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Serum levels of angiopoietin-related growth factor are increased in metabolic syndrome

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Abstract

Angiopoietin-related growth factor (AGF), a novel hepatokine, showed therapeutic implications in diabetic and obese animal models. Although the physiologic functions of human AGF have not yet been identified, serum levels of AGF displayed up-regulation in groups with diseases including preeclampsia and diabetes; and there was little association between genetic variability of AGF and metabolic syndrome–related phenotypes. We analyzed serum levels of AGF and other biochemical and anthropometric markers in 216 Korean persons—the numbers of healthy controls and those with metabolic syndrome were 138 and 78, respectively—to confirm research data from animal models. Women had higher AGF than men (265.01 vs 311.84 ng/mL, $P = .003$). This study showed that serum AGF levels were significantly higher in subjects with metabolic syndrome (325.89 ng/mL) than those in the healthy group (272.44 ng/mL) ($P = .003$). Among the components of metabolic syndrome, subjects with high waist circumference or decreased high-density lipoprotein cholesterol had significantly increased serum AGF (271.92 vs 313.68 ng/mL, $P = .013$; 271.01 vs 310.58 ng/mL, $P = .023$, respectively). According to multivariate regression analysis, metabolic syndrome itself and waist circumference could be used, in addition to sex and age, as predictors of serum AGF level. In conclusion, serum AGF levels were paradoxically increased in metabolic syndrome, in comparison with data from animal experiments and data on sex, age, and waist circumference. Metabolic syndrome can be a predictor of serum AGF level. Further studies are needed to explore the possibilities of compensatory up-regulation, or AGF resistance, to explain the physiologic roles of AGF in metabolic syndrome.
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1. Introduction

Metabolic syndrome is a cluster of cardiovascular disease risk factors that includes obesity, insulin resistance, and dyslipidemia [1,2]. It also reflects complex interactions among organs such as adipose tissue, pancreas, skeletal muscle, liver, and the central nervous system [3-7]. To explain the pathogenesis of metabolic syndrome, a variety of cytokines have been studied to date, including leptin, adiponectin, tumor necrosis factor, interleukins, and retinol-binding protein 4 [8-12]. As most of them are adipocytokines, the so-called adipocentric view has remained the main theory of pathogenesis [13,14]. However, liver, as well as adipose tissue, is newly recognized as an endocrine organ and target of metabolic fitness [15] that releases hepatokines just like adipocyte releases adipokines [16].

Angiopoietin-related growth factor (AGF, or angiopoietin-like 6 [ANGPTL6]) is known to be a novel hepatokine that modulates angiogenesis and metabolism [17]. In animal experiments, AGF increased energy expenditure and improved insulin sensitivity and lipid profiles [18]. In vitro assays showed decreased hepatic gluconeogenesis after treatment with AGF [19]. These results support the hypothesis that AGF therapy can result in improved insulin and lipid profiles; thus, AGF is

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anticipated as a new therapeutic target of diabetes, obesity, and metabolic syndrome.

However, human studies have not supported this hypothesis so far. One research group has published 2 articles about human AGF targeting preeclampsia [20] and diabetes [21]. Both studies showed that serum AGF levels were paradoxically higher in subjects with preeclampsia and diabetes than in the healthy group. The authors explained this paradox as either a compensatory mechanism or AGF resistance, like insulin resistance in diabetes. To confirm the presence of these up-regulations in metabolic syndrome, we determined serum AGF levels in 216 persons from Korean populations.

2. Subjects and methods

2.1. Subjects

We used serum samples and anthropometric data from the Korean Rural Genomic Cohort study. All participants agreed to allow use of their data for this study. The Institutional Review Board at Wonju Christian Hospital, Korea, approved this study on December 6, 2005 (CR105024); and the study has been reapproved every year. We randomly selected 110 male subjects and 110 female subjects for this study, and excluded 4 subjects who showed extremely high levels of serum AGF. We defined metabolic syndrome according to modified criteria from the National Cholesterol Education Program–Adult Treatment Panel III [22] that defines impaired glucose tolerance (IGT) as having a fasting glucose greater than 110 mg/dL and visceral obesity according to the Korean Society for the Study of Obesity [23] as having a waist circumference greater than 90 cm in males or 85 cm in females.

2.2. Assays

Serum AGF levels were determined using an enzyme-linked immunosorbent assay kit from Adipogen (Seoul, Korea) and ^{125}I-human leptin radioimmunoassay kit from Millipore (St Charles, MO), respectively. A variety of biochemical markers such as high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, albumin, glucose, insulin, creatinine, and adiponectin were measured at the Seoul Medical Science Institute (Seoul, Korea). Total body fat and visceral fat were checked using Zeus 9.9 (Jawon Medical, Seoul, Korea).

