude patient who didn't understand BDI II quosionnaire.

Subjects basic datas were recorded like names, medical record numbers, age, sex, education level, ethnicity, marital status, previous comorbidities. The BDI-II scores were assessed and the depression level of each study subject was carried out. Depressed study subjects were then examined their VEGF levels

In addition, we also analysed laboratory results like VEGF, hemoglobin (Hb), white blood cells (WBC), platelets (Plt), fasting blood glucose levels (Fasting), 2 hours after meal blood glucose level (after meal), HbA1C, total cholesterol(TC), triglycerides (TG), high density lipid (HDL), Low density lipid (LDL).

### Data Analysis

We analysed descriptive data, univariat and bivariate analysis to find correlation of BDI II Score and VEGF levels in type 2 diabetes mellitus. Spearmen for abnormal distribution and Pearson for normal distribution. Coinfidence interval was 95%.

### Results

From all type 2 diabetes mellitus patients who treated at the Endocrine and Metabolic Disorder clinic, Hospital of H. Adam Malik Medan in November 2019, 50 people included in this study. Men were 10 persons (20%) and 40 persons were women (80%). Data on age, BDI II, VEGF, hemoglobin, leukocytes, platelets, fasting blood glucose levels, 2 hours after meals blood glucose level, HbA1C, total cholesterol, triglycerides, HDL, LDL. The normality test used was Kolmogorov Smirnov. The results were hemoglobin, leukocytes, platelets, fasting blood glucose levels, 2 hours after meal blood glucose levels, HbA1C, total cholesterol, HDL, LDL normal. Age, BDI II, VEGF, (TG) scores were abnormal.



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE &amp; MANAGEMENT

*Table 1. Characteristic of Type 2 Diabetes Mellitus Patients*

Characteristic	n (%)
Sex	
Man	10(80)
Woman	40(20)
Age <sup>a</sup>	56 ± 8.433
Marital status	
Characteristic	n (%)
Single	3(6)
Married	47(94)
Ethnic	
Batak	25 (50)
Jawa	10(20)
Melayu	4 (8)
Karo	6 (12)
Padang	1(2)
Mandailing	2(4)
Education	
Primary School	1 (2)
Middle School	1 (2)
High School	6 (12)
College	42(84)
Occupation	
Civil Cervant	33(66)
Entrepreneur	6 (12)
Retired	2 (4)
Housewife	8 (16)
BDI II Scores <sup>a</sup>	5±5.14
Not Depression	48(96)
Mild Depression	0
Moderate Depression	2(4)
Severe Depression	0

*Table 2. Laboratory Results*

Data	Results
VEGF (mean ±SD)	431.75±494.86
Hb ( Median (min-max))	12.81 (9.4-16)
WBC( Median (min-max))	8980 (4789-15.960)
PLT( Median (min-max))	209.000 (162.000-670.000)
Fasting( Median (min-max))	208.5 (98-383)
After Meal( Median (min-max))	246 (102-479)
HbA1C ( Median (min-max))	8.9 (5.3-15.6)
TC ( Median (min-max))	194 (116-290)
TG(mean ±SD)	162.86 ± 72.764
HDL ( Median (min-max))	44.5 (23-78)
LDL ( Median (min-max))	113.5 (67-190)

