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Hepatocyte Growth Factor as an Indicator of Reduced Handgrip Strength among Non-Overweight Hypertensive Elderly Men

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Abstract

Background: Age-related loss of skeletal muscle mass and function is reported to be associated with impairment of capillary functions. Hepatocyte growth factor (HGF) has been evaluated as a possible biochemical index of hypertension-induced vascular damage which also impairs capillary functions.

Aims: The present study aimed to clarify the clinical importance of HGF on handgrip strength (marker of loss of skeletal muscle mass and function) in hypertensive elderly men.

Methods: We conducted a cross-sectional study of 191 hypertensive elderly men (60-69 years). Since low body mass index (BMI) is one of the well-known risk factors for age-related loss of skeletal muscle mass and function, non-overweight (BMI<25 kg/m^2) subjects are a high risk group for this phenomenon. To investigate the association between HGF and handgrip strength BMI status also should be accounting.

Results: From multivariable linear regression analysis adjusted for known cardiovascular risk factors, we found a significant inverse association between handgrip strength and the logarithm of serum HGF concentration for non-overweight elderly men but not for overweight elderly men; B (parameter estimate)=-2.59, β (standardized parameter estimate)=-0.23, p=0.010 for non-overweight and B=0.32, β=0.03, p=0.842 for overweight, respectively.

Conclusion: We found a significant inverse association between handgrip strength and HGF in non-overweight hypertensive men. This result indicates that HGF and status of BMI may be a useful indicator to evaluate hypertension-related loss of skeletal muscle mass and function.

Keywords: Hepatocyte growth factor; Handgrip strength; Non-overweight; Hypertension

Introduction

Handgrip strength is an efficient tool to evaluate the loss of skeletal muscle mass and function since handgrip strength is regarded as a predictor of old age disability [1]. Common age-related disease including hypertension and sacropenia are reported to be exacerbated by disruption of the micro-vascular endothelium and impair blood flow by increasing in age-related inflammatory agents [2].

Previously we reported positive association between handgrip strength and circulating CD34-positive cells in hypertensive men but not in non-hypertensive men [3]. This study indicates that vascular maintenance attributed by circulating CD34-positive cells might compensate for the disturbed handgrips strength triggered by hypertension induced vascular damage.

On the other hands, hepatocyte growth factor (HGF) is an endothelial-specific growth factor whose serum concentration significantly positively correlates with blood pressure [4]. And other studies have reported HGF as a possible biochemical index of vascular damage due to hypertension [5-10]. Therefore serum HGF concentration might positively correlate with a loss of skeletal muscle mass and function such as sarcopenia among subjects with age-related hypertension by indicating hypertension-induced vascular injury.

To investigate the association between HGF and handgrip strength, we conducted a cross-sectional study of 191 elderly hypertensive Japanese men aged 60-69 years who underwent a general health check-up in 2014-2015.

Materials and Methods

Subjects

Because our present study is aimed to clarify the impact of HGF on age-related handgrip strength reduction (marker of loss of skeletal muscle mass and function), our present study was conducted during a medical screening program for members of the presenium general population aged 60-69 years who were living in Goto city, Nagasaki Prefecture, Japan. After obtaining informed consent, 453 Japanese men aged 60-69 years were enrolled. HGF is known to be a biochemical index of vascular damage due to hypertension [5-10] and a loss of skeletal muscle mass and function might be associated with age-related hypertension by indicating hypertension-induced vascular injury. Therefore, subjects were limited to participants with hypertension.

Among 453 Japanese men 307 males were diagnosed as having hypertension. Among those with hypertension, subjects lacking handgrip data (27 males) and HGF data (89 males) were excluded, leaving a total of 191 subjects participating in the study. There were no differences in known cardiovascular risk factors between participants for whom data of serum HGF measurements were available and those for whom they were not. Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was provided by the participants. This study was approved by the Ethics Committee for Human Use of Nagasaki University (project registration number 14051404).