2.3. Statistical analysis

All data were analyzed using SPSS software version 12.0 (Chicago, IL). The Kolmogorov-Smirnov test was used to determine normal distribution of all variables. Nonnormally distributed variables were log-transformed before analysis. χ^2, Student t test, Pearson correlation, 1-way analysis of variance, and multivariate stepwise linear regression were also used. We considered P value < .05 as statistically significant.

3. Results

3.1. Serum levels of AGF

Anthropometric and biochemical markers of the study population are summarized in Table 1. The prevalence of metabolic syndrome was higher in women. Subjects with metabolic syndrome showed significantly increased serum AGF levels. Among the components of metabolic syndrome, AGF levels increased in a statistically significant manner in subjects with increased waist circumference or decreased HDL cholesterol (Table 2). The AGF levels in female subjects were higher than those in men in comparison with those within the entire population and in the healthy group (Table 3). There was no significant correlation between

Table 1
Characteristics of study population

	Healthy (n = 147)	Metabolic syndrome (n = 69)	P value
Sex (M/F)	79/68	24/45	.014
Age (y)	55.97 (49.00, 67.00)	57. 06 (51.00, 64.00)	.350
AGF (ng/mL)	272.44 (195.67, 335.73)	325.89 (239.59, 392.16)	.003
Waist circumference (cm)	81.67 ± 9.97	92.54 ± 8.16	<.001
SBP (mm Hg)	124.38 (110.00, 134.25)	137.49 (130.00, 148.00)	<.001
DBP (mm Hg)	80.31 (70.00, 90.00)	87.45 (80.00, 90.00)	<.001
BMI (kg/m^2)	23.80 (20.10, 25.10)	28.79 (25.10, 30.65)	<.001
TG (mg/dL)	116.73 (75.00, 133.00)	218.86 (154.50, 253.50)	<.001
HDL cholesterol (mg/dL)	49.82 (41.00, 56.00)	39.77 (35.50, 43.50)	<.001
LDL cholesterol (mg/dL)	115.52 ± 33.85	118.22 ± 32.07	.579
Albumin (g/dL)	4.60 ± 0.29	4.65 ± 0.24	.221
Glucose (mg/dL)	92.85 (86.00, 97.00)	106.36 (88.00, 116.00)	<.001
Insulin (mU/L)	7.48 (5.10, 9.20)	11.39 (6.95, 12.50)	<.001
Creatinine (mg/dL)	0.96 (0.85, 1.05)	0.95 (0.84, 1.09)	.642
HOMA-IR	1.74 (1.13, 2.03)	3.10 (1.71, 3.43)	<.001
Adiponectin (ng/mL)	10.89 ± 5.13	8.58 ± 4.16	.001
Leptin (ng/mL)	5.59 (1.51, 7.57)	10.78 (4.33, 15.72)	<.001
Total body fat (kg)	16.21 ± 8.34	23.60 ± 7.48	<.001
Visceral fat (kg)	2.15 ± 1.26	3.39 ± 1.17	<.001

Means ± standard deviation for normally distributed variables or means (25th percentile, 75th percentile) for nonnormally distributed variables are shown. Nonnormally distributed ones are log-transformed before analysis. All variables were analyzed by Student t test except sex, which was analyzed by χ^2 test. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2
Serum AGF levels according to components of metabolic syndrome

Components	Absent		Present		*P* value
	n	AGF (ng/mL)	n	AGF (ng/mL)	
High WC	125	271.92 (181.32, 344.87)	91	313.68 (233.08, 369.37)	.013
Low HDL	115	271.01 (191.06, 333.75)	101	310.58 (222.73, 363.32)	.023
High BP	87	292.98 (195.67, 347.26)	129	287.18 (211.27, 352.94)	.988
High TG	135	285.05 (214.20, 342.84)	81	296.96 (196.83, 370.11)	.497
High glucose	188	290.37 (215.02, 349.55)	28	283.75 (178.52, 379.50)	.397

Means (25th percentile, 75th percentile) are shown. Serum AGF levels were log-transformed before Student *t* test. Definitions of components are made on the basis of National Cholesterol Education Program–Adult Treatment Panel III guidelines. WC indicates waist circumference, BP, blood pressure; TG, triglyceride.

number of metabolic syndrome components and AGF levels (data not shown).

