Association between growth hormone and hypertension in a general population

Hideki Ohshima,[1] Hisashi Adachi,[1,2]; Mika Enomoto,[1]; Ako Fukami,[1]; Sachiko Nakamura,[1] Yume Nohara,[1] Akiko Sakaue,[1] Nagisa Morikawa,[1] Hitoshi Hamamura,[1] Kenta Toyomasu,[1] Maki Yamamoto,[1] and Yoshihiro Fukumoto[1]

1. Division of Cardio-Vascular Medicine, Department of Internal Medicine, Kurume University School of Medicine
2. Department of Community Medicine, Kurume University School of Medicine

Total word count=3,009 words
Abstract=248 words
Five tables
References=32

Running title: Growth hormone and hypertension

Address for correspondence; Hisashi Adachi, MD, PhD.
Department of Community Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, 830-0011, Japan
TEL: +81-942-31-7586, FAX: +81-942-31-7896
E-mail: hadac@med.kurume-u.ac.jp

Abstract

Insulin-like growth factors are polypeptides, with arrays similar to insulin, and insulin-like growth factor 1 (IGF-1) is secreted by the stimulation of growth hormone (GH) in the liver. The lack of both GH and IGF-1 leads to physiological age-related changes in the cardiovascular system; however, the role of IGF-1 and GH in hypertension has not been fully elucidated. Thus, we examined the association between plasma IGF-1 and GH levels and hypertension. Among 1,368 participants of a health check-up examination in the town of Tanushimaru, 1,094 subjects were analyzed, after excluding subjects with diabetes mellitus or impaired liver function. Multiple linear and logistic regression analyses were performed for factors related to systolic and diastolic BPs. Characteristics of participants stratified by IGF-1 and GH quartiles were compared using analysis of co-variance. We calculated odds ratios per 1-standard deviation increase of IGF-1 and GH levels for hypertension, which was defined as those with BP≥140/90mmHg and/or those receiving antihypertensive medication. Multivariable analysis showed that, FPG, insulin, HOMA-IR, eGFR, total cholesterol, triglycerides, and medication for hypertension were associated with Z-score of IGF-1

measurement quartiles. Next, we found that BMI, systolic and diastolic BPs, insulin, HOMA-IR, total cholesterol, HDL-cholesterol, triglycerides, smoking, and alcohol intake were associated with GH quartiles, indicating that hypertensive subjects were inversely associated with GH level but not IGF-1. A significant and inverse relationship between serum GH and hypertensives was found after adjustment for confounders. In conclusion, decreased GH levels, but not IGF-1, were associated with hypertensives in a general population.

Keywords: Epidemiology · Insulin-like growth factor 1 · Growth hormone · Hypertension

Introduction

Growth hormone (GH) is secreted in pulses, mostly during the early hours of sleep; however, after about the age of 30 years, the secretion of GH by the pituitary gland tends to decline [1,2]. Further, after the age of 60 years, serum insulin-like growth factor 1 (IGF-1) levels also decline with age in healthy adults [1-3], which supports the idea that the decrease of IGF-1 results from diminished GH secretion [4]. The diminished secretion of GH is accompanied not only by a decrease of IGF-1, but also by atrophy of the lean body mass and expansion of the mass of adipose tissue [1]. Based on the relationship between GH and IGF-1, subjects with diminished GH and low circulating IGF-1 concentrations are documented to have an increased risk of developing cardiovascular diseases (CVD) and cerebrovascular diseases [5]. The lack of both GH and IGF-1 leads to physiological age-related changes in the cardiovascular system, such as a decrease in the number of cardiomyocytes, fibrosis, collagen accumulation, as well as a physiological decrease in the synthesis of proteins, including contractile action and myosin [6,7].

On the other hand, increased serum levels of GH within the physiologic range can cause insulin resistance, due to the decrease in both hepatic and extrahepatic effects of insulin [8]. The lack of GH in adults is characterized by central obesity, hypertension, dyslipidemia, and glucose intolerance, all features of the metabolic syndrome [9]. Isgaard J [10] also examined the various roles of GH on CVD and its the risk factors, and reported that GH-deficient subjects were at risk of hypertension.

