Original Article

Low haemoglobin levels contribute to low grip strength independent of low-grade inflammation in Japanese elderly women

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Muscle strength declines with age. However, factors that contribute to such declines are not well documented and have not been extensively studied in elderly populations of Asian origin. Correlations of grip strength with a broad range of factors associated with declines in muscle strength were examined in 202 community-living elderly Japanese women. After adjustment for age, grip strength was positively correlated with body weight, height, serum albumin, haemoglobin, high-density lipoprotein cholesterol (HDL-C) and serum iron and inversely with serum copper, and log high-sensitivity C-reactive protein (hsCRP). Multiple linear regression analysis with grip strength as a dependent variable showed that 47.0% of variability of grip strength could be accounted for by height, age and haemoglobin in order of increasing R^2. In conclusion, low haemoglobin may contribute to low muscle strength independently of age, anthropometric, nutritional, and inflammatory markers in the elderly, and may represent an important confounder of the association between grip strength and functional decline in community-living Japanese elderly women.

Key Words: grip strength, haemoglobin, height, age, elderly women

INTRODUCTION

The rapid increase in the prevalence of older persons in the general population has been accompanied by substantial interest in identifying those biomarkers which are able to predict functional decline and mortality in the elderly.[1] Among the biomarkers which predict functional decline in the elderly population, C-reactive protein (CRP), an inflammatory marker, and serum albumin, a laboratory variable commonly used to assess nutritional status, seem to play a major role.[2,3] We have recently shown that a modest increase in serum copper and subtle decreases in serum iron and zinc are associated with inflammatory markers in community-living Japanese elderly women.[4,5]

Grip strength, an approximation of total body muscle strength, has been found to be a robust predictor of functional decline, frailty and mortality.[6-13] However, underlying mechanisms of these associations are poorly understood and have not been extensively studied in elderly populations of Asian origin. Women as compared to men and older people as compared to younger people are known to have lower absolute and relative muscle strength.[14] Therefore, we examined relationships between grip strength and a broad range of factors associated with declines in muscle strength in community-living Japanese elderly women.

PARTICIPANTS AND METHODS

We examined 202 free-living elderly women whose details have previously been reported elsewhere.[4,5,15] Participants were residents in central urban area of Nishinomiya, Hyogo, Japan and were recruited as volunteers by local welfare commissioners. None of the subjects reported to have cancer, or clinically diagnosed acute or chronic inflammatory diseases. However, information was not available on drugs and nutritional supplements which the subjects consumed. Of 202 women, 105 had hypertension (systolic/diastolic blood pressure ≥140/90 mmHg) and 14 had glucose dysregulation (casual plasma glucose ≥140 mg/dL). This research followed the tenets of the Declaration of Helsinki. The study was approved by the Ethics

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Manuscript received 25 July 2014. Initial review completed 19 August 2014. Revision accepted 05 October 2014.
doi: 10.6133/apjcn.2015.24.3.11

Committees of Mukogawa Women's University (No.11-07) and written informed consent was obtained from each participant.

Anthropometric indices and blood pressure were measured between breakfast and lunch and thereafter, and the blood samples were obtained from the cubital vein. Fat mass was measured using an impedance method (In Body 430, Biospace, Tokyo, Japan). Blood pressure was measured using an automated sphygmomanometer (BP-203RV II, Colin, Tokyo, Japan) after participants had rested at least 5 mins.

Grip strength was measured with a handheld dynamometer (T.K.K.5401, Takei Scientific Instruments, Tokyo, Japan). The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand to make sure that the middle phalanx rested on the inner handle. Two trials for the dominant hand were performed and the stronger results were used in analyses. Grip strength was expressed in kilograms (Kg).

Plasma glucose, serum insulin, lipids and lipoproteins were assayed as previously reported.[16,17] Because of non-fasted blood sampling, non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. Adiponectin, leptin and high-sensitivity CRP (hsCRP), a marker of very low levels of inflammation in healthy individuals,[16] were assayed by respective commercially available kits as previously reported.[16,17] Complete blood cell count was analyzed using an automated blood cell counter (Sysmex XE-2100, Sysmex, Kobe, Japan). Serum iron, zinc and copper were measured as previously reported.[4,5]

Serum creatinine was measured enzymatically using an autoanalyzer (AU 5200, Olympus, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was determined using the equation recommended by the Japanese Society for Nephrology.[18]

