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ORIGINAL RESEARCH

The Correlation Between Angiopoietin-Like 3 and Metabolic Markers of Some Lipid and Glucose in Type 2 Diabetes Mellitus Patients at the First Diagnosis

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Purpose: Angiopoietin-Like3 is a protein that plays an important role in regulating plasma triglyceride concentrations by inhibiting the enzyme lipoprotein lipase. Lipid metabolism and glucose metabolism are closely related and interact with each other. ANGPTL3 may also be a factor involved in blood glucose regulation through an increase in free fatty acids generated from enhanced lipolysis in adipose tissue leading to insulin resistance. This study aimed to investigate plasma ANGPTL3 concentrations and their correlation with lipid and glucose metabolic markers in newly diagnosed type 2 Diabetes Mellitus patients.

Subject and Methods: A cross-sectional descriptive study was conducted on 98 healthy subjects (control group) and 103 patients with type 2 diabetes at the first diagnosis, without any treatment (patient group). Plasma ANGPTL3 concentration was quantified by the ELISA method. The study determines the correlation of ANGPTL3 concentration with some indicators reflecting lipid and glucose metabolism.

Results: The concentration of ANGPTL3 in the newly diagnosed type 2 Diabetes Mellitus patient group was lower than in the control group, the difference was statistically significant with $p < 0.05$. In the patient group: there was an inverse correlation between ANGPTL3 concentration and HDL-C concentration ($r = -0.37$; $p < 0.001$), and a positive correlation with triglyceride concentration ($r = 0.275$; $p < 0.05$). There was no correlation between plasma ANGPTL3 levels and anthropometric indices, total cholesterol, HDL-C, glucose, HbA1C, insulin, and HOMA-IR. In the control group: there was no correlation between ANGPTL3 and any of the indicators mentioned above.

Conclusion: ANGPTL3 levels in newly diagnosed type 2 diabetes mellitus patients were statistically significantly lower than in healthy subjects. Plasma ANGPTL3 was positively correlated with triglyceride levels and inversely correlated with HDL-C levels in newly diagnosed type 2 Diabetes mellitus patients.

Keywords: type 2 diabetes, ANGPTL3, HDL-C, triglyceride

Introduction

Diabetes Mellitus (DM) is a common chronic disease worldwide. According to published data, the global prevalence of diabetes in 2019 was estimated at 9.3% (463 million people), increasing to 10.2% (578 million people) in 2030 and 10.9% (700 million people) by 2045. About 50.1% of people who live with DM do not know they have suffered from DM. The global prevalence of glucose intolerance was estimated at 7.5% (374 million) in 2019, projected at 8.0% (454 million) in 2030, and 8.6% (548 million) in 2045.¹

The alarming increase in incidence has prompted research to understand the pathogenesis of type 2 diabetes, including the correlation between lipid and glucose metabolism. The scientific evidence in the last decade shows that this relationship is very complex, dyslipidemia is not only the consequence but also the cause of impaired glucose

metabolism.² Besides the role of an energy reserve, adipose tissue has also been regarded as an endocrine organ, secreting many hormones, adipokines, cytokines, and free fatty acids. Some studies have shown that disorders of adipose tissue secretion, especially free fatty acids and cytokines, would increase the degree of obesity and decrease the insulin sensitivity of the target tissue (insulin resistance).³ Insulin resistance causes a compensatory response that increases blood insulin, and long-term damage to the β -cells of the islets of the pancreas, leading to disturbances in the maintenance of glucose balance and the development of type 2 diabetes.⁴

The findings of biomarkers regulating lipid metabolism and insulin resistance are extremely meaningful, especially in type 2 Diabetes mellitus (T2DM). Recently, a new family of proteins named “Angiopoietin-like protein” has been discovered due to its similar structure to angiopoietin, which plays an important role in neovascular activity.⁵ Angiopoietin-like 3 (ANGPTL3), a 70 kDa molecular, not only regulates angiogenesis but also plays an important role in regulating plasma triglyceride levels by inhibiting lipoprotein lipase enzyme which binds to capillary endothelium and catalyzes the cleavage of triglycerides into fatty acids.⁶ Besides, ANGPTL3 also increases insulin resistance.⁷ It is suggested that ANGPTL3 may also be a factor involved in blood glucose regulation. The mechanism by which ANGPTL3 inhibits glucose reduction is due to an increase in FFA derived from adipose tissue leading to insulin resistance.⁸