Still, it is unknown whether serum GH is associated with hypertension in the general population. Thus, we carried out an epidemiological survey to investigate the role of GH on hypertension in a Japanese general population, in whom the prevalence of obesity was low.

Methods

Study population

A periodic epidemiological survey was performed in 2018 in a rural farming community located in southwestern Japan (Tanushimaru, a cohort of the Seven Countries Study [11-14]). The study subjects were 1,368 participants (554 males and 814 females: mean age 68.8 years) of a health check-up

examination in a Japanese general population aged over 40 years.

Of 1,368 subjects, we excluded 147 diabetic subjects, namely subjects with high fasting plasma glucose (FPG) ≥126 mg/dl, subjects with hemoglobin A_{1c} (HbA_{1c}) ≥6.5% and/or those taking oral hypoglycemic agents or receiving insulin injections. Further, because their GH/IGF-1 levels in subjects with liver dysfunction might be lower than healthy subjects, we also excluded 127 subjects with Fib-4 index≥2.67 [15]. Eventually, 1,094 subjects were analyzed.

Data collection

The subjects' medical history, history of cardio-cerebrovascular diseases, use of alcohol and smoking were ascertained by questionnaire. Alcohol intake and smoking were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (square meters) as an index of obesity. Waist circumference was measured at the level of the umbilicus in the standing position. Blood pressure (BP) was measured in the supine position twice at 3-min intervals using an upright standard

sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP with the fifth-phase diastolic pressure was used for analysis. Hypertensive subjects were defined as those with systolic BP≥140mmHg and/or those with diastolic BP≥90mmHg and/or those receiving antihypertensive medication. Subjects with FPG ≥6.99mmol/l (126mg/dl) and/or subjects taking oral hypoglycemic agents or receiving insulin injection were considered diabetic. Subjects with dyslipidemia were defined as those with low density lipoprotein cholesterol (LDL-c) ≥3.62mmol/l (140mg/dl) and/or triglycerides ≥1.69mmol/l (150mg/dl) and/or high-density lipoprotein cholesterol (HDL-c) <1.03mmol/l (40mg/dl) and/or those taking lipid-lowering drugs.

Fasting blood samples were taken in the morning and centrifuged within 1 hour after collection. Serum levels of IGF-1 and GH were measured by ELISA and ECLIA methods in 1,368 subjects who were able to provide blood for testing. The blood was submitted to a commercially available laboratory (SRL Inc. Fukuoka, Japan), and the intra- and inter-assay coefficient of variations of IGF-1 and GH at the laboratory that performed the assays were 2.56%, 0.75% and 3.06%, 0.73%, respectively [16,17]. The

homeostasis model assessment index (HOMA-IR) [FPG (mg/dl) × insulin (μU/ml)/405] was calculated from fasting glucose and insulin level as a marker of insulin resistance [18]. Estimated glomerular filtration rate (eGFR) was calculated by the following estimation formula that has been recommended by the Japan Society of Nephrology: eGFR (ml/min/1.73^2) = (194×Scr$^{-1.094}$×age$^{-0.287}$) × (0.739 for females) [19].

This study was approved by the Tanushimaru branch of the Japan Medical Association and by the local mayor, as well as by the ethics committee of Kurume University School of Medicine. All the participants gave informed consent. The Research Ethics Committee of the Kurume University School of Medicine (Process numbers 09019/2018) approved the study in conformity with the principles embodied in the declaration of Helsinki.