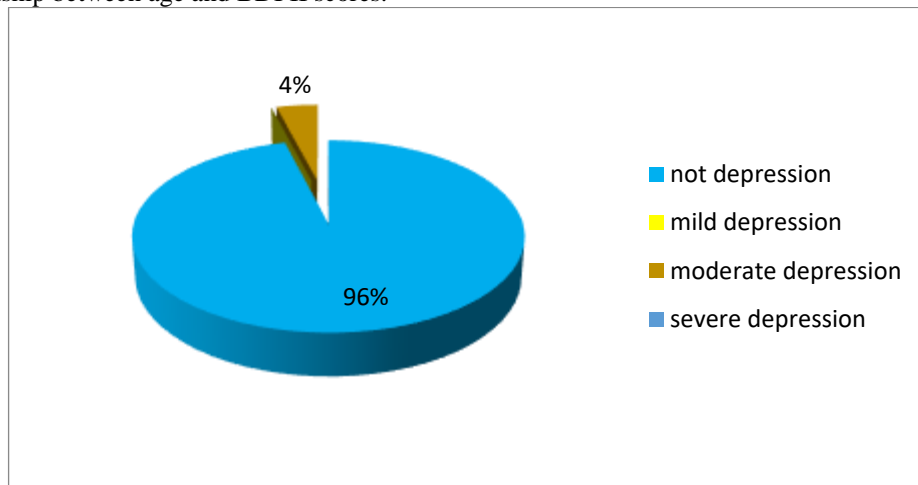


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Correlation of BDI II scores with age, sex, VEGF, complete blood, blood glucose level and lipid profile in type 2 DM patients.

Statistical tests were conducted on several socio demographic variables. Based on table 3, the results were:

1. Based on BDI II Score, 48 samples (96%) got 0-13 which meant no depression. While 2 samples (4%) had a BDI II score between 20-28 which meant moderate depression. No sample experienced mild or severe depression
2. The average age was 54.44 + 8,433. We analysed correlation between age and BDI II scores by spearman’s test, coefficient correlation were 0.116 and p = 0.424. It meant there was no significant relationship between age and BDI II scores.



3. To determine the relationship of BDI II Score with gender, a Mann Whitney test was performed. As a result, 9 men were not depressed and 2 men were moderately depressed. Meanwhile, of the 39 women, none were depressed. With the Mann-Whitney test, p = 0.007 was obtained. Because the p value <0.05, there is a statistically significant relationship between BDI scores II and gender, men had a tendency to experience moderate depression compared to women.

Table 3.correlation between gender and depression

Gender	Depression				P Value
	No Depression		Moderate Depression		
	n	%	n	%	
Men	9	18	2	4	0,007
Women	39	78	0	0	

This study also sought correlations between BDI II scores with age, hemoglobin(Hb), white blood cells (WBC), Platelets, Fasting blood glucose level (fasting), 2-hours after meal glucose levels(after meal), total cholesterol (TC), triglycerides(TG), HDL, LDL as shown in table 4. But there was no significant correlation between BDI II scores with these variables.



**Table 4. Correlation between BDI II scores and Hb, WBC, Plt, N blood glucose level, 2 PP blood glucose level, TC, TG, HDL, LDL**

Variabel	R	P
Age	0,116	0,424
Triglyceride	-0,142	0,326
Hb	-0,023	0,873
WBC	0,241	0,092
PLT	0,035	0,810
Fasting	0,028	0,847
After Meal	0,048	0,743
HbA1C	0,132	0,361
TC	0,130	0,369
HDL	0,277	0,051
LDL	-0,158	0,272

Significant correlations were obtained between several variables, hemoglobin and age, fasting blood glucose level and 2 hours after meal blood glucose level, 2 hours after meal blood glucose level and HbA1c.

1. Correlation between hemoglobin and age showed significant result ( $r = -0.483$ ,  $p = 0.0001$ ). It meant that the older a person is, the lower the hemoglobin level, as shown in table 5.
2. Correlation between 2 hours after meal blood glucose level with fasting blood glucose levels showed significant result ( $r = 0.554$ ,  $p = 0.0001$ ) meaning the higher fasting blood glucose level the higher 2 hours after meal blood glucose level, as shown in table 4.6.
3. Correlation between 2 hours after meal blood glucose level with HbA1C showed the higher 2 hours after meal blood glucose the higher HbA1C levels, as shown in table 6.

**Table 5. Correlation between hemoglobin and age**

Variable	R	P
Age	-0,483**	0,0001

**Table 6. Correlation between 2 hours after meal and fasting blood glucose, HbA1C**

Variable	R	P
N blood glucose level	0,554	0,0001
HbA1C	0,706	0,0001

### Correlation of BDI II Scores and VEGF Levels

In this study, the Spearman test was performed to look for correlations between BDI II scores and VEGF levels. The results showed that there was a significant correlation between BDI II scores and VEGF levels in type 2 DM patients. With  $P < 0.0001$  and a correlation coefficient 0.896. It meant that the higher BDI II score, the higher VEGF levels in type 2 DM patients (table 7).