Some recent studies have shown that blood ANGPTL3 levels in patients with type 2 diabetes are lower than in non-diabetic subjects and are associated with several lipid indices.^{9,10} Studies of the Finnish population ($n = 250$) and the US population ($n = 1770$) also show a positive correlation between ANGPTL3 and HDL-c. However, ANGPTL3 levels were associated with triglyceride levels in opposite directions in these two populations.^{11,12} A Japanese study of 84 subjects with type 2 diabetes found that ANGPTL3 was positively correlated with HDL-C. By contrast, no clear association was observed between ANGPTL3 and glucose metabolism markers.¹³ Yu et al, when studying 1192 patients with type 2 diabetes, concluded that ANGPTL3 is strongly associated with the development of diabetic retinopathy. Blockade of ANGPTL3 signaling in the retina may delay the onset and development of retinal damage in patients with type 2 diabetes.

ANGPTL3 is independently and strongly associated with DR progression in all stages.¹⁴ The role of ANGPTL3 in lipid metabolism is unequivocal, but the link between ANGPTL3 and glucose metabolism remains unclear.¹⁵ This study was conducted to investigate the plasma ANGPTL3 concentration and its relationship with some markers of lipid and glucose metabolism in patients with newly diagnosed type 2 diabetes mellitus in Vietnam.

Patients and Methods

Subjects

A cross-sectional descriptive study was performed on 98 healthy subjects (control group) and 103 patients with first diagnosed type 2 diabetes (patient group) in 103 Military Hospital from August 2021 to June 2022.

The newly diagnosed T2DM patients were chosen according to the ADA 2019 criteria,¹⁶ untreated, age > 30 years old. The exclusions include patients using drugs that affect blood glucose levels such as thiazide diuretics, corticosteroids, beta-blockers, and estrogen-containing contraceptives. patients with type 2 diabetes have cirrhosis of the liver, kidney failure, pyelonephritis, myocardial infarction, and cancer. The control group contained healthy people, who have similar in age and gender to the T2DM group, ranged in BMI from 18 to 22, having no disease, fasting plasma glucose ≤ 5.6 mmol/l based on 2019 ADA statement. No other comorbidities.

Clinical Examination and Testing

The clinical characteristics of all the subjects were recorded when they took the clinical examination in the hospital.

Blood pressure was measured in the right arm with a mercury sphygmomanometer after 20 min of rest with the patient in the sitting position. Height and body weight were measured by an electronic scale. Body mass index is calculated as the ratio of body weight (in kilograms) to the square of body height (in meters).

Blood samples were collected after fasting for at least 8 hours. The plasma in Heparin tube was used to determine biochemical indicators, insulin, and ANGPTL3. The biochemical indicators were analyzed on the automatic analyzer system AU5800 (Beckman, USA). Plasma glucose level were accessed by hexokinase method (mmol/L). Plasma

cholesterol level were accessed by enzyme colorimetric (mmol/L). Plasma creatinine were determined by Jaffe method B ($\mu\text{mol}/\text{L}$). Plasma insulin was quantified by chemiluminescence on the DXI 800 system (Beckman, USA). ANGPTL3 was determined in plasma by double antibody sandwich enzyme-linked immunosorbent assay (ELISA). The kit was human ANGPTL3 ELISA kit (ThermoFisher Scientific, USA). The EDTA anticoagulant tube is used to collect samples for HbA1C. %HbA1c was quantified by high-performance liquid chromatography (HPLC) on a PREMIER9210 (Trinity Biotech, USA).

The insulin resistance index (HOMA - IR: Homeostasis Model AssInsulin insulin Resistance), was calculated according to the formula:¹⁷ HOMA-IR = FPG (mmol/L) x Fasting IRI (mIU/L)/22.5.