Statistical analysis

Because of skewed distributions, the natural logarithmic transformation was performed for GH, FPG, HOMA-IR and triglycerides. The standard deviation (SD) score (Z-score) of serum IGF-1 measurement was calculated

from LMS method reported by Isojima T, et al. [20]. Mean values and upper and lower 95% confidence limits were exponentiated and presented geometric mean (SD), where the SD was approximated as the difference of the exponentiated confidence limits divided by 3.92, the number of SD in a 95% confidence interval for normally distributed data. Chi-square tests were used for evaluation of categorical parameters. Mean Z-score of serum IGF-1 and GH levels were classified into quartiles. Characteristics of participants stratified by GH quartile were compared using analysis of covariance adjusted for age and sex. Multiple logistic regression analyses were performed for factors related to hypertensive subjects after adjustment for confounding factors. Eventually, odds ratios per 1-SD increase of Z-score of serum IGF-1 and GH levels for hypertensives were calculated after adjustment for confounding factors. All statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

Results

Clinical characteristics of enrolled subjects were shown in Table 1. Mean age was 66.8 years. The systolic and diastolic blood pressures and body weights of the subjects were 138.1±20.9mmHg, 80.7±11.7mmHg, and 57.6±11.0kg,

respectively, and the distribution was normal. Significant associations were observed between Z-score of IGF-1 and FPG, insulin, HOMA-IR, eGFR, total cholesterol, triglycerides, and medication for hypertension (Table 2). Significant associations of GH were observed with BMI (inversely), systolic (inversely) and diastolic (inversely) BPs, insulin (inversely), HOMA-IR (inversely), total cholesterol (inversely), HDL-cholesterol, triglycerides (inversely), smoking (inversely), and alcohol intake (inversely) after adjustment for age and sex (Table 3). No significant association was seen between Z-score of serum IGF-1 levels and hypertension (Table 4); however, a significant and inverse association between serum GH levels and hypertension was observed in each model (Table 5).

Discussion

In the present study, we demonstrated for the first time that serum GH levels, but not IGF-1, was significantly and inversely associated with hypertensive subjects in a Japanese general population aged over 40 years. Compared to the previous studies [21-23], the subjects enrolled in the present study had comparatively lower BMI, and plasma IGF-1 and GH were measured simultaneously.

In human studies [24,25], IGF-1 may be directly or indirectly involved in the pathogenesis of atherosclerosis. However, Page JH, et al. [20] suggested that IGF-1 did not indicate a monotonic relationship with myocardial infarction among predominantly postmenopausal women. Ameri P, et al. [22] also suggested that IGF-1 was significantly and inversely associated with carotid intima-media thickness. Our data revealed that Z-score of IGF-1 levels were not protective against increasing FPG, blood insulin levels, insulin resistance, eGFR, lipid profiles and medication for hypertension (Table 2). Based on the results shown in Tables 2 and 4, serum IGF-1 levels had no informative relationship with systolic and diastolic BPs. Also, the CARDIA Study did not support a strong link between IGF-1 and BP; however, it did support the possibility of an important relation between IGF-1 and lipid levels in young adult men [26]. Recently, Erlandsson MC, et al. have reported the association between serum IGF-1 and hypertension in female patients with rheumatoid arthritis or ischemic stroke without rheumatic disease [27], in which the impact of low IGF-1 on cardiovascular risk factors, including hypertension, was bigger in rheumatoid arthritis than ischemic stroke without rheumatic disease, indicating that IGF-1 might work

differently depending on the clinical background.

Data to support a significant association between serum GH levels and hypertension has been scant. Strazhesko ID, et al. [28] suggested that GH/IGF-1 was the most important parameter of arterial aging. Subjects with GH deficiency were documented to have an increased risk of developing CVD and cerebrovascular diseases in the Rancho Bernardo Study [29]. Although hypertension is one of the main components of metabolic syndrome (MS), the prevalence of the MS in patients with GH deficiency was significantly higher than in healthy controls [30]. A survey study in Japan also reported that dyslipidemia and hypertension were more common in a GH deficiency group than in a GH intact group in 863 adult patients. Their results indicated that GH deficiency increased the prevalence of cardiovascular risk factors in Japan, as is the case in Western countries [31].

