Elevated Plasma Angiopoietinlike Protein 5 (ANGPTL5) Is More Positively Associated with Glucose Metabolism Disorders in Patients with Metabolic Syndrome

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Background: Angiopoietinlike protein 5 (ANGPTL5) is an adipocytokine and has an important role in metabolic processes including lipid metabolism, obesity, and type 2 diabetes mellitus. On the basis of these roles, the present study aimed to investigate the level and role of plasma ANGPTL5 in metabolic syndrome (MS) patients.

Material/Methods: A total of 139 participants was enrolled in this study; 69 of them were diagnosed with MS. Plasma ANGPTL5 levels were measured by enzyme-linked immunosorbent assay. Sex, age, and other laboratory tests were compared statistically. Correlations between ANGPTL5 and biochemical parameters such as lipid levels and insulin resistance were all evaluated statistically.

Results: In patients with MS, plasma ANGPTL5 levels were higher than in those without MS (P<0.05). Moreover, after adjusting for the glucose profiles, positive correlations were found between plasma ANGPTL5 levels and body mass index (BMI), waist circumference, and waist-hip ratio (WHR); a weak negative correlation was found between ANGPTL5 concentration and high-density lipoprotein cholesterol. After controlling the lipid profiles, positive correlations were found between ANGPTL5 concentration and BMI, WHR, fasting plasma glucose, fasting insulin, glycated hemoglobin, and homeostatic model assessment (HOMA) of insulin resistance; a negative correlation was found between plasma ANGPTL5 concentration and HOMA of β-cell function. The area under the curve was approximately 0.912 in receiver operating characteristic curve analysis.

Conclusions: The findings in the present study showed that plasma ANGPTL5 was more positively correlated with glucose metabolism disorders than with lipid metabolism disorders in patients with MS, which suggested that ANGPTL5 might serve as a potential and useful clinical predictor of MS.

MeSH Keywords: Glucose Metabolism Disorders • Lipid Metabolism Disorders • Metabolic Syndrome
**Background**

Metabolic syndrome (MS), also variously known as syndrome X, is a cluster of cardiovascular disease risk factors that is manifested in the clinical syndromes of obesity, dyslipidemia, hyperglycemia, and hypertension [1]. As it progresses, it promotes the occurrence and development of cardiovascular diseases such as type 2 diabetes, nonalcoholic fatty liver disease, and some tumors [2,3]. Cases of MS have rapidly increased, so effective diagnostic and therapeutic approaches are of great clinical value for the prevention and treatment of MS [1]. Currently, biomarkers are widely used in clinical diagnosis, evaluation, and prognosis [4–6]. Therefore, exploring novel biomarkers for MS has important clinical value that could further promote diagnosis and treatment strategies for MS.

A novel family of proteins has been identified and recognized as “angiopoietinlike proteins” (ANGPTLs), which exhibit structural similarities to antigenic-regulating factors [7–9]. Many studies have found that the ANGPTL family has autoimmune or paracrine activities in endocrine metabolism such as lipid regulation, glucose metabolism, inflammation, and angiogenesis [10–13]. ANGPTL3, ANGPTL4, and ANGPTL8 have been confirmed to regulate serum triacylglycerol levels, which are potential targets for reducing triacylglycerol levels and improving lipid metabolism-related diseases [14–16]. Additionally, reducing the levels of ANGPTL4 and ANGPTL8 could improve glucose tolerance [11]. Therefore, ANGPTLs as predictive biomarkers related to glucose and lipid metabolism have become current research hot spots in metabolic diseases.