Data were presented as mean±SD unless otherwise stated. Due to deviation from normal distribution, hsCRP was logarithmically transformed for analysis. Differences between 2 groups were analyzed by *t* test and frequencies of conditions by Chi-square tests. Differences among 3 groups or more were analyzed using analysis of variance. When *p* values in analysis of variance were $p<0.05$, Bonferroni's multiple comparison procedure was performed. Bivariate correlations were evaluated by Pearson correlation analysis. Stepwise multiple linear regression analyses were performed to further indentify the most significant variables contributing to the variation of grip strength. Confounder variables included were age, comorbidities (hypertension and glucose dysregulation) and variables which showed significant associations with grip strength after adjustment for age. The independent association of low grip strength with non-parametric data was examined by multiple logistic analysis. A two-tailed $p<0.05$ was considered statistically significant. All calculations were performed with SPSS system 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

As previously reported,[4,5] participants were apparently healthy, ambulatory elderly women with a similar prevalence of anaemia (haemoglobin <12 g/dL) and reduced renal function (eGFR <60 mL/min/1.73 m^2) to Japanese women aged 70 years and older in the general population. Severe anaemia (haemoglobin <11.0 g/dL) was found only in 11 women (5.4%) and moderate-severe renal insufficiency (eGFR <45 mL/min/1.73 m^2) only in 12 women (5.9%).

Mean grip strength in our participants (20.4±5.3 kg) was slightly lower than an average of 22.2±3.9 kg of Japanese women aged 75-79 years.[19] In Pearson's correlation analysis (Table 1), height and body weight were strongly and positively, and age was strongly and inversely correlated with grip strength. Although there was a modest correlation between grip strength and BMI, there was no correlation with percentage body fat, abdominal circumference and serum leptin. Grip strength showed a positive correlations with serum albumin, iron and zinc. Further, grip strength was inversely correlated with serum TNF-α and adiponectin, and positively correlated with PAI-1. Finally, grip strength showed positive correlations with red blood cell count, haemoglobin and haematocrit.

After adjustment for age (Table 1), correlations with body weight, height, serum albumin, iron and haemoglobin remained significant whereas correlations with BMI, serum zinc, TNF-α, adiponectin, PAI-1, red blood cell count and haematocrit were abolished. Correlations became significant with HDL cholesterol (positive), serum copper (negative), log hsCRP (negative) after controlling for age. Although there was no significant correlation between grip strength and eGFR (r=0.13, not significant) in simple regression analysis, the correlation became significant after adjustment for age but it was inverse (r=-0.20, $p<0.05$). From the pathophysiological point of view, the direction of the correlation is the opposite of what is expected. It may result from over-adjustment for age because eGFR is calculated using the formula including age.

Multiple linear regression analysis was conducted with grip strength as a dependent variable (Table 2). Confounder variables included were age, comorbidities (hypertension and glucose dysregulation) and variables which showed significant associations with grip strength after adjustment for age. We found that 47.0% of variability of grip strength can be accounted for by height, age and blood haemoglobin in order of increasing R^2. We excluded eGFR from dependent variables due to reasons described above.

In our samples, 40 women (19.8%) had anaemia by the WHO criteria (haemoglobin <12 g/dL). Women with anaemia were older and had lower grip strength compared with women without anaemia (Table 3). After adjustment for the same confounder variables as in Table 2, women with anaemia had weaker grip strength than women without anaemia (17.6±0.9 [SE] vs 20.7±0.4 kg, p=0.003). As previously reported[15] and confirmed in the present study, anaemic women had elevated serum adiponectin and creatinine, and lower eGFR and higher prevalence of eGFR <45 mL/min/1.73 m^2 (22.5 vs 1.9%, $p<0.0001$). However, there was no difference in serum levels of inflammatory markers and the prevalence of eGFR ≤45-<60 mL/min/1.73 m^2 between the 2 groups of women.

In order to further confirm the relationship between haemoglobin levels and grip strength, women were divided into quintiles of haemoglobin. This was done because anaemic women belonged to the lowest quintile of haemoglobin. Anaemic women (the lowest quintile; haemoglobin <12.0 g/dL) had lower grip strength than women in the highest (≥13.8 g/dL) and second highest quintiles (13.2-13.9 g/dL) after adjustment for the same confounder variables as in Table 2 (Figure 1). Women in the median quintile (12.6-13.2 g/dL) also had lower grip strength than women in the highest quintile. However, there was no difference in grip strength between anaemic women and non-anaemic women in the second lowest (12.0-12.5 g/dL) and median quintiles of haemoglobin.