Data collection and laboratory measurements

Trained interviewers obtained information on medical history. Body weight and height of patients wearing light clothing were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan), and body mass index (BMI; kg/m^2) was calculated. Handgrip strength was recorded as the grip strength from 2 measurements performed with each hand using a handgrip dynamometer (Smedley, Matsumiya Ika Seiki Seisakujo, Tokyo, Japan), with the maximum value used.

Blood samples collected in a siliconized tube were centrifuged after coagulation and the separated serum was isolated. To measure HGF, serum samples were diluted fourfold with specific Bio-Plex sample diluents. HGF concentration was determined using a fluorescent bead-based immunosorbent assay on a suspension array. This method is recommended by the International Committee for Standardization in hematology. Serum triglycerides (TG), serum high density lipoprotein (HDL) cholesterol, serum γ-glutamyltranspeptidase (γ-GTP), hemoglobin A1c (HbA1C) and serum creatinine were measured using standard laboratory procedures at SRL, Inc. (Tokyo, Japan). To measure HGF, serum samples were diluted fourfold with specific Bio-Plex sample diluents. HGF concentration was determined using a fluorescent bead-based immunosorbent assay on a suspension array.

Measurement of carotid intima media thickness (CIMT) was determined by ultrasonography of the left and right carotid arteries performed by an experienced vascular technician using a LOGIQ Book XP with a 10-MHz transducer, GE Healthcare, Milwaukee, WI, USA), with mean values of the left and right CIMT calculated by using automated digital edge-detection software (Intimascope; MediaCross, Tokyo, Japan. The protocol used has been described in detail elsewhere [11]). Glomerular filtration rate (GFR) was estimated using an established method with three variations that were recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative [12]. According to this adaptation, GFR (mL/min/1.73 m^2) = 194 × (serum creatinine (enzyme method))-1.094 × (age)-0.287. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or antihypertensive medication use.

Statistical analysis

Because low body mass index (BMI) is a well-known risk factor for age-related loss of skeletal muscle mass and function [13] while high BMI is well established as being associated with hypertension [14], an analysis limited to non-overweight subjects with hypertension might enhance the influence of age-related microvascular disruption among this high risk group. Therefore, BMI status (BMI<25 kg/m^2, BMI ≥ 25 kg/m^2) stratified analysis were performed. Characteristics of the study population by BMI status are expressed as mean ± standard deviation (SD). Simple correlation analysis (correlation coefficient) of HGF and other variables was performed. In order to determine the association between HGF and other variables, simple and multiple linear regression analyses were performed. In our present study handgrips strength is significantly inversely associated with age whereas significantly positively associated with systolic and diastolic blood pressure. And HGF shows significantly positively associated with taking antihypertensive medication and BMI. Therefore, to investigate the association between HGF and handgrip strength, adjustments were made for known cardiovascular risk factors such as age, systolic blood pressure (mmHg), antihypertensive medication (yes or no), body mass index (BMI) and HDL (mg/dL). Because TG, γ-GTP and HGF levels had a skewed distribution, logarithmic transformation was performed. To investigate the impact of HGF on vascular remodeling, we also performed simple and partial correlation analysis (correlation coefficient) of HGF and mean CIMT. All statistical analyses were performed using the SAS system for Windows (version 9.4; SAS Inc., Cary, NC). Probability values less than 0.05 were considered to be statistically significant.

Results

Characteristics of the study population

The characteristics of the study population by BMI status are shown in **(Table 1)**. The serum concentration of HGF was 342.3 ± 184.8 pg/mL for subjects with non-overweight (BMI<25 kg/m^2) and 342.3 ± 184.8 pg/mL for subjects with overweight (BMI ≥ 25 kg/m^2), P=0.491. The prevalence of taking antihypertensive medication use was 62.5% for non-overweight and 74.6% for overweight, p=0.085.

Association between handgrip strength and HGF

To determine the association between handgrip strength and other variables we used simple correlation analysis by BMI status **(Table 2)** and scatter plot of handgrip strength and HGF **(Figure 1)**.

Table 1 Characteristics of the study population.