Ethical Consideration

All participants provided signed, written informed consents. The protocol was approved by the Ethical Review Committee of Vietnam Military Hospital 103 (Reference No.176/2021/CNChT-HĐĐĐ). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Statistical Analysis

The data were statistical using Microsoft office excel 2019 and SPSS22.0. Normally distributed variables were expressed as mean (\pm) and standard deviation (SD). Non-normally distributed variables were expressed as median and interquartile range 1–3 (IQ 25–75). The normally distributed variables were compared using the test. To compare the mean of more than 2 normally distributed groups the ANOVA test was used. Mann–Whitney U-test, one-way Kruskal–Wallis analysis of variance and Friedman test were performed for non-normally distributed variables. Correlation and linear regression within variables were analyzed by using Pearson or Spearman analysis. $p < 0.05$ was considered to be statistically significant.

Results

Characteristics of the Subjects

There were no significant differences between the control group and the disease group in age, gender, creatinine, and uric acid levels. There were statistically significant differences in blood pressure, BMI, fasting blood glucose, HbA1C, blood lipids, fasting insulin, HOMA-IR, blood urea, liver enzymes, and hematological indices between the two groups ($p < 0.05$) (Table 1).

Table 1 Characteristics of Research Subjects

Characteristics	Control Group (n = 98)	Patient Group (n = 103)	p
Gender			
Male (n, %)	59 (60.2%)	66 (64.1%)	> 0.05*
Female (n, %)	39 (39.8%)	37 (35.9%)	
Age (mean \pm SD, year)	50.71 \pm 6.36	52.51 \pm 9.26	>0.05*
Systolic blood pressure (mean \pm SD, mmHg)	116.38 \pm 5.2	127.52 \pm 12.68	0.000**
Diastolic blood pressure (mean \pm SD, mmHg)	71.22 \pm 6.05	79.51 \pm 10.37	0.000**
BMI (mean \pm SD, kg/m ²)	21.58 \pm 0.84	23.493 \pm 1.18	0.000**
Fasting blood glucose (mean \pm SD, mmol/l)	4.94 \pm 0.38	12.82 \pm 3.66	0.000**

(Continued)

Table I (Continued).

Characteristics	Control Group (n = 98)	Patient Group (n = 103)	p
HbA1C (mean ± SD, %)	4.98 ± 0.36	9.76 ± 2.17	0.000**
Total cholesterol (mean ± SD, mmol/L)	4.67 ± 0.34	5.59 ± 1.27	0.000**
HDL-C (mean ± SD, mmol/L)	1.31 ± 0.20	1.11 ± 0.2	0.000**
LDL-C (mean ± SD, mmol/L)	2.22 ± 0.21	3.47 (2.44–4.09)	0.000***
Triglycerid (mean ± SD, mmol/L)	1.18 ± 0.29	2.67 (1.54–4.21)	0.000***
Insulin (mean ± SD, mIU/L)	6.01 (4.32–6.87)	6.37 (4.67–7.92)	0.024***
HOMA-IR	1.32 (0.92–1.56)	3.56 (2.51–4.6)	0.000***
Ure (mean ± SD, mmol/L)	4.79 ± 1.09	5.48 ± 0.83	0.000**
Creatinin (mean ± SD, μmol/L)	76.44 ± 15.04	78.96 ± 13.18	0.208**
Acid uric (mean ± SD, μmol/L)	317.19 ± 60.16	328.61 ± 61.17	0.172**
GOT (mean ± SD, U/L)	20.95 (13.98–33.88)	23.6 (18.7–32.45)	0.002***
GPT (mean ± SD, U/L)	18.29 (18.24–23.57)	29.3 (20.09–44.51)	0.000***
GGT (mean ± SD, U/L)	23.02 (17.64–32.78)	46.49 (37.36–98.56)	0.000***
White blood cells (mean ± SD, G/L)	6.39 ± 1.37	7.66 ± 2.09	0.000**
Red blood cells (mean ± SD, G/L)	4.6 ± 0.35	4.92 ± 0.51	0.000**
Hemoglobin (g/L)	140.22 ± 11.29	146.53 ± 12.43	0.000**
Hematocrit (mean ± SD, L/L)	0.42 ± 0.03	0.43 ± 0.03	0.008**
Platelet (mean ± SD, T/L)	232.1 ± 50.49	260.63 ± 57.04	0.000**
ANGPTL3 (ng/mL)	169.4 (130.44–246.2)	147.38 (96.98–223.31)	0.017***

Notes: Data with normal distribution were reported as mean ± SD (standard deviation) and data with non-normal distribution were reported as median and interquartile range (IQR). *Chi-Square test; **Independent – Samples T-test; ***Mann–Whitney test; p < 0.05 was considered to be statistically significant.