Elderly women were divided into 2 groups according to a median value of grip strength; low and high groups. Multiple logistic regression analysis was conducted with low grip strength as a dependent variable. Independent variables included were the same as in the multiple regression analysis in Table 2, except for haemoglobin. Instead anaemia was included as an independent variable. In this model, height, weight and serum albumin were independently associated with low grip strength, but not anaemia (Table 4).

Table 1. Anthropometric and biochemical characteristics of Japanese elderly women studied and correlation coefficients of grip strength before (simple) and after (partial) adjustment for age

Variables	Mean±SD	Grip strength	
		Simple	Partial
Age (years)	76.3±8.2	-0.55***	adjusted
Height (cm)	149±6.2	0.58***	0.47***
Body weight (kg)	49.9±7.7	0.43***	0.33***
BMI (kg/m^2)	22.5±3.1	0.15*	0.09
Body fat percentage (%)	31.8±7.1	-0.01	-0.06
Abdominal circumference (cm)	86.5±9.3	0.03	0.12
Grip strength (kg)	20.4±5.3	1.00	1.00
Systolic blood pressure (mmHg)	143±22	-0.11	-0.10
Diastolic blood pressure (mmHg)	84±13	-0.03	-0.10
Albumin (g/dL)	4.39±0.26	0.39***	0.19
Plasma glucose (mg/dL)	100±29	-0.03	-0.12
Insulin (μU/mL)	8.3±7.5	-0.17	-0.15
Total cholesterol (mg/dL)	219±31	0.12	-0.03
HDL-cholesterol (mg/dL)	64±14	0.09	0.20
Non-HDL-cholesterol (mg/dL)	155±33	0.07	-0.12
TG (mg/dL)	142±79	0.10	-0.09
Serum creatinine (mg/dL)	0.69±0.15	-0.11	0.11
Iron (μg/dL)	94±28	0.18*	0.20*
Copper (μg/dL)	109±15	-0.06	-0.20*
Zinc (μg/dL)	78±12	0.28***	0.12
hsCRP (μg/dL)	85±109	-0.11	-0.18*
Log hsCRP	1.7±0.4	-0.09	-0.20*
TNF-α (pg/mL)	1.6±1.0	-0.22**	-0.12
Leptin (ng/mL)	7.7±4.7	0.03	-0.10
Adiponectin (μg/mL)	14.1±7.8	-0.24***	-0.09
PAI-1 (ng/mL)	26.5±16.5	0.16*	0.07
White blood cells (×10^3/μL)	6.1±1.6	-0.04	-0.12
Red blood cells (×10^4/μL)	424±38	0.30***	0.12
Haemoglobin (g/dL)	12.9±1.2	0.33***	0.21*
Haematocrit (%)	40.9±3.4	0.29***	0.12
Platelets (×10^4/μL)	22.9±5.6	-0.06	-0.17

hsCRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor-α; PAI-1:plasminogen activator inhibitor-1.
Blood was drawn between breakfast and lunch.
*p<0.05, **p<0.01, ***p<0.001.

Table 2. Stepwise multiple linear regression analysis for grip strength as a dependent variable in Japanese elderly women

	Standardized β	p	Cumulative R^2
Height	0.41	<0.001	0.34
Age	-0.32	<0.001	0.44
Haemoglobin	0.17	0.003	0.47

Model included as independent variables age, comorbidities (hypertension and glucose dysregulation) and all variables that showed significant associations with grip strength after age adjustment; height, weight, albumin, iron, haemoglobin, HDL cholesterol, serum creatinine, copper and log high-sensitivity CRP.

Table 3. Characteristics of Japanese elderly women with anaemia using the World Health Organization criteria (haemoglobin <12.0 g/dL)