ANGPTL5 was extracted by Zeng et al. in 2003 [17]. Similar to others, ANGPTL5 has a classic N-terminal coil-coil-like domain and a C-terminal fibrinogen-like domain [13]. Loss-of-function mutations of ANGPTL5, ANGPTL3, and ANGPTL4 could significantly reduce the plasma triglyceride (TG) concentration, which suggested that ANGPTL5 may be closely related to regulation of TGs [18]. Recently, Alghanim et al. found that compared with nonobese type 2 diabetes patients, the plasma ANGPTL5 concentration was increased in obese patients with type 2 diabetes. It was also positively correlated with fasting plasma glucose (FPG), TG, and homeostatic model assessment of insulin resistance (HOMA-IR) [19]. These suggest that ANGPTL5 may be related to glucose and lipid metabolism, obesity, and diabetes, and is expected to become one of the important biomarkers for the above diseases. Therefore, the present study aimed to detect plasma ANGPTL5 levels in patients with MS and further investigate the correlations of ANGPTL5 with MS-related components such as glucose and lipid profiles and obesity indicators.

**Material and Methods**

**Study population**

The study included 139 patients, 70 with MS and 69 without MS, who were recruited from June 2018 to June 2019 in the Department of Cardiology at Renmin Hospital of Wuhan University (Wuhan, China). The present study was approved by the Medical Ethics Review Committee of Renmin Hospital and was conducted in line with the principles of the Declaration of Helsinki.

The inclusion criteria for MS patients in the study were the presence of 3 or more of the following: (1) central obesity, waist ≥90 cm (men) or ≥80 cm (women); (2) hypertriglyceridemia, TG ≥1.7 mmol/L; (3) high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L (men) or <1.30 mmol/L (women); (4) blood pressure ≥130/85 mmHg; (5) blood glucose >5.6 mmol/L [20]. Individuals were excluded if they had other severe illnesses such as thyroid disease, tuberculosis, liver and kidney dysfunction, malignant tumor, blood disease, infectious disease, or autoimmune disease.

All subjects were examined for the presence of diabetes, hypertension, cardiovascular disease, history of smoking, and family histories. Height, weight, and waist circumference were measured. After the measurement of height and weight, the calculation of body mass index (BMI) was achieved by dividing the weight (kg) by the squared height (m²). Insulin resistance was calculated using the HOMA-IR formula: FPG (mmol/L)×fasting insulin (FINS, μU/mL)/22.5, and the calculation of HOMA of β-cell function (HOMA-β) was achieved by the following formula: 20+FINS (μU/mL)/FPG [mmol/L]–3.5)×100%.

**Sample preparation**

Blood was collected intravenously in the morning after overnight fasting within 24 h after hospital admission. Venous blood samples were collected into tubes and centrifuged at 3500 revolutions per minute for 15 min at room temperature. Next, the plasma was separated and then stored at -80°C until measurement.

**Measurement of biochemical parameters**

Concentrations of total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), and glucose were measured using enzymatic methods with the Siemens Advia 2400 biochemistry analyzer. Concentration of high-sensitivity C-reactive protein (hs-CRP) was detected using a polyethylene glycol-enhanced immunoturbidimetric assay. Double antigen sandwich chemiluminescence detection was applied for insulin. High-performance liquid affinity chromatography was used for investigation of...
glycated hemoglobin (HbA1c). To assess the plasma level of human ANGPTL5, we adopted commercial enzyme-linked immunosorbent assay kits purchased from ELK Biotechnology (catalog no.: ELK8375). The test principle of this kit was sandwich enzyme immunoassay. The range of values detected by this assay was 62.5–4000 pg/mL. All measurements of plasma ANGPTL5 were performed in duplicate for each sample.

**Statistical analysis**

SPSS 22.0 (IBM, Armonk, NY, USA) and Graphpad Prism 8.0 were used for the statistical analysis. Data for continuous variables were summarized as mean value±standard deviation (SD), and categorical data were expressed as percentages or frequency. In comparisons between 2 groups, the statistical significance of differences in continuous variables was assessed using the independent-sample t test for normally distributed data or the Mann-Whitney U test for skewed data. The chi-square test was used to compare categorical variables. For correlation analysis between 2 variables, normally distributed variables were evaluated using Pearson’s correlation analysis and nonnormally distributed variables were assessed using Spearman’s correlation analysis. Potential association of ANGPTL5 with MS was evaluated by multivariate logistic regression. The relationship between ANGPTL5 and the anthropometric biochemical variables were assessed by multivariate linear regression. The receiver operating characteristic (ROC) curves for ANGPTL5 were used to evaluate diagnostic accuracy for MS. Results associated with a 2-tailed P<0.05 were considered significant.