3.2. Correlations between serum AGF levels and biochemical and anthropometric markers

Simple correlations between serum AGF levels and biochemical and anthropometric markers were analyzed by Pearson correlation test within the total, healthy, and metabolic syndrome groups (Table 4). Age and serum creatinine levels were negatively correlated; and waist circumference, body mass index, serum insulin and leptin levels, total body fat mass, and visceral body fat mass showed positive correlation in both total and healthy groups. Subjects with metabolic syndrome showed negative correlation with systolic blood pressure, serum glucose levels, and serum insulin levels. The homeostasis model assessment of insulin resistance (HOMA-IR) index, which showed no correlation in the total population, correlated positively in the healthy group and negatively in the metabolic syndrome group.

3.3. Factors affecting serum AGF levels

To determine the factors affecting serum AGF levels, multivariate stepwise linear correlation analysis was performed (Table 5). Sex, age, and metabolic syndrome were analyzed as statistically significant factors affecting AGF level; female subjects or subjects with metabolic syndrome showed a positive association, whereas association with age was negative. Among serum and anthropometric markers of the components of metabolic syndrome, waist circumference could be used as a predictor of serum AGF level independent of other components, including systolic blood pressure, serum glucose level, body mass index, serum triglyceride, and serum HDL cholesterol level.

4. Discussion

After AGF was first identified as a stimulator of epidermal proliferation and remodeling [24], research was targeted to angiogenesis [25] and wound healing [26]. Now, like other members of the angiopoietin-like protein family, Angptl3 and Angptl4, AGF has been studied to confirm the relationship with insulin resistance, energy expenditure, obesity, and metabolic syndrome [27-29].

Our data showed that serum AGF levels were higher in subjects with metabolic syndrome than in the healthy group, and metabolic syndrome itself is a predictor of serum AGF level. Although results showing that AGF is a “good hepatokine” for diabetes and obesity in animal experiments were very dramatic [18], serum AGF levels in humans displayed paradoxical up-regulation in the disease group with diabetes, preeclampsia, and metabolic syndrome.

What is the reason for such a paradox? The following can be considered: (1) AGF may have improved the metabolic profile in the disease groups; (2) subjects with disease may have decreased sensitivity to AGF, leading to AGF resistance; and (3) function of AGF may be different between humans and animals. To confirm the actual mechanism of this phenomenon, function of human AGF should be defined. However, these experiments have not yet been performed. In addition, studies to identify membrane receptors for AGF will need to be performed to prove the hypothesis of AGF resistance because AGF so far remains an orphan ligand.

Table 3
Serum AGF levels according to sex and disease group

Group	Male		Female	
	N	AGF (ng/mL)	N	AGF (ng/mL)
Entire population	103	265.02 (184.46, 314.19)	113	311.84* (230.75, 363.32)
Healthy controls	79	252.78 (176.34, 308.48)	68	295.27* (221.26, 350.31)
Metabolic syndrome group	24	305.31† (204.41, 386.59)	45	336.86 (247.80, 399.55)

Means (25th percentile, 75th percentile) are shown. Serum AGF levels were log-transformed before Student *t* test.

* *P* value < .05 compared with the same group of male subjects.

† *P* value < .05 compared with the healthy group of the same sex.

Table 4
Correlation between serum AGF levels and biochemical and anthropometric markers

	All (n = 216)	Healthy (n = 147)	Metabolic syndrome (n = 69)
Age (log)	−.160*	−.168†	−.198
Waist circumference	.168*	.136	−.059
SBP (log)	−.003	−.011	−.253*
DBP (log)	−.021	−.042	−.202
BMI (log)	.163*	.226†	−.254*
TG (log)	.029	−.153	−.002
HDL cholesterol(log)	−.052	.048	.028
LDL cholesterol	.111	.093	.137
Albumin	−.004	.019	−.127
Glucose (log)	−.052	.067	−.375†
Insulin (log)	.135*	.254†	−.320†
Creatinine (log)	−.177†	−.160	−.202
HOMA-IR (log)	.102	.251†	−.419†
Adiponectin	−.072	−.085	.122
Leptin (log)	.227†	.242†	−.020
Total body fat (kg)	.179†	.229†	−.124
Visceral fat (kg)	.225†	.209*	.064

Pearson correlation coefficients with log-transformed serum AGF levels are shown. (log): nonnormally distributed variables were log-transformed before analysis.

* P value <.05.

† P value <.01.