	Anaemic (n=40)	Non-anaemic (n=162)	*p*
Age (years)	79.9±8.6	75.4±7.9	0.002
Height (cm)	147±6.4	150±6.0	0.045
Body weight (kg)	48.1±8.2	50.5±7.4	0.068
BMI (kg/m^2)	22.1±3.0	22.7±3.1	0.325
Body fat percentage (%)	30.8±7.5	32.0±7.0	0.356
Abdominal circumference (cm)	86.9±8.7	86.4±9.5	0.779
Grip strength (kg)	18.1±5.9	20.9±5.1	0.003
Systolic blood pressure (mmHg)	141±23	144±22	0.415
Diastolic blood pressure (mmHg)	80±12	85±13	0.022
Albumin (g/dL)	4.24±0.27	4.43±0.24	<0.0001
Plasma glucose (mg/dL)	102±44	99±23	0.615
Insulin (μU/mL)	8.2±6.4	8.3±7.9	0.933
Total cholesterol (mg/dL)	206±25	222±32	0.003
HDL-cholesterol (mg/dL)	64±13	64±15	0.984
Non-HDL-cholesterol (mg/dL)	142±25	158±34	0.005
TG (mg/dL)	129±73	145±81	0.276
Serum creatinine (mg/dL)	0.77±0.25	0.67±0.11	0.000
Iron (μg/dL)	80±27	98±27	0.000
Copper (μg/dL)	109±15	109±15	0.715
Zinc (μg/dL)	73±10	79±12	0.002
hsCRP (μg/dL)	79±95	87±113	0.688
Log hsCRP	1.7±0.4	1.7±0.4	0.862
TNF-α (pg/mL)	1.7±0.8	1.6±1.1	0.540
Leptin (ng/mL)	7.1±4.6	7.8±4.7	0.404
Adiponectin (μg/mL)	18.2±10.4	13.1±6.6	<0.0001
PAI-1 (ng/mL)	20.5±7.4	28.0±17.7	0.010
White blood cells (×10^3/μL)	5.9±1.5	6.1±1.6	0.360
Red blood cells (×10^4/μL)	382±31	434±31	<0.0001
Haemoglobin(g/dL)	11.3±0.6	13.3±0.9	<0.0001
Haematocrit (%)	36.5±2.1	42.0±2.7	<0.0001
Platelets (×10^4/μL)	23.1±5.2	22.9±5.7	0.833

Mean±SD or n, %.
hsCRP: high-sensitivity C-reactive protein; TNF-α:tumor necrosis factor-α; PAI-1:plasminogen activator inhibitor-1.

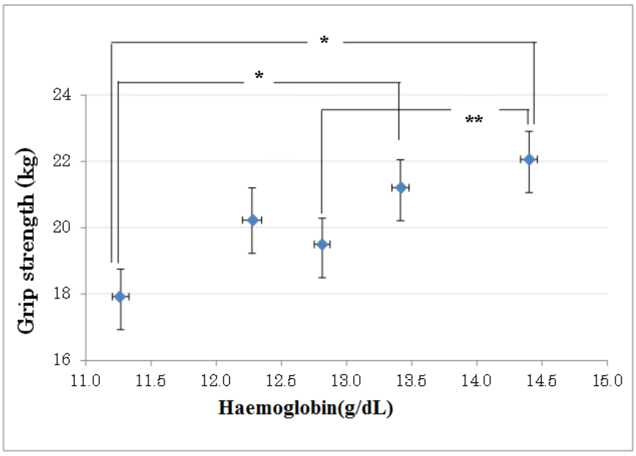

Figure 1. Relationship between grip strength and quintiles of blood haemoglobin in community-living elderly Japanese women. Data are mean±SE after adjustment for the same confounder variables as in Table 2. $^{*}p<0.01$, $^{**}p<0.05$

DISCUSSION

In the present study, we showed that grip strength was correlated with higher hsCRP and serum copper, and lower HDL cholesterol, serum albumin and haemoglobin in community-living elderly women. Among those, low blood haemoglobin was correlated with low grip strength independently of age, comorbidities, anthropometric, nutritional, and inflammatory markers although the relationship between grip strength and haemoglobin was not linear. It is noted that these findings were observed in free- and community-living elderly women who had fewer indicators of disease or malnutrition, such as low BMI, hypoalbuminemia, hypocholesterolemia or renal failure, which are usually considered hallmarks of malnutrition and frailty.