Abbreviations: BMI, Body mass index; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, low-density lipoprotein-cholesterol; GOT, Glutamate Oxaloacetate Transaminase; GPT, Glutamate Pyruvate Transaminase; GGT, Gamma Glutamyl Transferase; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ANGPTL-3, Angiopoietin-Like3.

The Concentration of Plasma ANGPTL3

The concentration of ANGPTL3 in the patient group was lower than in the control group ($p < 0.05$) (Table 1 and Figure 1).

The Relationship Between Plasma ANGPTL3 Concentration and Some Lipid and Glucose Metabolism Index

The correlation coefficient between plasma ANGPTL3 concentration and some indexes in the patient and control groups were described in Table 2. In the patient group, ANGPTL-3 was negatively correlated to HDL-C concentration ($r = -0.37$, $p < 0.05$), slightly positive correlated to triglyceride concentration ($r = 0.275$, $p < 0.05$) (Table 2, Figures 2 and 3). There was no correlation between ANGPTL3 with BMI, blood pressure, cholesterol TP, LDL-C, fasting blood glucose, HbA1C, insulin, and HOMA-IR. In the control group, there was no relationship between ANGPTL3 and any of the above-mentioned indicators (Table 2).

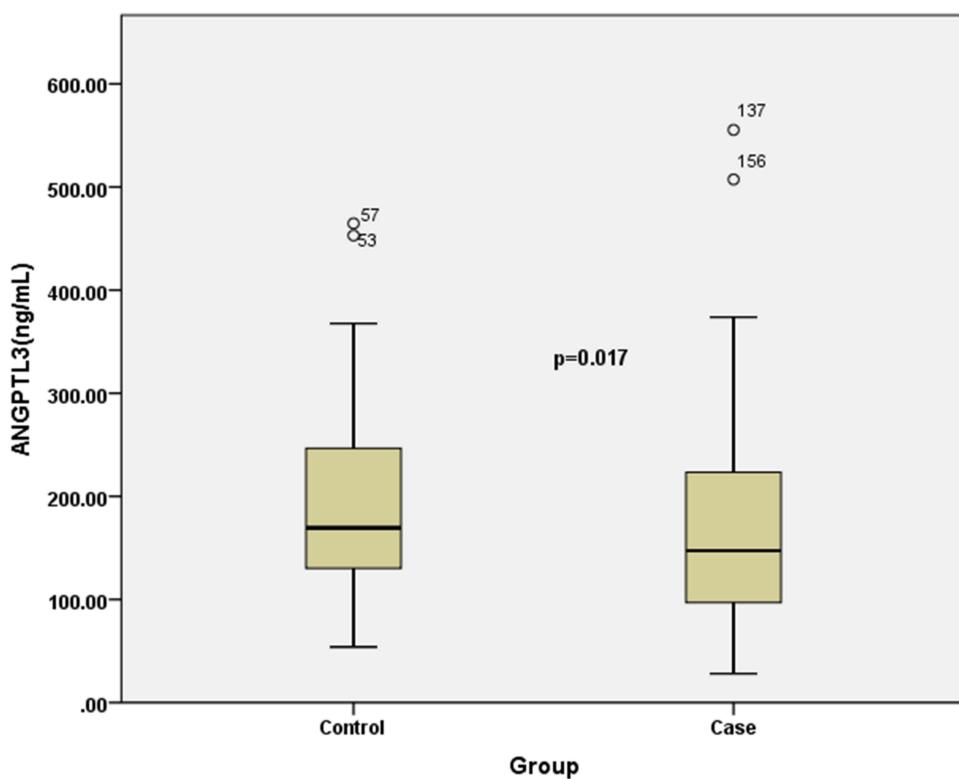


Figure 1 Plasma concentrations of ANGPTL3 in control and disease groups.

Notes: The concentration of ANGPTL3 in plasma increased from healthy control to diabetes groups. The group control was significantly higher than group disease. p-values in Mann–Whitney test were showed in figure.