	BMI< 25.0 kg/m^2	BMI ≥ 25 kg/m^2	p
No. of participants	120	71	
Age (years)	65.6 ± 2.6	65.5 ± 2.6	0.771
Hepatocyte growth factor (HGF), pg/mL	348.3 ± 188.2	366.5 ± 159.6	0.491
Systolic blood pressure, mmHg	143 ± 16	142 ± 16	0.654
Diastolic blood pressure, mmHg	88 ± 11	89 ± 12	0.373
Antihypertensive medication use, %	62.5	74.6	0.085
Body mass index (BMI), kg/m^2	22.2 ± 2.1	27.0 ± 1.7	<0.001
Serum triglycerides (TG), mg/dL	110 ± 83	133 ± 113	0.096
Serum HDL-cholesterol (HDL), mg/dL	60 ± 15	53 ± 13	<0.001
Serum γ-glutamyltranspeptidase (γ-GTP)	43 ± 34	56 ± 50	0.028
Hemoglobin A1c (HbA1c), %	5.7 ± 0.7	5.8 ± 0.6	0.336
Serum creatinine, mg/dL	0.84 ± 0.16	0.86 ± 0.14	0.269
Glomerular filtration rate (GFR), mL/min/1.73 m^2	72.9 ± 14.2	72.9 ± 14.2	0.163
Handgrip strength, kg	38.6 ± 5.9	38.9 ± 6.1	0.763
Values are mean ± standard deviation			

Table 2 Simple correlation analysis of handgrip strength and other variables.

	Total subjects		BMI<25.0 kg/m^2		BMI ≥ 25 kg/m^2	
	r	p	r	p	r	p
No. of participants	191		120		71	
Age	-0.24	<0.001	-0.27	0.003	-0.19	0.118
Systolic blood pressure	0.17	0.019	0.16	0.072	0.18	0.136
Diastolic blood pressure	0.26	<0.001	0.19	0.041	0.35	0.002
Antihypertensive medication use	-0.13	0.083	-0.14	0.141	-0.12	0.319
Body mass index (BMI)	0.04	0.591	0.11	0.232	-0.12	0.338
Serum triglycerides (TG)	-0.04	0.554	-0.07	0.473	-0.02	0.889
Serum HDL-cholesterol (HDL)	0.07	0.332	0.14	0.13	-0.04	0.743
Serum γ-glutamyltranspeptidase (γ-GTP)	-0.08	0.277	0.01	0.953	-0.21	0.079
Hemoglobin A1c (HbA1c)	-0.09	0.205	-0.13	0.143	-0.02	0.878
Glomerular filtration rate (GFR)	-0.04	0.57	-0.13	0.143	0.14	0.256
Hepatocyte growth factor (HGF)	-0.14	0.059	-0.25	0.006	0.05	0.698