Our data showed that BMI, systolic and diastolic BPs, insulin, HOMA-IR, total cholesterol, and triglycerides except for HDL-cholesterol were significantly and inversely associated with plasma GH levels. These findings are consistent with previous studies [28-31]. The discrepancy between GH and IGF-1 in terms of the correlation with hypertension in our

study is still unclear. Many clinical studies [28-32] have supported the concept that normal levels of GH and IGF-1 are necessary to maintain endothelial function. IGF-1 is involved in the synthesis of nitrogen monoxide (NO) in endothelial cells, which causes additional vasodilation of the arteries, decreases the concentration of free fatty acids (FFA), and increases the sensitivity to insulin. Recently, the importance of activities of IGF-1 and GH as a key determinant of stroke risk has been reported [28,32]. Strazhesko ID, et al. [28] found that patients with GH deficiency and low circulating IGF-1 had an increased risk of CVD. Although IGF-1 may promote the structural integrity of cerebral arteries, thereby offering protection from hemorrhagic stroke, GH deficiency increases the stroke risk. It is interesting to note that these two parameters showed entirely inverse findings with regard to blood pressure even in healthy Japanese participants. This inverse association of GH levels for hypertensive subjects may help to explain why GH deficiency increases stroke risk.

There are several limitations in our study. First, the study design was cross-sectional. Thus, nothing conclusive can be stated with regard to the association of serum IGF-1 and GH. We are planning future prospective

studies to investigate the role of these markers in subjects with hypertension. Second, results from only a single blood testing were used to evaluate the association between serum IGF-1 and GH levels and hypertension. The third limitation was a relatively small sample size. This could have caused a selection bias. Nevertheless, a clear inverse relationship between serum GH and hypertension was striking and further investigation should be performed.

In conclusion, decreased plasma GH levels, but not IGF-1, were associated with hypertensives in a general population.

Acknowledgements

This study was supported in part by the Kimura Memorial Heart Foundation, Fukuoka, Japan, and by a Grant-in-Aid for Scientific Research (C), from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to the members of the Japan Medical Association of Ukiha, the elected officials and residents of Tanushimaru, and the team of physicians who carried out the health examinations.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Rudman D. Growth hormone, body composition, and aging. J Am Geriatr Soc. 1985; 33:800-807.
2. Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone secretion in the adult population: relation to age and adiposity. J Clin Invest. 1981; 67:1361-9.
3. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med. 1990; 323:1-6.
4. Florini JR, Prinz PN, Vitiello MV, Hintz RL. Somatomedin-C levels in healthy young and old men: relationship to peak and 24-hour integrated levels of growth hormone. J Gerontol. 1985; 40:2-7.
5. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: The Rancho Bernardo Study. J Clin Endocrinol Metab. 2004; 89:114-20.
6. LeRoith D, Werner H, Beitner-Johnson D, Roberts CT Jr. Molecular and

cellular aspects of the insulin-like growth factor I receptor. Endocr Rev. 1995; 16:143-63.

7. Caicedo D, Díaz O, Devesa P, Devesa J. Growth Hormone (GH) and Cardiovascular System. Int J Mol Sci. 2018; 19:E290.
8. Rizza RA, Mandarino LJ, Gerich JE. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes. 1982; 31:663-9.
9. Ciresi A, Radellini S, Guarnotta V, Giordano C. The visceral adiposity index is associated with insulin sensitivity and IGF-I levels in adults with growth hormone deficiency. Endocrine. 2017; 56:579-88.
10. Isgaard J. Cardiovascular disease and risk factors: the role of growth hormone. Horm Res. 2004; 62 Suppl 4:31-8.
11. Toshima H, Tashiro H, Sumie M, Koga Y, Kimura N. Nutritional prevention of cardiovascular disease. In: Lovenberg W, Yamori Y (eds) Changes in risk factors and cardiovascular mortality and morbidity within Tanushimaru 1958-1982. Academic Press, New York, pp 203-210. 1984.
12. Hirai Y, Geleijnse JM, Adachi H, Imaizumi T, Kromhout D. Systolic

blood pressure predicts cardiovascular mortality in a farming but not in a fishing community. -A 40-year follow up of the Japanese cohorts of the seven countries study-. Circ J. 2011; 75:1890-6.