Discussion

This is the first study in Vietnam to determine the concentration of ANGPTL3 in the plasma of healthy people and newly diagnosed type 2 diabetes mellitus. Our results showed that the plasma concentration of ANGPTL3 in the disease group was significantly reduced compared to the control group. There was a significant positive correlation between ANGPTL3 concentration and plasma triglycerides, and an inverse correlation with plasma HDL-C concentration in the T2DM group. However, no correlation was observed between plasma ANGPTL3 levels and %HbA1c, glucose, anthropometric indices, HOMA-IR, and insulin. In the control group, ANGPTL3 levels were not associated with any of the above-mentioned indicators.

The mechanism by which ANGPTL3 decreased glucose metabolism is due to an increase in FFA induced by enhanced lipolysis in adipose tissue leading to insulin resistance.⁸ ANGPTL3 attenuates endogenous adipogenesis resulting in decreased insulin sensitivity. After a meal, ANGPTL3 promotes the influx of FFA to white adipose tissue to replenish TG stores depleted during fasting. In turn, glucose induction induces and activates transcription factor-binding protein (ChREBP), which enhances lipogenesis.^{18,19} Increased lipogenesis in white adipose tissue is associated with insulin sensitivity. Therefore, it is likely that the increased uptake of glucose into white adipose tissue and the subsequent increase in lipogenesis explain the increased insulin sensitivity associated with the inactivation of ANGPTL3. However, in our study, the ANGPTL3 concentration in the untreated type 2 diabetes group was statistically significantly lower than in healthy people. This result is similar to the study of some authors such as Zhao et al⁹ or Cinkajzlová et al.^{9,10} This raises the question that there is a negative insulin upregulation of ANGPTL3. Research by Nidhina Haridas et al showed that insulin reduces plasma ANGPTL3 by reducing ANGPTL3 expression in the liver in normal subjects.²⁰ Diabetic patients in our study were newly diagnosed and untreated. Although there was a higher index of insulin resistance than the control group, the plasma insulin concentration was also significantly higher than that of the control group (Table 1). Even so, the data of our study were not sufficient to clarify the effect of insulin on plasma ANGPTL3 concentrations in patients with type 2 diabetes because no correlation was found between plasma insulin

Table 2 Correlation Between ANGPTL3 Concentration and Some Clinical and Subclinical Characteristics in the Patient Group

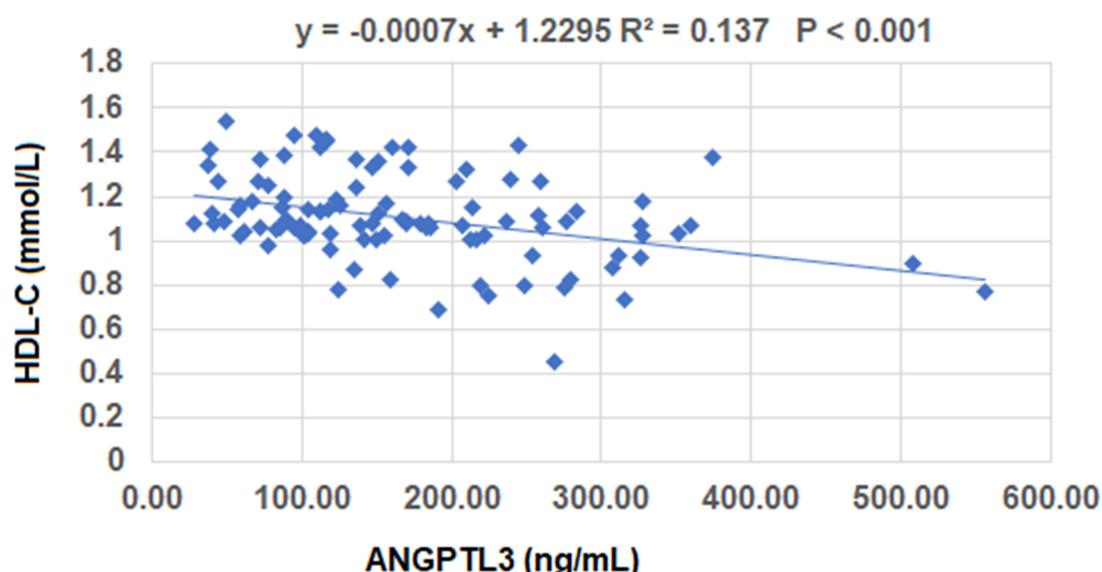
Parameter	Control Group		Patient Group	
	r	p*	r	p*
BMI (kg/m^2)	0.072	0.482	-0.076	0.447
Systolic blood pressure (mmHg)	0.097	0.344	-0.03	0.976
Diastolic blood pressure (mmHg)	0.029	0.778	0.023	0.819
Fasting Glucose Blood (mmol/L)	0.016	0.879	-0.018	0.86
HbA1C (%)	-0.116	0.256	-0.044	0.66
Insulin (mIU/mL)	-0.038	0.708	0.136	0.171
HOMA-IR	-0.04	0.699	0.125	0.208
Total Cholesterol(mmol/L)	0.074	0.47	-0.009	0.932
HDL-C (mmol/L)	0.009	0.929	-0.37	0.000
LDL-C (mmol/L)	-0.161	0.113	-0.002	0.981
Triglyceride (mmol/L)	0.059	0.063	0.275	0.005