**Results**

**Characteristics of the study population**

The demographic and clinical characteristics of the subjects included in the present study are summarized in Table 1. In the obesity parameters, MS patients showed higher waist circumference, waist-hip ratio (WHR), and BMI. For glucose metabolism, the MS population displayed unfavorable glucose profiles, with higher concentrations of FPG, FINS, HbA1C, and HOMA-IR, and lower HOMA-β. Additionally, the MS individuals had unfavorable lipid profiles, with higher TC, TG, and LDL-C, and lower HDL-C levels. Plasma ANGPTL5 concentration of the MS group was nearly twice that of the non-MS group (Figure 1A). These results indicate that the MS subjects presented features of obesity, hyperlipidemia, abnormal glucose metabolism, and elevated plasma ANGPTL5.

**Plasma ANGPTL5 level elevated in subjects with glucose disorders**

It was found that the plasma ANGPTL5 concentration of the diabetes patients was significantly higher than that of subjects without diabetes (Figure 1B). The ANGPTL5 level in the diabetes group was also higher than that of the prediabetes group (Figure 1C).

**Elevated plasma ANGPTL5 more positively correlated with glucose metabolism disorders**

Associations between plasma ANGPTL5 concentration and laboratory parameters were assessed. In unadjusted analyses, ANGPTL5 was strongly positively correlated with waist circumference, WHR, BMI, FPG, FINS, HbA1c, TG, TC, LDL-C, and HOMA-IR. ANGPTL5 had negative correlations with HDL-C and HOMA-β (Table 2, Figure 2). However, ANGPTL5 had no correlation with laboratory parameters including obesity and lipid and glucose metabolism in the non-MS group (Table 2). As ANGPTL5 was significantly elevated in subjects with glucose disorders, this study further investigated the correlations of ANGPTL5 and lipid profiles after controlling for glucose profiles, and then again glucose profile correlations after controlling for lipid profiles. After adjustment of age and glucose profiles, ANGPTL5 was positively correlated with BMI, waist circumference, and WHR, but weakly negatively correlated with HDL-C (r=-0.180, P=0.039). Of interest, after adjustment for age and lipid profiles, ANGPTL5 was still strongly positively correlated with FPG (r=0.525, P<0.001), FINS (r=0.390, P<0.001), HbA1c (r=0.443, P<0.001), and HOMA-IR (r=0.556, P<0.001), whereas it showed a strong negative correlation with HOMA-β (r=-0.360, P<0.001) (Table 3). All of the above results indicated that elevated plasma ANGPTL5 presented a stronger association with glucose metabolism disorders than with lipid disorders.

**Multivariate linear regression analyses**

As Table 4 shows, in the model of multiple linear regression, with MS-related indicators as the independent variable and ANGPTL5 as the dependent variable, ANGPTL5 was strongly correlated with these parameters, including FPG and HOMA-β (F=50.435, P<0.001, adjusted R²=0.591). These data further reveal that ANGPTL5 was more likely correlated with glucose metabolism in MS subjects.

**Multivariate logistic regression analyses**

Different logistic regression models were applied to assess the association between plasma concentration of ANGPTL5 and MS (Table 5). In unadjusted analysis, ANGPTL5 concentration was associated with the presence of MS; the odds ratio (OR) per SD increase was 1.026 (95% confidence interval [CI] 1.018–1.035, P<0.001). The association persisted after adjustment for conventional MS risk indicators including sex, age, BMI, family history of diabetes, family history of hypertension, smoking, and hs-CRP; the OR per SD increase was 1.044 (95%
Table 1. Demographic and clinical characteristics of subjects included.