**Table 7. Correlation between BDI II Score and VEGF**

Variable	R	P
VEGF	.896**	.0001

### Discussion

This was an observational cross-sectional study. The aim of this study was to determine correlation between BDI II score and VEGF levels in patients with type 2 diabetes mellitus.



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Demographic variables were important determinants in depressed patients who had type 2 diabetes mellitus. In this study the number of respondents who suffered from type 2 diabetes mellitus were 10 men and 40 women. According to BDI II Score variable, majority samples had BDI II score between 0-13 which means no depression. It was found in 48 samples. While 2 samples had BDI II scores between 20-28 which means that they had moderate depression. There was no relationship between sex and BDI II score. This might be due to the method of consecutive sampling in a predetermined time span and the researcher did not analyze relation of sex and BDI II scores based on each question. Previous studies in Taiwan examined correlation between sex and BDI II scores which were translated into Chinese. As a result, both men and women had the same pattern to answer the same questions. But men had lower BDI II scores on questions about pessimism, failure, and concentration difficulties. This might be caused of culture in Taiwan. Men in Taiwan got higher appreciation and expectations from parents.<sup>9</sup> The results of this study are in line with previous studies in Taiwan in 2010. They obtained significant results on the relationship of gender to BDI II score.<sup>10</sup>

In this study, the average age of people with depression in type 2 diabetes mellitus was  $56 \pm 8,433$  (age range 48-64 years). Spearman analysis between age and BDI II score result was 0.116 and not significant (P value = 0.424). It was in line to previous studies in Netherlands which stated there was no significant relationship between age and depression.<sup>11</sup> But the results of this study contradicted to study in 2001 which stated that depression would increase by age.<sup>12</sup> The results also added the list of previous studies which stated the relationship between BDI II and age in psychiatric outpatients.<sup>13</sup> Likewise to research in Japan in 2002, BDI II score higher in women than men but there was no significant difference between BDI II score and age.<sup>14</sup>

BDI II scores and VEGF levels had a significant correlation between BDI II scores and VEGF levels in type 2 DM patients (P < 0.0001, r = 0.896). It showed that the higher the BDI II score, the higher the VEGF level in type 2 DM patients.

### Depression level in patients with type 2 diabetes

Based on BDI II score, it was concluded that majority BDI II score was between 0-13, which means they were not depressed. While 2 samples have BDI II scores between 20-28 which means that they got moderate depression. This could have been influenced by the administration of diabetes drugs where all samples had received type 2 DM treatment. Data that confirmed the possibility of depression levels affected by diabetes medications were previous studies that had significant results on decrease of depression stage among patients before using insulin, at week 12, and at week 24.<sup>15</sup> A study stated the incidence of depression in type 2 diabetes mellitus patients increased 2-fold compared to patients with type 2 diabetes mellitus.<sup>16</sup> For 5-year study of type 2 DM patients, mild depression was found in 25% of the sample, moderate depression in 12.5% of the sample. And severe depression in 1.3% of the sample.<sup>17</sup>

Previous study concluded that insulin would improve symptoms and depression rates. The meta-analysis study was assumed that the use of insulin was a symbol of insulin absence so metabolic instability was greater than patients who did not use insulin. The patients would be more vulnerable to depression or even worsening of depression.<sup>18</sup> From statistical tests, BDI II scores do not have a significant correlation to HbA1C. It was contradictive to previous research about the relationship between HbA1C levels and BDI II scores. Patients with HbA1c between 6.5% and 7.5% had a normal interpretation of BDI II scores.<sup>19</sup>

Kubler-Ross theory who stated there were 5 stages in which a person could accept sadness, illness or death might be the answer why 96% sample did not get depression. The 5 stages were denial, anger, bargaining, depression, acceptance. Denial was a stage where the individual does not deny that something bad has happened. Anger was a form of outlet for sadness in the form of anger. Bargaining was when someone start to make an offer on sadness. Depression was a state of mental disorders as previously explained and acceptance of a stage an individual could accept the bad conditions that have befallen.<sup>20</sup> Most of the samples in this study have suffered from diabetes mellitus for more than 1 year even there are some samples suffering from diabetes mellitus for more than 5 years. So that the samples in this study had been through a period of depression and entering a period of acceptance. This reinforces the reason why although there was a very strong and significant



## INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

correlation between BDI II scores and VEGF levels in type 2 DM patients, but based on the results of BDI II scores, 96% of the sample did not experience depression.