13. Adachi H, Enomoto M, Fukami A, Kumagai E, Nakamura S, Yoshimura A, et al. Plasma renin activity and resting heart rate in a population of community-dwelling Japanese: The Tanushimaru Study. Am J Hypertens. 2015; 28:894-9.

14. Nakamura S, Adachi H, Enomoto M, Fukami A, Kumagai E, Nohara Y, et al. Trends in coronary risk factors and electrocardiogram findings from 1977 to 2009 with 10-year mortality in Japanese elderly males - The Tanushimaru Study. J Cardiol. 2017; 70:353-8.

15. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009; 7:1104-12.

16. Guha N. Assays for GH, IGF-I, and IGF binding protein-3. Methods Mol Biol. 2013; 1065:117-28.

17. McGrath MF, Bogosian G, Fabellar AC, Staub RL, Vicini JL, Widger

LA. Measurement of bovine somatotropin (bST) and insulin-like growth factor-1 (IGF-1) in bovine milk using an electrochemiluminescent assay. J Agric Food Chem. 2008; 56:7044-8.

18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412-9.

19. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al.; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009; 53:982-92.

20. Isojima T, Shimatsu A, Yokoya S, Chihara K, Tanaka T, Hizuka N, et al. Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocr J. 2012; 59:771-80.

21. Page JH, Ma J, Pollak M, Manson JE, Hankinson SE. Plasma insulinlike growth factor 1 and binding-protein 3 and risk of myocardial infarction in women: a prospective study. Clin Chem. 2008; 54:1682-8.

22. Ameri P, Canepa M, Fabbi P, Leoncini G, Milaneschi Y, Mussap M, et al. Vitamin D modulates the association of circulating insulin-like growth factor-1 with carotid artery intima-media thickness. Atherosclerosis. 2014; 236:418-25.
23. Bian A, Ma Y, Zhou X, Guo Y, Wang W, Zhang Y, Wang X. Association between sarcopenia and levels of growth hormone and insulin-like growth factor-1 in the elderly. BMC Musculoskelet Disord. 2020; 21:214.
24. Schneider DJ, Sobel BE. Augmentation of synthesis of plasminogen activator inhibitor type 1 by insulin and insulin-like growth factor type I: implications for vascular disease in hyperinsulinemic states. Proc Natl Acad Sci USA. 1991; 88:9959-63.
25. Bennett MR, Evan GI, Schwartz SM. Apoptosis of human vascular smooth muscle cells derived from normal vessels and coronary atherosclerotic plaques. J Clin Invest. 1995; 95:2266-74.
26. Colangelo LA, Liu K, Gapstur SM; CARDIA Male Hormone Study. Insulin-like growth factor-1, insulin-like growth factor binding protein-3, and cardiovascular disease risk factors in young black men and white men: the CARDIA Male Hormone Study. Am J Epidemiol. 2004; 160:

750-7.

27. Erlandsson MC, Lyngfelt L, Åberg ND, Wasén C, Espino RA, Silfverswärd ST, Nadali M, Jood K, Andersson KME, Pullerits R, Bokarewa MI. Low serum IGF1 is associated with hypertension and predicts early cardiovascular events in women with rheumatoid arthritis. BMC Med. 2019; 17:141.

28. Strazhesko ID, Tkacheva ON, Akasheva DU, Dudinskaya EN, Plokhova EV, Pykhtina VS, et al. Growth hormone, insulin-like growth factor-1, insulin resistance, and leukocyte telomere length as determinants of arterial aging in subjects free of cardiovascular diseases. Front Genet. 2017; 8:198.

29. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: The Rancho Bernardo Study. J Clin Endocrinol Metab. 2004; 89:114-20.