| Variables                      | non-MS (n=70) | MS (n=69) | Total (n=139) | P value |
|--------------------------------|---------------|-----------|---------------|---------|
| Age (years)                    | 54.96±17.04   | 60.14±12.91 | 57.52±15.30   | 0.045   |
| Male (%)                       | 48.57%        | 53.62%    | 51.08%        | 0.551   |
| Smoking (%)                    | 51.43%        | 49.28%    | 50.36%        | 0.800   |
| Family history                 |               |           |               |         |
| Diabetes (%)                   | 15.71%        | 40.58%    | 28.06%        | 0.002   |
| Hypertension (%)               | 65.71%        | 62.32%    | 64.03%        | 0.677   |
| Waist circumference (cm)       | 84.38±2.85    | 94.35±3.52 | 89.58±5.94    | <0.001  |
| Men                            | 81.22±2.34    | 89.56±4.07 | 85.15±5.30    | <0.001  |
| WHR                            | 0.82±0.05     | 0.98±0.08 | 0.90±0.10     | <0.001  |
| BMI (kg/m²)                    | 21.86±1.22    | 27.04±2.75 | 24.43±3.35    | <0.001  |
| SBP (mmHg)                     | 127.47±11.81  | 141.91±20.22 | 134.64±10.27 | <0.001  |
| DBP (mmHg)                     | 77.71±10.26   | 81.22±2.34 | 79.56±4.07    | <0.001  |
| FPG (mmol/L)                   | 5.10 (5.00–5.30) | 6.80 (6.25–7.65) | 5.50 (5.10–6.80) | <0.001  |
| FINS (μU/ml)                   | 10.10 (9.08–11.60) | 11.90 (10.45–13.55) | 10.80 (9.40–12.60) | <0.001  |
| HbA1c (%)                      | 5.30 (5.10–5.50) | 5.90 (5.70–6.90) | 5.60 (5.30–5.90) | <0.001  |
| TC (mmol/L)                    | 4.02±0.63     | 4.82±0.90 | 4.42±0.87     | <0.001  |
| TG (mmol/L)                    | 1.02 (0.78–1.41) | 1.77 (1.47–2.35) | 1.43 (0.96–1.81) | <0.001  |
| HDL-C (mmol/L)                 | 1.32±0.25     | 1.20±0.26 | 1.26±0.26     | 0.009   |
| LDL-C (mmol/L)                 | 2.19±0.51     | 3.11±0.78 | 2.64±0.80     | <0.001  |
| hs-CRP (mg/L)                  | 2.80 (1.85–3.63) | 3.90 (1.30–7.78) | 3.15 (1.50–4.43) | 0.006   |
| BUN (mmol/L)                   | 4.92 (3.84–5.64) | 5.05 (4.32–6.05) | 4.99 (3.99±5.90) | 0.128   |
| CREA (μmol/L)                  | 66.50 (55.00–81.25) | 69.00 (54.50–80.00) | 68.00 (55.00–81.00) | 0.895   |
| URIC (μmol/L)                  | 264.43±59.78  | 318.52±72.86 | 291.28±71.69  | <0.001  |
| TBIL (μmol/L)                  | 13.54±5.48    | 14.13±5.27 | 13.83±5.36    | 0.519   |
| DBIL (μmol/L)                  | 4.71±2.26     | 4.27±1.95 | 4.49±2.12     | 0.251   |
| I Bil (μmol/L)                 | 8.80±3.52     | 9.85±3.69 | 9.32±3.63     | 0.088   |
| AST (U/L)                      | 15.00 (12.00–20.25) | 16.00 (13.00–20.00) | 16.00 (12.00–20.00) | 0.485   |
| ALT (U/L)                      | 14.00 (10.00–20.00) | 15.00 (11.00–19.00) | 15.00 (10.00–20.00) | 0.848   |
| GGT (U/L)                      | 19.50 (12.75–33.50) | 20.00 (16.00–29.50) | 20.00 (18.00–33.00) | 0.537   |
| HOMA-IR                        | 2.23 (2.04–2.67) | 3.56 (3.05–4.53) | 2.88 (2.23–3.58) | <0.001  |
| HOMA-β                         | 121.91 (107.22–150.61) | 70.77 (50.95–89.29) | 103.33 (70.77–128.00) | <0.001  |
| ANGPTL5 (pg/ml)                | 184.70±68.59  | 321.21±79.30 | 252.47±100.71 | <0.001  |