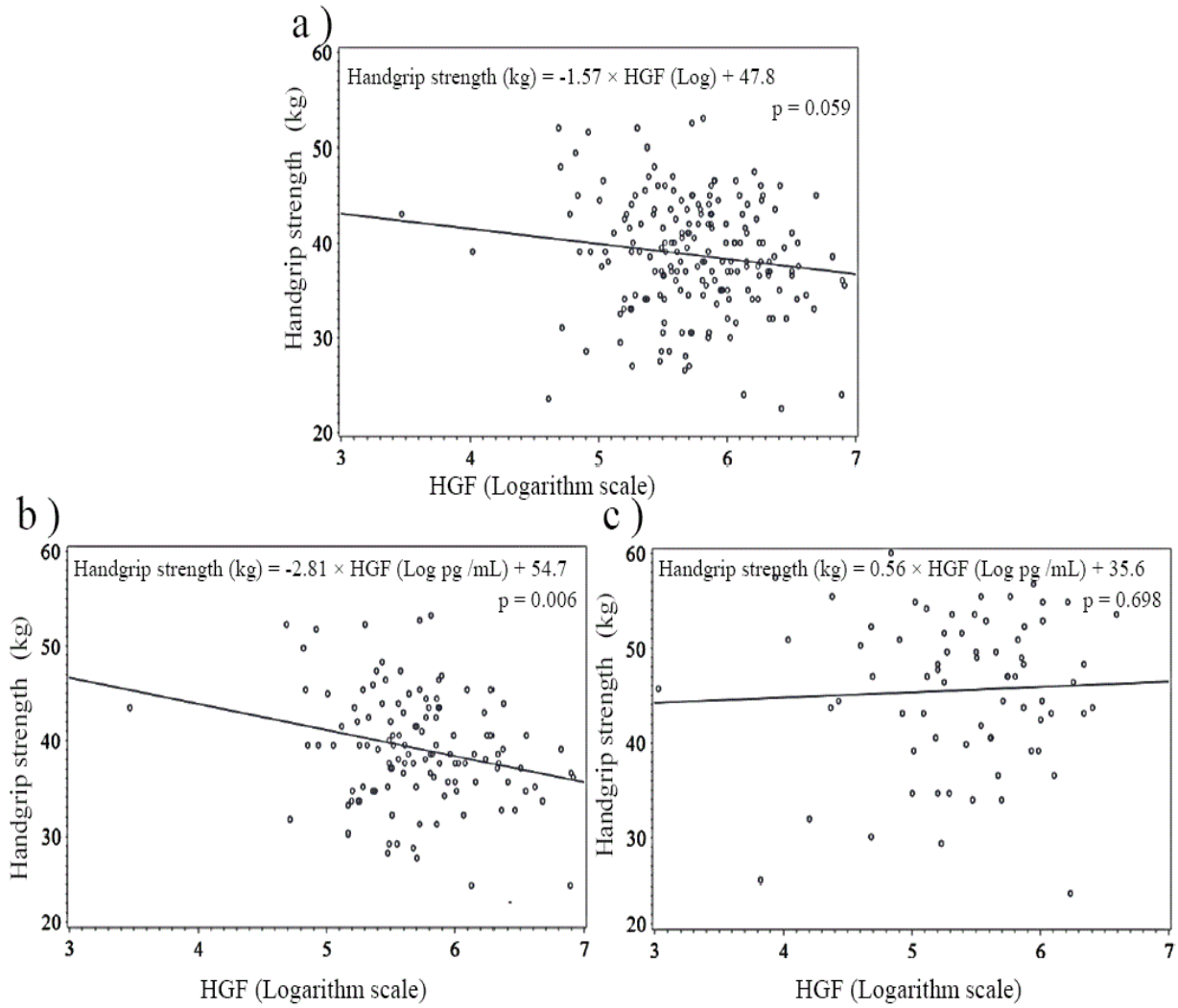

Figure 1 Scatter plot of hand grip strength and Logarithm of hepatocyte growth factor (HGF) a) Total subjects b) subjects with BMI < 25.0 kg/m^2 and c) subjects with BMI 25 kg/m^2

We found significant inverse association between handgrip strength and HGF for non-overweight (r=-0.25, p=0.006) but not among overweight (r=0.05, p=0.698), respectively.

For subjects with non-overweight, handgrip strength was found to be inversely associated with age, diastolic blood pressure and HGF, while positively correlated with HDL. And for subjects with overweight diastolic blood pressure is positively associated with handgrip strength. As shown in **(Table 3)**, multiple regression analysis adjustment for confounding factors showed that handgrip strength is inversely associated with HGF (B (parameter estimate)=-2.34, β(standardized parameter estimate)=-0.20, p=0.031) for subjects with non-overweight but not for subjects with overweight B=0.87, β=0.07, p=0.585), respectively.

Table 3 Multiple linear regression analysis of handgrip strength with relevant factors adjusted for confounding factors.