Among the study population of 216 subjects, increased serum AGF levels, in addition to metabolic syndrome, were present in women, perhaps because of the higher prevalence of metabolic syndrome in women. Previous studies using Korean rural population [30,31] have shown that the prevalence of metabolic syndrome is higher in women than in men. Therefore, up-regulation of AGF might reflect female composition of the groups. In multivariate regression analysis, we concluded that metabolic syndrome is a predictor of AGF independent of sex and age. When divided into groups according to sex and metabolic syndrome, AGF levels were significantly increased in women compared with the entire population or the healthy group. Sex-dependent difference in AGF may be due to the effect of sex hormones; therefore, large-scale studies are needed to confirm this up-regulation.

We used the same enzyme-linked immunosorbent assay kit for human AGF used in previous human studies [20,21]; however, our data from Korean subjects showed serum AGF levels twice as high or more than those of whites. This noticeable variation may exist on the basis of ethnic or lifestyle differences. In addition, we found other results that differed from previous ones, which came from correlation analysis of serum AGF. Systolic and diastolic blood pressure, which showed positive correlation in 44 pregnant whites, showed no correlation in our total of 216 cases, as well as 138 healthy controls. Serum creatinine, which showed both positive and negative correlation in previous articles, showed negative correlation in our data. As study populations differ from one another, there appears to be no coherence between correlation analyses, according to the studies. We noticed that the HOMA-IR index showed paradoxical correlation between the groups; positive in the healthy group and negative in the metabolic syndrome group. We think this paradox shows a possibility of AGF resistance; in healthy groups, up-regulated AGF may compensate for disease-associated metabolic profile; that is, people with higher HOMA-IR also had higher AGF levels. However, in the group with diseases like β-cell failure in diabetes [32], AGF levels might decrease with severity of disease, which is still higher than in the healthy group. To investigate this possibility, we categorized our study population on the basis of glucose tolerance test. Among 216 subjects, 59 and 32 subjects had IGT and diabetes mellitus (DM), respectively; serum AGF levels were significantly higher in IGT subjects than in healthy controls, but DM subjects had similar levels compared with healthy controls (data not shown). This might be due to small proportion of DM subjects; further study with large sample is needed to answer it.

We identified sex, age, and metabolic syndrome as factors affecting serum AGF levels by multivariate regression analysis. In female subjects, those who were of young age or with metabolic syndrome showed increased levels of serum AGF. Among the components of metabolic syndrome, waist circumference was statistically significant as a predictor of serum AGF level. Although AGF is known as a hepatokine, it is also expressed in adipose tissue. We compared relative expression of AGF in hepatocytes and adipocytes of healthy humans; expression in hepatocytes was about 10 times higher than in adipocytes (unpublished data); and total body fat or visceral fat, and serum leptin levels showed positive correlation with serum AGF. Thus, up-regulation of AGF in subjects with a high waist circumference may be due to compensation by increased AGF synthesis in liver or by other sources like adipose tissue. In addition, we expected to confirm the correlation between albumin and serum AGF and see which hepatokine might reflect liver function; but there was no correlation between albumin and AGF. This also suggests the possibility that AGF may function as an adipokine as well as a hepatokine. Angiopoietin-related growth factor has been known as a kind of hepatokine. However, we could get the products from adipocyte by reverse transcriptase polymerase chain reaction; and serum AGF levels have positive correlation with total body fat, visceral fat, and leptin. Therefore, we concluded that AGF may play a role as an adipokine as well as a hepatokine.

Table 5
Stepwise multivariate linear regression with serum AGF levels

Model	Independent variable	Unstandardized β	P value
1	Sex	.053	.032
	Age	−.416	.023
	Metabolic syndrome	.074	.005
2	Sex	.064	.009
	Age	−.362	.047
	Waist circumference	.003	.017

1: Sex, metabolic syndrome, and age.

2: Sex, age, waist circumference, systolic blood pressure, glucose, body mass index, triglyceride, and HDL cholesterol.

Although there are some discrepancies, or even opposing data, compared with those reported in previous studies, our study has significance in that it has the largest scale of study size, with 216 people, and the composition of the study population is based on a rural cohort. In previous reports, population sizes were 40 and 120, respectively; and target subjects were hospitalized people. Although our data are cross-sectional, by using these cohort samples, we expect to acquire follow-up data to compare levels of AGF with previous ones, including changes in biochemical, anthropometric, and clinical markers, and the severity of metabolic problems (outcomes of metabolic syndrome or other metabolic diseases such as diabetes and obesity) in our next reports.

In conclusion, serum AGF levels are higher in metabolic syndrome or female subjects; and waist circumference can be used as a predictor of serum AGF independent of other components of metabolic syndrome. Further studies are needed to determine physiologic function of AGF and also to check consistency of up-regulation in other metabolic disease.

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