Data are presented as the mean±SD and median (interquartile range). Differences between groups were analyzed by the independent t test, chi-square test, or Mann-Whitney U test. MS – metabolic syndrome; WHR – waist-hip ratio; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; FINS – fasting insulin; HbA1c – glycosylated hemoglobin; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; hs-CRP – high-sensitivity C-reactive protein; BUN – blood urea nitrogen; CREA – creatinine; URIC – uric acid; TBIL – total bilirubin; DBIL – direct bilirubin; I Bil – indirect bilirubin; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – glutamine transpeptidase; HOMA-IR – homeostasis model assessment of insulin resistance; HOMA-β – HOMA of β-cell function; ANGPTL5 – angiopoietinlike protein 5.
ANGPTL5 is elevated in metabolic syndrome

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Discussion

Consistent with previous studies, when compared with non-MS individuals in the present study, subjects with MS were accompanied by a series of clinical symptoms of metabolic disorders such as central obesity, hypertension, hyperglycemia, insulin resistance, and dyslipidemia [1–3]. Most important, the present study was the first to evaluate the potential association between plasma ANGPTL5 and MS. It was observed that the plasma ANGPTL5 level was elevated in MS subjects in a cohort of the Chinese population. ANGPTL5 concentration was also increased in subjects with glucose disorders. Plasma ANGPTL5 concentration was positively associated with the parameters of glucose metabolism disorders even after adjustment for lipid factors.

In 2019, Alghanim et al. found that the plasma ANGPTL5 concentration of obese patients was higher than that of nonobese patients; compared with nonobese patients with type 2 diabetes, the plasma ANGPTL5 concentration was significantly higher in obese patients with type 2 diabetes, which was closely related to insulin resistance [19]. In 2020, it was further found that ANGPTL5 levels were elevated in obese adolescents, and associated with cardiovascular disease risk factors including hs-CRP and oxidized LDL [21]. It jointly suggested that the concentration of ANGPTL5 might be strongly correlated with obesity, diabetes, and lipid metabolism, and is expected to become a powerful biomarker or an important therapeutic tool for metabolic diseases. However, the role and mechanism of ANGPTL5 in the above metabolic diseases need to be discussed in depth.

Figure 1. Characterization of plasma angiopoietinlike protein 5 (ANGPTL5) levels in patients with metabolic syndrome (MS) or without MS. (A) Level of plasma ANGPTL5 in the MS group and the non-MS group. (B) Plasma ANGPTL5 concentration of the diabetes and the non-diabetes subjects. (C) Plasma ANGPTL5 level of patients with diabetes and prediabetes.