Notes: The bold value showed the variables had correlation to markers with $p < 0.05$. ANGPTL3 had negative correlation to HDL-C and positive correlation to Triglyceride. *Pearson's analysis.

Abbreviations: r, Pearson correlation coefficient; p-value, correlation is significant at 0.05; BMI, Body mass index; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, low-density lipoprotein-cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

levels, HOMA-IR with ANGPTL-3 in the subjects. Therefore, to confirm this in patients with type 2 diabetes requires further confirmation from larger sample sizes with different ethnic groups.

Genetic and in vitro studies have suggested an inhibitory effect of human ANGPTL3 on LPL activity. Therefore, it is reasonable to expect that a decrease in ANGPTL3 concentration will decrease triglyceride concentration. According to Kersten Sander, in a study on mice, the inactivation of ANGPTL3 reduced plasma concentrations of triglycerides and free fatty acids, and at the same time prevented the process of atherosclerosis. In humans, homozygous loss-of-function

**Figure 2** The relationship between ANGPTL3 and HDL-cholesterol in the patient group.

Notes: r, p-value with Pearson correlation between plasma ANGPTL3 and HDL-C were showed on the figure.

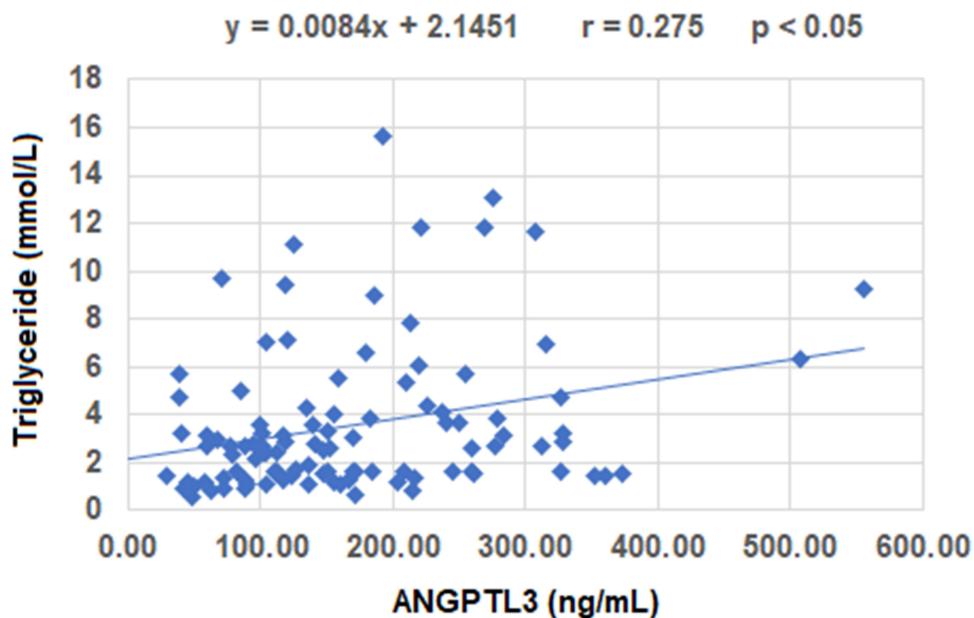


Figure 3 The relationship between ANGPTL3 and Triglyceride in the patient group.