### VEGF levels in type 2 DM patients

Median of VEGF levels in type 2 DM patients was  $431.75 \pm 494.8$ . the standard calibration range of VEGF was 31.3 - 2000 pg / ml. Normal value was 62-707 pg / ml. VEGF levels were found to be increased in type 2 diabetes mellitus patients.<sup>21,22,23</sup> As explained before, mechanism of complications due to diabetes mellitus occurs through 4 main pathways. There were aldose reductase pathway, cytoplasmic oxidative stress pathway, protein kinase C (PKC) activation pathway and the formation of Reactive Oxygen Species (ROS) pathway. These four pathways run together until finally increasing VEGF levels of type 2 DM patients. Previous studies assessed differences of VEGF levels in diabetic patients without retinopathy, with retinopathy and healthy controls. The results showed that VEGF average levels of diabetic mellitus patients without retinopathic complications was  $137.29 \pm 84.45$  pg / ml. with retinopathy  $177 \pm 119.5$  pg / ml.<sup>24</sup> In addition, other studies had found that the average level of VEGF was higher in tears of diabetic retinopathy patients than the serum VEGF level. Mean serum VEGF of diabetic patients without retinopathy was 305.4, in non-proliferative Diabetic Retinopathy patients was 288.7 and in proliferative diabetic retinopathy patients was 342.4.<sup>25</sup> Median levels of VEGF in type 2 diabetes mellitus patients 331 (242-467), and VEGF levels in patients without type 2 diabetes mellitus was 418 (329-555).<sup>26</sup>

This study got correlation between hemoglobin and age. The results were significant (p value <0.0001,  $r = -4.83$ , similar to previous studies.<sup>27,28</sup> Perhaps it caused by appetite would decrease with age. In addition, hematopoietic activity would be decrease (cellular bone marrow) so that reduced hemoglobin levels.<sup>29</sup>

Correlation between fasting blood glucose levels and 2 hours after meals blood glucose levels showed positive correlation ( $r = 0.554$ ,  $P < 0.0001$ ) meaning the higher fasting blood glucose levels the higher 2 hours after eating blood glucose levels. The higher 2 hours after eating blood glucose level, the higher HbA1C level. There have been many studies in line with current results. In 2013, study which examined 60 inpatients assessed for fasting blood glucose levels, blood glucose levels 2 hours after meals and HbA1C.<sup>30</sup> However, blood glucose levels 2 hours after meals had a closer relationship to HbA1C levels than fasting blood glucose levels.

### Research Limitations

1. Although correlation of BDI II scores and VEGF levels was significant in this study, it cannot be determined whether VEGF levels change because of type 2 diabetes or depression.
2. This study did not assess data on anti diabetic treatment, duration of treatment and socioeconomic factors so that it could be confounding the results of the study.
3. There were small number and proportion of samples, so the results could be not relevance to some variables.

### Conclusion

1. There was a significant strong positive correlation between BDI II scores and VEGF levels in patients with type 2 diabetes mellitus ( $P = 0.0001$ ).
2. There were 96% of outpatients in Endocrine Divison Haji Adam Malik General Hospital Medan not depression, and 4% moderate depression. It can be caused all samples have received anti-diabetic drugs even though the average of HbA1C level was 8.9.
3. There were 37 samples had normal range of VEGF levels (62-707 pg / ml).
4. There were 13 samples had increase in VEGF level.

According to limitation of this study, we suggested other factors that could affect BDI II scores and VEGF levels would be measured. Socioeconomic factors, the administration of type 2 diabetes mellitus treatment, classification of anti-diabetic types ,duration of medication.

In addition, next study suggested to compare VEGF levels and BDI II scores between before diabetes treatment compare to the last visit to reduce confounders.



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