ANGPTL5 has a classic N-terminal coil-coillike domain and a C-terminal fibrinogenlike domain [13]. As mentioned before, loss-of-function mutations of ANGPTL5, ANGPTL3, and ANGPTL4 could significantly reduce the level of TG; however, whether the mechanism of ANGPTL5 in mediating metabolism is closely related to ANGPTL3 or ANGPTL4 is still unknown [18]. ANGPTL3 is known as the downstream target of the liver X receptor (LXR), which plays a critical role in lipid metabolism by regulating the expression of ANGPTL3 [22]. When treated with LXR activator T0901317, the concentration of ANGPTL3 in HepG2 cells was elevated significantly, and the levels of TC and TG were also markedly increased [23]. Inducement of the expression of LXR in the liver by intervening LXR ligand could promote the production of ANGPTL3 and fatty acid enzymes, which leads to a large accumulation of TG in mice. However, when the LXRs ligands interfered, it did not cause the development of hypertriglyceridemia in ANGPTL3-deficient mice. Additionally, ANGPTL3 could also significantly inhibit the activity of lipoprotein lipase (LPL), which then could lead to a significant increase in TG [24]. Similarly, ANGPTL4 is a potent LPL inhibitor, and plays an important role in regulating LPL activity. ANGPTL4-null mice exhibited lower plasma TG and increased plasma LPL activity; conversely, transgenic overexpression of ANGPTL4 increased plasma TG and inhibited the activity of LPL [25]. However, here, it was found that ANGPTL5 was weakly correlated with HDL-C when controlling for the glucose profiles. ANGPTL5 presented more correlation with glucose and insulin metabolism than that of TG and other lipid profiles. In other words, differently from ANGPTL3 and ANGPTL4, ANGPTL5 might regulate lipid metabolism through other pathways in the process of MS.

Free fatty acid (FFA) is an important factor leading to insulin resistance. It has been reported that ANGPTL3 can decompose fat cells; the decomposed fat cells release a large amount of FFA [26]. The accumulated FFA will affect glucose metabolism, which then could result in the occurrence of insulin resistance. The expression of ANGPTL3 was significantly increased in the
liver of insulin-deficient mice, and the injection of insulin could gradually decrease the level of ANGPTL3 and control the blood glucose within the normal range in the insulin-deficient mice. Insulin sensitivity was increased in ANGPTL3 knockout mice, indicating that ANGPTL3 could affect insulin sensitivity and then play an important role in the process of glucose metabolism [27]. Further, we found that plasma ANGPTL5 was more correlated with glucose disorders. Collectively, this indicates that the role and mechanism of ANGPTL5 in insulin resistance and insulin sensitivity can be observed, which then can reveal information on its role and mechanism in glucose metabolism in the process of MS.

However, certain limitations exist in the present study. First, a limited number of MS patients were recruited at a single center. Although we have proposed the association of the ANGPTL5 level with MS-related factors in Chinese patients, this has prevented us from drawing conclusions about the causal relationship between the ANGPTL5 level and MS pathogenesis. Therefore, future prospective studies with large-scale populations or

| Variables              | Non-MS   |      | MS    |      | Total |      |
|------------------------|----------|------|-------|------|-------|------|
|                        | r₁       | P₁   | r₂    | P₂   | r₃    | P₃   |
| Age                    | 0.160    | 0.186| 0.172 | 0.186| 0.233 | 0.006|
| BMI                    | 0.098    | 0.419| 0.194 | 0.111| 0.602 | <0.001|
| Waist circumference    | -0.062   | 0.610| 0.252 | 0.037| 0.591 | <0.001|
| WHR                    | 0.155    | 0.200| 0.077 | 0.532| 0.563 | <0.001|
| SBP                    | 0.070    | 0.564| -0.078| 0.523| 0.256 | 0.002|
| DBP                    | -0.084   | 0.489| -0.016| 0.896| -0.120| 0.159|
| FPG                    | 0.176    | 0.145| 0.364 | 0.002| 0.690 | <0.001|
| FINS                   | 0.075    | 0.535| 0.634 | <0.001| 0.470 | <0.001|
| HbA1c                  | -0.042   | 0.729| 0.189 | 0.119| 0.590 | <0.001|
| TC                     | 0.065    | 0.593| -0.011| 0.929| 0.325 | <0.001|
| TG                     | -0.033   | 0.787| 0.038 | 0.758| 0.454 | <0.001|
| HDL-C                  | -0.223   | 0.064| -0.087| 0.476| -0.257| 0.002|
| LDL-C                  | 0.100    | 0.412| 0.012 | 0.925| 0.419 | <0.001|
| hs-CRP                 | 0.132    | 0.275| -0.009| 0.942| 0.210 | 0.014|
| BUN                    | 0.108    | 0.374| -0.173| 0.156| 0.066 | 0.438|
| CREA                   | -0.103   | 0.396| -0.030| 0.806| -0.031| 0.719|
| URIC                   | -0.105   | 0.386| -0.051| 0.674| 0.207 | 0.014|
| TBIL                   | -0.073   | 0.549| -0.097| 0.426| -0.025| 0.770|
| DBIL                   | -0.063   | 0.607| -0.025| 0.840| -0.104| 0.225|
| IBIL                   | -0.091   | 0.452| -0.126| 0.304| 0.019 | 0.825|
| AST                    | 0.249    | 0.038| -0.049| 0.687| 0.111 | 0.192|
| ALT                    | 0.072    | 0.551| 0.020 | 0.868| -0.024| 0.783|
| GGT                    | -0.005   | 0.970| -0.149| 0.222| 0.000 | 0.996|
| HOMA-IR                | 0.144    | 0.235| 0.635 | <0.001| 0.685 | <0.001|
| HOMA-β                 | -0.127   | 0.294| -0.052| 0.673| -0.553| <0.001|