	Total subjects			BMI<25.0 kg/m^2			BMI ≥ 25 kg/m^2		
	B	β	p	B	β	p	B	β	p
No. of participants	191			120			71		
AGE	-0.51	-0.22	0.002	-0.53	-0.23	0.011	-0.51	-0.22	0.09
Systolic blood pressure	0.06	0.15	0.043	0.04	0.12	0.204	0.08	0.22	0.088
Medication	-0.31	-0.02	0.751	-0.07	-0.01	0.948	-0.51	-0.04	0.779
BMI	0.2	0.1	0.184	0.54	0.19	0.033	-0.36	-0.1	0.448

HDL	0.02	0.06	0.458	0.06	0.14	0.112	-0.05	-0.1	0.421
HGF	-1.39	-0.12	0.095	-2.34	-0.21	0.02	0.87	0.07	0.585
Medication: anti-hypertensive medication use, BMI: body mass index, HDL: HDL-cholesterol, HGF: hepatocyte growth factor. B: parameter estimate. β: Standardized parameter estimate. HGF is calculated in logarithm values.									

Association between HGF and other variables

To clarify the influence of HGF on known cardiovascular risk factor, we also evaluate the association between HGF and other variables **(Table 4)**. Even no factor reveals to be significantly associated with HGF for non-overweight, for overweight BMI shows significantly positively associated with HGF.

Table 4 Simple correlation analysis of hepatocyte growth factor (HGF) and other variables.

	Total subjects		BMI<25.0 kg/m^2		BMI ≥ 25 kg/m^2	
	r	p	r	p	r	p
No. of participants	191		120		71	
Age	0.07	0.339	0.15	0.109	-0.06	0.613
Systolic blood pressure	-0.03	0.704	-0.03	0.752	-0.02	0.872
Diastolic blood pressure	-0.04	0.571	-0.09	0.332	0.02	0.866
Antihypertensive medication use	0.19	0.008	0.15	0.095	0.25	0.037
Body mass index (BMI)	0.17	0.019	0.1	0.298	0.38	0.001
Serum triglycerides (TG)	0.03	0.684	0.04	0.691	-0.01	0.908
Serum HDL-cholesterol (HDL)	-0.15	0.036	-0.15	0.096	-0.12	0.334
Serum γ-glutamyltranspeptidase (γ-GTP)	-0.01	0.871	-0.05	0.575	0.02	0.864
Hemoglobin A1c (HbA1c)	0.08	0.254	0.12	0.18	-0.01	0.929
Glomerular filtration rate (GFR)	-0.02	0.75	-0.01	0.926	-0.03	0.788

Impact of HGF on CIMT

To evaluate the BMI status specific impact of HGF as an index of hypertension-induced vascular damage, we analysis the correlation between HGF and CIMT by BMI status. Simple correlation analysis indicated a significant positive association between HGF and CIMT for non-overweight but not for overweight. Even after adjustment for age, BMI, HDL, HbA1c, And GFR, significant correlation remained **(Table 5).**

Table 5 Correlation analysis of HGF and CIMT.

	Total		BMI<25.0 kg/m^2		BMI ≥ 25 kg/m^2	
	Correlation coefficient	p	Correlation coefficient	p	Correlation coefficient	p
No. of participants	191		120		71	
Model 1	0.18	0.015	0.26	0.004	0.0001	1
Model 2	0.14	0.061	0.22	0.022	0.05	0.717
Model 1: Crude model; Model 2: Adjusted for Age, SBP, anti-hypertensive medication use, BMI, HDL, HbA1c; HGF: Hepatocyte Growth Factor; CIMT: Carotid Intima Media Thickness.						

Discussion

The major finding of present study showed that handgrip strength is significantly inversely associated with HGF in non-overweight hypertensive men. This result indicates that HGF and BMI status may be a useful indicator to evaluate the loss of skeletal muscle mass and function in elderly Japanese men.

HGF is known to play an important role in endothelial maintenance (vascular maintenance) and endothelial repair (vascular repair) [15,16]. Other studies have reported HGF as a possible biochemical index of vascular damage due to hypertension [5-10].