30. van der Klaauw AA, Biermasz NR, Feskens EJ, Bos MB, Smit JW, Roelfsema F, et al. The prevalence of the metabolic syndrome is increased

in patients with GH deficiency, irrespective of long-term substitution with recombinant human GH. Eur J Endocrinol. 2007; 156:455-62.

31. Irie M, Itoh Y, Miyashita Y, Tsushima T, Shirai K. Complications in adults with growth hormone deficiency – A Survey Study in Japan – Endocr J. 2004; 51:479-85.

32. McCarty MF. IGF-I activity may be a key determinant of stroke risk--a cautionary lesson for vegans. Med Hypotheses. 2003; 61:323-34.

Table 1. Clinical characteristics of 1,094 subjects

Characteristics	Total	Males	Females
Age, years	66.8 (11.3)	67.5 (10.9)	66.5 (11.5)
Sex, n (%)	1,094 (100.0)	402 (36.7)	692 (63.3)
Body weight, kg	57.6 (11.0)	65.1 (9.9)	53.1 (8.9)
BMI, kg/m^2	22.9 (3.4)	23.5 (3.1)	22.6 (3.5)
SBP, mmHg	138.1 (20.9)	139.8 (19.7)	137.1 (21.6)
DBP, mmHg	80.7 (11.7)	82.7 (12.1)	79.6 (11.3)
AST, IU/L	23.4 (6.8)	24.4 (7.0)	22.7 (6.6)
ALT, IU/L	20.6 (11.6)	23.1 (13.8)	18.3 (9.7)
γ-GTP, IU/L	30.9 (27.7)	40.5 (33.9)	25.3 (21.4)
eGFR, $ml/min/1.73m^2$	70.2 (15.3)	68.7 (16.5)	71.1 (14.5)
TC, mg/dL	212.8 (35.5)	202.4 (32.6)	219.0 (35.7)
TG, mg/dL[a]	104.6 (27-996)	113.1 (30-996)	99.9 (27-657)
HDL-C, mg/dL	65.7 (17.2)	59.9 (15.3)	69.2 (17.4)
LDL-C, mg/dL	127.8 (30.2)	122.0 (28.3)	131.2 (30.7)
FPG, mg/dL	94.6 (12.6)	95.9 (13.2)	93.9 (12.3)
Insulin, uU/mL[a]	5.6 (0.6-159.8)	5.7 (0.6-97.4)	5.5 (0.8-159.8)
HOMA-IR[a]	1.3 (0.1-42.6)	1.3 (0.1-31.0)	1.3 (0.2-42.6)
Hemoglobin A_{1C} (%)	5.6 (0.3)	5.6 (0.3)	5.6 (0.3)
Z score of IGF-1	-0.669 (0.941)	-0.717 (0.860)	-0.641 (0.985)
GH (ng/mL)[a]	0.73 (0.03-18.5)	0.41 (0.03-12.6)	1.02 (0.03-18.5)
Smoking, n (%)	115 (10.5%)	95 (23.6%)	20 (2.9%)
Alcohol, n (%)	504 (46.1%)	278 (69.2.%)	226 (32.7%)
Medication for HT, n (%)	346 (31.6%)	142 (35.3%)	204 (29.5%)
Medication for HL, n (%)	231 (21.1%)	74 (18.4%)	157 (22.7%)

Data are mean (SD), geometric mean, range, or percent.

Abbreviations: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure;

AST: Aspartate transaminase; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase;

eGFR: estimated glomerular filtration rate; TC: Total cholesterol; TG: Triglycerides;

HDL: high-density lipoprotein; LDL: low-density lipoprotein; FPG: fasting plasma glucose;

HOMA-IR: homeostasis model assessment; IGF-1: insulin-like growth factor 1; GH: Growth hormone;

HT: Hypertensive; HL: Hyperlipidemic

[a] These variables are shown in the original scale after analysis using log (natural)-transformed values.