Notes: r, p-value with Pearson correlation between plasma ANGPTL3 and Triglyceride were showed on the figure.

mutations in ANGPTL3 lead to decreased blood levels of LDL, HDL, and triglycerides, a condition known as familial lipid hypoplasia.¹³ In this study, we observed that ANGPTL3 was positively correlated with TG and negatively correlated with HDL-C in patients with type 2 diabetes at first diagnosis. However, there was no significant association between ANGPTL3 levels and LDL-C levels and total cholesterol, BMI in both the disease and control groups. This result has some similarities with the results of some previous studies.^{12,21} The concentration of HDL-C increased, triglyceride decreased when the concentration of ANGPTL3 decreased, possibly due to decreased hepatic lipase inhibitory activity, thus increasing the activity of this enzyme. Increased hepatic lipase activity in T2DM patients facilitates the removal of triglycerides from LDL and HDL.²² As above analysis, lower ANGPTL3 levels in type 2 diabetic patients may be due to insulin inhibition. This would contribute to counteracting typical dyslipidemia common in patients with type 2 diabetes, ie increased triglycerides, decreased HDL-C, and increased LDL-C.²² However, to clarify this mechanism needs to be further investigated in more detail with larger sample sizes.

ANGPTL3 deficiency improves insulin sensitivity in both humans and mice. Trial results have consistently shown an association between ANGPTL3 and glucose metabolism. Previous studies have clearly demonstrated that pathology associated with excess ANGPTL3 causes impaired glucose tolerance and increased insulin resistance in healthy subjects.^{14,18} However, when considering the relationship between ANGPTL3 and glucose metabolism, our study results show that there was no correlation between ANGPTL3 levels and markers of glucose metabolism in diabetics such as %HbA1C, fasting blood glucose, fasting insulin and HOMA-IR in both the patient and control groups. This result is similar to some previous studies. Robciuc et al analyzed ANGPTL3 concentrations in healthy subjects in Finland and found no correlation with fasting glucose, insulin and HOMA-IR concentrations.¹² Yu et al found no association between ANGPTL3 with fasting glucose and %HbA1C in patients with type 2 diabetes.¹⁴ Harada et al concluded that ANGPTL3 had no association with glucose fasting blood, %HbA1C and HOMA-IR.¹³ From these similarities, it could be seen that the effect of ANGPTL3 on glucose metabolism is rather lackluster. Previous pathophysiological studies have shown that the mechanism of action of ANGPTL3 on glucose metabolism is through free fatty acids affecting insulin sensitivity in target tissues.^{8,18} However, in patients with type 2 diabetes, when beta cell function is good, there is a response to increasing insulin secretion. It is the high concentration of insulin that inhibits the expression of ANGPTL3 in the liver,²⁰ reducing its concentration in plasma. This might be the reason for the weak relationship between ANGPTL3 levels and indicators of glucose metabolism in patients with type 2 diabetes.

In fact, studies on plasma ANGPTL3 concentrations have focused mainly on patients with obesity or cardiovascular disease to elucidate the role of ANGPTL3 in lipid metabolism.^{6,7,23} Research on the role of ANGPTL3 in glucose metabolism has recently been of interest.¹³ This is the first study in Vietnam on ANGPTL3 plasma concentrations of diabetic patients. Our study subjects are newly diagnosed type 2 diabetes patients, that is, patients who have not been treated at all. Untreated patients will accurately reflect the concentrations of lipid and glucose metabolism indicators in the study, eliminating errors caused by the use of lipid-lowering, blood-glucose-lowering drugs. Therefore, the data we give is reliable, contributing to enriching research data. The limitation of the study is that the sample size is small, the group of patients with and without dyslipidemia has not been divided so that a clearer comparison can be made. If the sample size is larger, we will divide patients with type 2 diabetes into two groups with dyslipidemia and no dyslipidemia. From here, it is possible to see more clearly the relationship between ANGPTL3 and glucose metabolism when the influence of dyslipidemia is excluded.

Conclusion

Plasma ANGPT3 was positively correlated with triglyceride levels but negatively correlated with HDL-C in patients with type 2 diabetes. Paradoxically, plasma ANGPTL3 levels were decreased in patients with diabetes. Type 2 sugar compared with healthy people. This suggests that plasma ANGPTL3 may be inhibited by reactive hyperinsulinemia in patients with type 2 diabetes to counteract dyslipidemia.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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