Table 2. Correlations of plasma angiotensinlike protein 5 (ANGPTL5) with laboratory parameters in patients with metabolic syndrome (MS).

Pearson correlation analysis was used for data conforming to normal distribution, and Spearman correlation analysis was used for data not conforming to normal distribution. r₁ and P₁ represent correlation coefficient and P value in the non-MS group; r₂ and P₂ represent correlation coefficient and P value in the MS group; r₃ and P₃ represent correlation coefficient and P value in the total population.
other genetically distinct populations will be needed, which can then be applied to determine at what point ANGPTL5 concentration begins to rise to enable early diagnosis or assessment of MS. This will help determine the role of ANGPTL5 in the pathophysiological mechanism of MS. Second, MS is a common cause of many chronic diseases including macrovascular diseases, cerebrovascular diseases, and microvascular diseases, which can cause damage to important organs such as the heart, brain, kidney, and liver. Therefore, the correlations between elevated ANGPTL5 levels and various components or survival-indicating factors (such as B-type natriuretic peptide, proteinuria) of MS should be further investigated. This study could not determine which biochemical factors might be responsible for elevated plasma ANGPTL5 level in MS patients. In other words, upstream factors involved in the regulation of

![Figure 2](image-url)

**Figure 2.** (A–L) Correlations between angiopoietinlike protein 5 level and obesity, glucose, and lipid metabolism indicators in participants.
Table 3. Correlations of plasma angiopoietinlike protein 5 (ANGPTL5) with laboratory parameters after controlling for the lipid or glucose profiles.

| Variables          | Ajusted* | Ajusted** | Ajusted*** |
|--------------------|----------|-----------|------------|
|                    | $r_1$    | $P_1$     | $r_2$      | $P_2$     | $r_3$      | $P_3$     |
| BMI                | 0.583    | <0.001    | 0.282      | 0.001     | 0.486      | <0.001    |
| Waist circumference| 0.567    | <0.001    | 0.240      | 0.005     | 0.453      | <0.001    |
| WHR                | 0.545    | <0.001    | 0.269      | 0.002     | 0.428      | <0.001    |
| SBP                | 0.255    | 0.003     | 0.159      | 0.068     | 0.198      | 0.022     |
| DBP                | -0.125   | 0.146     | -0.148     | 0.091     | -0.153     | 0.077     |
| FPG                | 0.617    | <0.001    | -          |          | -          |          |
| FINS               | 0.466    | <0.001    | -          |          | -          |          |
| HbA1c              | 0.526    | <0.001    | -          |          | 0.443      | <0.001    |
| TC                 | 0.324    | 0.081     | -0.004     | 0.961     | -          |          |
| TG                 | 0.310    | <0.001    | -0.016     | 0.853     | -          |          |
| HDL-C              | -0.258   | 0.002     | -0.180     | 0.039     | -          |          |
| LDL-C              | 0.416    | <0.001    | 0.152      | 0.081     | -          |          |
| BUN                | 0.259    | 0.002     | 0.056      | 0.520     | 0.139      | 0.057     |
| CREA               | -0.064   | 0.459     | -0.018     | 0.840     | -0.113     | 0.197     |
| URIC               | 0.059    | 0.217     | 0.055      | 0.531     | 0.064      | 0.464     |
| TBIL               | -0.012   | 0.885     | 0.052      | 0.553     | -0.004     | 0.965     |
| DBIL               | -0.092   | 0.284     | 0.080      | 0.365     | -0.010     | 0.907     |
| IBIL               | 0.031    | 0.717     | 0.024      | 0.785     | -0.004     | 0.960     |
| AST                | 0.004    | 0.962     | -0.027     | 0.763     | -0.005     | 0.950     |
| ALT                | 0.058    | 0.503     | 0.130      | 0.338     | 0.064      | 0.499     |
| GGT                | -0.070   | 0.416     | 0.053      | 0.549     | -0.093     | 0.285     |
| HOMA-IR            | 0.635    | <0.001    | -          |          | 0.556      | <0.001    |
| HOMA-β             | -0.460   | <0.001    | -          |          | -0.360     | <0.001    |