Table 2. Means of parameters stratified by Z-score of IGF-1 measurement quartile

	IGF-1 Q1	IGF-1 Q2	IGF-1 Q3	IGF-1 Q4	p value
Total number	273	273	274	274	
Z-score of IGF-1	-1.844(0.499)	-0.987(0.177)	-0.371(0.199)	0.517(0.487)	<0.001
Range	-4.712, -1.279	-1.279, -0.691	-0.683, -0.026	0.000, 3.563	
BMI, Kg/m^2	22.5 (3.6)	23.1 (3.5)	22.9 (3.2)	23.3 (3.4)	0.090
SBP, mmHg	137.7 (21.5)	138.3 (22.4)	136.8 (18.2)	139.5 (21.6)	0.516
DBP, mmHg	79.9 (12.3)	81.7 (12.4)	79.8 (11.2)	81.4 (10.9)	0.141
FPG, mg/dL	93.1 (12.3)	93.7 (12.4)	95.0 (12.0)	96.7 (13.6)	0.006
Insulin, μU/mL[b]	4.62	5.13	5.94	6.79	<0.001
Range	0.6-159.8	0.8-99.9	0.8-50.1	1.6-62.9	
HOMA-IR[b]	1.05	1.18	1.38	1.61	<0.001
Range	0.1-42.6	0.1-31.0	0.2-10.6	0.3-21.6	
eGFR, $mL/min/1.73m^2$	71.7 (15.1)	71.4 (15.4)	70.3 (14.7)	67.6 (15.6)	0.007
TC, mg/dL	205.9 (32.4)	213.9 (37.4)	211.9 (34.0)	219.6 (36.7)	<0.001
HDL-C, mg/dL	64.9 (16.2)	66.2 (19.3)	64.7 (15.3)	67.1 (17.8)	0.304
TG, mg/dL[b]	98.1	100.5	107.5	113.0	0.008
Range	27-743	30-996	32-572	33-573	
Smoking, n (%)	29 (10.6)	28 (10.3)	38 (13.8)	19 (6.9)	0.061
Alcohol, n (%)	117 (42.9)	125 (45.8)	136 (49.6)	124 (45.3)	0.386
Medication for HT	73 (26.7)	76 (27.8)	100 (36.5)	95 (31.0)	0.024
Medication for HL	48 (17.6)	49 (17.9)	67 (24.4)	66 (24.1)	0.074

Data are mean (SD), geometric mean, range, or percent.

Abbreviations: IGF-1: insulin-like growth factor 1, SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose HOMA-IR: homeostasis model assessment; eGFR: estimated glomerular filtration rate; TC: Total cholesterol; TG: Triglycerides; HDL: high-density lipoprotein, HT: Hypertensive; HL: Hyperlipidemic; DM: Diabetic

[a] Calculated from linear regression analysis for continuous variables and from logistic regression analysis for dichotomous variables.

[b] These variables are shown in the original scale after analysis using log (natural)-transformed values.