Anaemia has been shown to be associated with weaker muscle strength and poorer physical function in older adults.[20-23] In addition, in older women who are not

Table 4. Associations of grip strength with variables which showed significant associations with grip strength

Variables	OR	95% CI	*p*
Height	1.17	1.08-1.26	<0.001
Weight	1.09	1.03-1.15	0.003
Serum albumin	11.8	2.4-57.4	0.002

anaemic, grip strength[24] is weaker and functional status[25] is worse for those with low-normal haemoglobin (12.0-13.0 g/dL) than those with high-normal haemoglobin values (13.0-14.0 g/dL). These findings may be in line with our observation that grip strength was weaker for those in the median haemoglobin quintile (12.6-13.2 g/dL) than those in the highest haemoglobin quintile (≥13.8 g/dL) in older non-anaemic women. Further, in the present study, the relationship between grip strength and haemoglobin was not linear. Although anaemic women had lower grip strength than women in the highest and second highest haemoglobin quintiles, there was no significant difference in grip strength between anaemic women and those in non-anaemic women in the second lowest and median quintiles of haemoglobin. The failure to detect significant association between anaemia and grip strength (Table 4) may be due in part to a small sample size in anaemia or non-linear relationship between haemoglobin concentrations and grip strength in our sample.

Several biologically plausible mechanisms could explain the link between low haemoglobin and muscle strength in older adults as reviewed by Chaves.[26] Low haemoglobin levels can diminish the maximal capacity of the musculo-skeletal systems to consume oxygen, leading to decreased muscular conditioning. Synergistically, by decreasing oxygen-carrying capacity, low haemoglobin could lead to chronic tissue hypoxia, which in turn would promote further decline in physiologic reserve.

Studies have shown that higher levels of inflammatory markers are associated with lower grip strength.[27-33] Recent findings suggest possible contributions of obesity-associated inflammatory milieu, and impairment of muscle function/strength to adverse functional outcomes.[34] For example, the amount of body fat appears to be the best correlate of CRP[35,36] and randomized studies of weight reduction in older persons with knee osteoarthritis have found reductions in concentrations of CRP, IL-6 and soluble TNF-α receptor.[37] Most of these studies on the relationship between grip strength and inflammation have analyzed single biomarkers or biomarkers for a single pathway of inflammation. The present study examined associations between grip strength and a broad range of factors associated with declines in muscle strength including inflammatory markers and found a significant association of grip strength with haemoglobin independent of inflammatory markers. Another possible explanation is big differences in BMI and hence serum CRP levels. Mean BMI and CRP were 25.9 to 29.4 kg/m^2 and 3.2-3.76 mg/L, respectively, in the aforementioned studies.[27-33] They were 22.5 kg/m^2 and 0.85 mg/L, respectively, in the present study.

Body height was positively related to grip strength in the present study of community-dwelling Japanese elderly women, as previously reported in the elderly[38-40] as well as in the young population.[38] Greater heights would lead to longer arms, with greater lever arm for force generation, resulting in an efficient amount of force.[41]

Several limitations must be acknowledged. The cross-sectional design did not allow causal relationship. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, women who pay more attention to health may be more likely to participate. Biochemical parameters were measured only once. Information on nutritional supplements and drugs which they used to take was not available, so possible contribution of these supplements and drugs to grip strength or other parameters could not be completely excluded. Use of some drugs may or may not be associated with muscle strength.[42,43]

In conclusion, low-normal haemoglobin above the WHO cut-off may contribute to lower muscle strength independently of age, anthropometric, nutritional, and inflammatory markers in the elderly, and may represent important confounders of the association between grip strength and functional decline in community-living Japanese elderly women.

ACKNOWLEDGEMENTS

We are indebted to all the participants for their dedicated and conscientious collaboration. This study was supported by KAKENHI (21300260) of a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science.

AUTHOR DISCLOSURES

There were no conflicts of interest.

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Original Article

Low haemoglobin levels contribute to low grip strength independent of low-grade inflammation in Japanese elderly women

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日本老年妇女低血红蛋白水平是独立于轻度炎症影响低握力强度的因素

肌肉强度随年龄增长而下降。然而，导致这种下降的因素没有好的相关文献记录和广泛研究。该研究分析了 202 名社区居住的老年日本妇女握力强度相关因素与肌肉强度下降的关系。结果表明调整了年龄的影响后，握力强度与体重、身高、血清白蛋白、血红蛋白、高密度脂蛋白胆固醇（HDL-C）、血清铁、血清铜的倒数、高敏 C 反应蛋白（hsCRP）的对数呈正相关。多重线性回归分析显示：以握力强度作为因变量，依据增加的吻合度，握力强度的47%可以被身高、年龄和血红蛋白所解释。总之，在老年人群中，低血红蛋白是独立于年龄、人体测量学、营养和炎症标志物影响低肌肉强度的因素，对社区生活的日本老年妇女，低血红蛋白可能是握力强度和功能减退之间关系的一个重要混杂因子。

关键词：握力强度、血红蛋白、身高、年龄、老年妇女