* Adjusted for age; ** adjusted for age-glucose profiles; *** adjusted for age-lipid profiles. $r_1$ and $P_1$ represent correlation coefficient and $P$ value after controlling for age. $r_2$ and $P_2$ represent correlation coefficient and $P$ value after controlling for age and the glucose profiles including fasting plasma glucose (FPG), fasting insulin (FINS), glycated hemoglobin (HbA1c), homeostasis model assessment of insulin resistance (HOMA-IR), and HOMA of β-cell function (HOMA-β). $r_3$ and $P_3$ represent correlation coefficient and $P$ value after controlling for age and lipid profiles including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Table 4. Multivariate linear regression to examine association of metabolic syndrome (MS)-related indicators with plasma angiopoietinlike protein 5 (ANGPTL5).

| B (95% CI) | β | t Statistic | P value |
|------------|---|-------------|---------|
| Intercept  | 45.929 | 0.746 | 0.457 |
| BMI        | 6.823 (2.651–10.996) | 0.227 | 3.235 | 0.002 |
| FINS       | 16.791 (12.286–21.237) | 0.473 | 7.407 | <0.001 |
| HOMA-β     | -4.910 (-8.485–2.335) | -0.116 | -2.086 | 0.039 |

$F=50.435$, $P<0.001$, adjusted $R^2=0.591$. 
Table 5. Multivariate logistic regression to assess association of plasma angiopoietin-like protein 5 (ANGPTL5) with the risk of metabolic syndrome (MS).

| ANGPTL5 | OR (95% CI) | P value |
|---------|-------------|---------|
| Unadjusted | 1.026 (1.018–1.035) | <0.001 |
| Model1 | 1.030 (1.011–1.049) | 0.002 |
| Model2 | 1.044 (1.013–1.076) | 0.005 |
| Model3 | 1.044 (1.013–1.075) | 0.005 |

Model 1: adjusted for sex, age, body mass index; Model 2: adjusted for model 1+family history of diabetes, family history of hypertension, smoking; Model 3: adjusted for model 2+high-sensitivity C-reactive protein.

ANGPTL5 expression are little known, and focused studies to delineate the potential regulatory mechanism are required.

Conclusions

In summary, plasma ANGPTL5 level is elevated in MS patients. The results of the present study suggest that elevated plasma ANGPTL5 concentration is more associated with the parameters of glucose metabolism disorders than with lipid factors, and is expected to become one of the novel biomarkers for evaluating glucose metabolism disorders in MS subjects.

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Figure 3. Receiver operating characteristic curve of angiopoietin-like protein 5 (ANGPTL5) to identify patients at higher risk of metabolic syndrome. ANGPTL5: area under the curve=0.912, P<0.001, 95% confidence interval 0.862–0.962.

Conflicts of interest

None.
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