Table 3. Age and sex adjusted means of parameters stratified by GH quartile

	GH Q1	GH Q2	GH Q3	GH Q4	p value
Total number	273	273	274	274	
GH, ng/mL[b]	0.131	0.526	1.193	3.263	<0.001
Range	0.03-0.29	0.30-0.84	0.85-1.78	1.79-18.5	
BMI, Kg/m^2	24.1 (3.4)	23.1 (3.3)	22.6 (3.3)	22.1 (3.4)	<0.001
SBP, mmHg	141.8 (20.8)	140.2 (19.9)	137.4 (20.0)	133.0 (20.4)	<0.001
DBP, mmHg	83.1 (11.9)	82.0 (11.4)	79.6 (11.4)	78.0 (11.6)	<0.001
FPG, mg/dL	96.6 (12.7)	93.9 (12.2)	93.9 (12.3)	94.4 (12.5)	0.055
Insulin, μU/mL[b]	7.15	5.29	4.98	5.08	<0.001
Range	1.5-97.4	0.6-58.9	0.6-37.8	0.8-159.8	
HOMA-IR[b]	1.69	1.22	1.14	1.17	<0.001
Range	0.3-29.8	0.1-17.7	0.1-11.1	0.2-42.6	
eGFR, mL/min/1.73m^2	68.2 (14.4)	70.2 (13.8)	71.3 (13.9)	71.0. (14.1)	0.074
TC, mg/dL	218.1 (35.7)	213.6 (34.2)	212.2 (34.3)	207.3 (34.9)	0.009
HDL-C, mg/dL	62.3 (17.1)	65.3 (16.4)	65.7 (16.5)	69.8 (16.8)	<0.001
TG, mg/dL[b]	129.5	105.4	96.7	90.0	<0.001
Range	34-996	27-519	32-501	31-573	
Smoking, n (%)	46 (16.8)	42 (15.4)	27 (9.9)	22 (8.0)	0.003
Alcohol, n (%)	202 (74.0)	178 (65.2)	124 (45.2)	131 (47.8)	0.001
Medication for HT	84 (30.8)	92 (33.7)	84 (30.7)	83 (30.3)	0.798
Medication for HL	55 (20.1)	57 (20.9)	63 (23.0)	54 (19.7)	0.763

Data are mean (SD), geometric mean, range, or percent.

Abbreviations: IGF-1: insulin-like growth factor 1, SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose HOMA-IR: homeostasis model assessment; eGFR: estimated glomerular filtration rate; TC: Total cholesterol; TG: Triglycerides; HDL: high-density lipoprotein, HT: Hypertensive; HL: Hyperlipidemic; DM: Diabetic

[a] Calculated from linear regression analysis for continuous variables and from logistic regression analysis for dichotomous variables.

[b] These variables are shown in the original scale after analysis using log (natural)-transformed values.

Table 4. Odds ratios per 1-SD increase of Z-score of serum IGF-1 levels in hypertensive subjects

Model	Beta	Odds ratio (95% CI)	p value
Unadjusted	0.144	1.145 (1.011-1.297)	0.033
Model 1	0.120	1.119 (0.979-1.280)	0.098
Model 2	0.059	1.057 (0.921-1.213)	0.433
Model 3	0.047	1.045 (0.909-1.202)	0.535
Model 4	-0.023	0.978 (0.830-1.153)	0.794

Hypertensive subjects were defined as those with BP≥140/90mmHg and/or those receiving antihypertensive medication.

Abbreviations: IGF-1; insulin-like growth factor 1, CI, confidence intervals

FPG; fasting plasma glucose, eGFR; estimated glomerular filtration rate, HT; Hypertensive

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, FPG, insulin, and eGFR

Model 3: Adjusted for age, sex, FPG, insulin, eGFR, total cholesterol and triglycerides

Model 4: Adjusted for age, sex, FPG, insulin, eGFR, total cholesterol, triglycerides, and medication for HT

Table 5. Odds ratios per 1-SD increase of serum GH levels in hypertensive subjects

Model	Beta	Odds ratio (95% CI)	p value
Unadjusted	-0.106	0.821 (0.735-0.916)	<0.001
Model 1	-0.149	0.758 (0.670-0.858)	<0.001
Model 2	-0.088	0.849 (0.746-0.965)	0.012
Model 3	-0.086	0.852 (0.747-0.971)	0.016
Model 4	-0.084	0.855 (0.750-0.975)	0.019

Hypertensive subjects were defined as those with BP≥140/90mmHg and/or those receiving antihypertensive medication.

Abbreviations: GH; growth hormone, CI, confidence intervals BMI; body mass index, HDL; high-density lipoprotein

Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex, BMI, and insulin
Model 3: Adjusted for age, sex, BMI, insulin, total cholesterol, HDL-cholesterol, and triglycerides
Model 4: Adjusted for age, sex, BMI, insulin, total cholesterol, HDL-cholesterol, triglycerides, smoking, and alcohol intake