On the other hand, microvascular endothelium disruption and impaired blood flow could be exacerbated by common age-related diseases, including hypertension and sarcopenia [2]. Therefore, HGF might be correlated with age-related loss of skeletal muscle mass and function by indicating the occurrence of microvascular endothelial disruption. Endothelial dysfunction has been recognized as one of the initial mechanisms leading to atherosclerosis (increased arterial stiffness) [17], and another study reported a significant association between increased HGF concentration and carotid atherosclerosis [18]. In our present study, we also found a significant positive association between HGF and CIMT for non-overweight hypertensive men but not hypertensive men. This result partly supports the above-mentioned mechanism. In addition to those, a positive association between handgrip strength and circulating CD34-positive cells among hypertensive men is reported in our previous study [3]. This study indicates that vascular maintenance attributed by circulating CD34-positive cells might compensate for the disturbed handgrip strength triggered by hypertension-induced vascular damage.

The response to muscle injury also might influence the association between handgrip strength and HGF. HGF is present in uninjured myofibers, and may be secreted to the surrounding extracellular matrix upon muscle injury to quickly act on the satellite cell pool [19]. HGF is known to be capable of activating satellite cells [19,20]. This activation leads to myoblast proliferation and terminal differentiation and fusion [21,22] during the muscle repair process. Therefore, HGF might indicate the presence of muscle repair activity.

Our findings may have an important clinical implication. Previous cross-sectional study investigating the association between hypertension and handgrip strength reported inconsistent results. One study reported lower handgrip strength is associated with high blood pressure [23] and another study reported no significant association [24]. This study also reported that higher baseline blood pressure was related to batter muscle strength after 4-years follow up even hypertension is not associated with lower handgrip at baseline [24].

In present study, for hypertensive subjects with non-overweight, HGF was found to be inversely associated with handgrip strength while positively associated with CIMT. Since HGF is known to be a biochemical index of vascular damage due to hypertension [5-10], hypertension induced vascular injury is associated with reduced handgrip. Because hypertension induced vascular repair might prevent the loss of skeletal muscle and development of sarcopenia [3], not hypertension itself but the balance between hypertension induced vascular injury and hypertension induced vascular repair might act as an important determinant factor on the handgrip strength. Further investigation is necessary to clarify those mechanisms.

Potential limitations of this study warrant consideration. Although a significant association was shown between handgrip strength and HGF in non-overweight hypertensive subjects, the influence of micro vascular endothelium disruption on handgrip strength and hypertension are unknown. However, we also found significant association between HGF and CIMT. Satellite cells might also play an important role in the association between handgrip strength and HGF. However, no data on satellite cell activity was analyzed. Further investigation using satellite cell activity will be necessary. Since antihypertensive medication use might influence on the serum concentration of HGF value [25], and in our present study 62.5% of non-overweight and 74.5% of overweight are taking antihypertensive agents, the status of antihypertensive medication use might act as a strong confounding factor on the association between handgrip and HGF. However even we limited the analysis among subjects without taking antihypertensive medication use we found essentially same associations are observed by simple correlation analysis; r=-0.31, p=0.036 for non-overweight (n=45) and r=-0.39, p=0.111 for overweight (n=18). Further study with larger population is necessary. Although the association between handgrip strength and HGF among non-overweight shown to be independent of known cardiovascular risk factors, we did not be adjusted for other potential confounding factors whose values are associated with disruption of micro-circulation such as cytokines (tumor necrosis factor α), advanced glycation products (AGEs), matrix metalloproteinases (MMPs), and mast cells [2]. Even we found significant positive association between handgrip strength and HGF among non-overweight subjects the statistical power is weak (r (simple correlation coefficient) =-0.25, p = 0.006). However, when we limited those analyzes to subjects without taking antihypertensive medication, the statistical power became slightly stronger; r (simple correlation coefficient)=-0.31, p=0.036. Further study with larger study population is necessary. Finally, since this study was cross-sectional, no causal relationships were able to be established.

Conclusions

In conclusion, handgrip strength significantly inversely correlates with HGF in non-overweight hypertensive Japanese men. This result indicates that HGF may be a useful indicator to evaluate loss of skeletal muscle mass and function in the elderly.

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