INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

# Association between the Hemoglobin Levels and Hypertension in Relation to the BMI Status in a Rural Japanese Population: The Nagasaki Islands Study

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## Abstract

**Objective** The hemoglobin levels and blood pressure has been reported in a few studies, and a positive association between the hemoglobin levels and the body mass index (BMI) status has also been documented. A higher BMI may therefore affect the association between the hemoglobin levels and hypertension. However, no published studies have examined this association in relation to the BMI status. The primary purpose of this study was to assess the association between the hemoglobin levels and hypertension in relation to the BMI status.

**Methods** A cross-sectional study of 3,203 non-anemic subjects (1,191 men and 2,012 women, 30-79 years old) who were undergoing general health checkups was conducted.

**Results** A positive association between the hemoglobin levels and hypertension was established for both men and women. For a one SD (standard deviation) increment in hemoglobin, the multivariable odds ratio (ORs) and 95% confidence interval (CIs) for hypertension were 1.21 (95%CI: 1.05-1.40) for men and 1.25 (95%CI: 1.13-1.39) for women. We also found that a significant association was confined to the participants with a BMI of <25 kg/m$^2$. Among the participants with a BMI of <25 kg/m$^2$, the multivariable ORs and 95% CIs for hypertension of a one SD increment in hemoglobin were 1.34 (95%CI: 1.12-1.60) for men and 1.31 (95%CI: 1.16-1.47) for women. Meanwhile, among those with a BMI of ≥25 kg/m$^2$, the corresponding values were 1.01 (95%CI: 0.79-1.30) and 1.09 (95%CI: 0.87-1.37).

**Conclusion** An independent positive association between the hemoglobin levels and the risk of hypertension was observed for both non-anemic Japanese men and women, confined to participants with a BMI of <25 kg/m$^2$.

**Key words:** hemoglobin, BMI, cross-sectional study, hypertension

**(Intern Med 53: 435-440, 2014)**
**(DOI: 10.2169/internalmedicine.53.1353)**

## Introduction

High blood pressure is the leading risk factor for mortality worldwide (1, 2). A Japanese national survey of cardiovascular disease including 10,558 subjects 30 years of age or over reported that the blood pressure levels were significantly related to mortality from stroke, cardiovascular disease and all causes of death in both men and women (3).

Previous studies have found a positive association between the hemoglobin levels and blood pressure (4, 5). Another study reported that treatment with erythropoiesis-stimulating proteins used to treat anemia in hemodialysis patients is related to elevated blood pressure (6). Moreover, a

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Received for publication July 11, 2013; Accepted for publication August 19, 2013
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Dutch study with a large number of healthy volunteer blood donors reported a positive association between the hemoglobin levels and blood pressure (7).

On the other hand, elevated hemoglobin levels have been found in subjects with metabolic syndrome (8, 9), and an Ethiopian study reported a positive association between the hemoglobin levels and BMI in men (9).

However, no studies have been published on the association between the hemoglobin levels and hypertension in relation to the BMI status.

We therefore investigated this association in a Japanese population who took part in a general health checkup between 2005 and 2012.

## Materials and Methods

### Subjects

The survey population comprised 3,940 participants (1,412 men and 2,528 women) 30 to 79 years of age. Residents of a western rural community of the Goto Islands participated in this study between 2005 and 2012. A total of 217 individuals (86 men and 131 women) with missing data, and 520 individuals (135 men and 385 women) with anemia were excluded. There were no differences in cardiovascular disease risk factors between the participants with and without measured blood data. The remaining 3,203 participants (1,191 men and 2,012 women), with a mean age of 63.5 (standard deviation (SD): ±9.7; range: 30-79) years for men and 62.4 (SD: ±9.9; range: 30-79) years for women, were enrolled in this study. This study was approved by the Ethics Committee for Human Use of Nagasaki University (project registration number 0501120073).

### Data collection and laboratory measurements

Systolic and diastolic blood pressures were recorded at rest. Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time of blood collection. Trained interviewers obtained information on the smoking status, drinking status, medical history, use of antihypertensive agents and use of medications for diabetes mellitus. Fasting blood samples were obtained with a EDTA-2K tube and siliconized tube. The serum was separated and centrifuged after blood coagulation using samples obtained from the siliconized tube. The levels of hemoglobin were measured according to the SLS (sodium lauryl sulfate)-hemoglobin method using samples from the EDTA-2K tube. The serum concentrations of triglycerides(TGs), alanine aminotransferase(ALT), γ-glutamyltranspeptidase(γGTP), hemoglobin A1c (HbA1c) and creatinine were measured using standard laboratory procedures. The glomerular filtration rate (GFR) was estimated using an established method with three variations recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative (10), as follows: GFR (mL/min/1.73 $m^2$)=194×(serum creatinine (enzyme method))$^{-1.094}$×(age)$^{-0.287}$× (0.739 for women).

### Definition of disease

Anemia was defined according to the recommendation of the World Health Organization (WHO) Study Group as follows: 13 g/dL > hemoglobin for men and 12 g/dL > hemoglobin for women (11). Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg and/or the use of antihypertensive medications. The HbA1c level (NGSP: National Glycohemoglobin Standardization Program) was calculated using the following equation recently proposed by a working group of the Japanese Diabetes Society (JDS): HbA1c(NGSP)= HbA1c(JDS)+ 0.4% (12). Diabetes was defined as an HbA1c (NGSP) level of ≥6.5% and/or the initiation of glucose-lowering medications or insulin therapy (13).

### Statistical analysis

To prevent the lowering effects of chronic disease on the hemoglobin levels, we selected only participants without anemia and established a reference group for the lowest quartiles of the hemoglobin levels. Differences in the age-adjusted mean values or prevalence of potential confounding factors in relation to the hemoglobin levels were calculated using ANOVA or logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) of hypertension associated with the hemoglobin levels were calculated with the aid of logistic regression models. Two different approaches were used to make adjustments for confounding factors. First, we adjusted only for age. Second, we included other potential confounding factors, that is, the smoking status (never smoker, former smoker, current smoker), alcohol consumption [non-drinker and current light to moderate drinker (1-6 times/week), current heavy drinker (every day)], BMI (kg/$m^2$), history of cardiovascular disease (no, yes), TGs (mg/dL), ALT (IU/L), γGTP(IU/L) and estimated GFR. All statistical analyses were performed with the SAS system for Windows (version 9.3; SAS Inc., Cary, USA). All p values for the statistical tests were two-tailed, and values of < 0.05 were regarded as being statistically significant.

## Results

### Study population

Of the 1,191 men and 2,012 women enrolled in this study, 740 men and 1,158 women were diagnosed with hypertension.

For both men and women, systolic blood pressure, diastolic blood pressure, BMI and the ALT levels exhibited a significant positive association with the hemoglobin levels. A significant positive association between the hemoglobin levels and γGTP levels was observed only in men. In women only, a significant positive association was observed between the hemoglobin and creatinine levels, while a significantly inverse association was observed between the he-

**Table 1. Age-adjusted Mean Values and Percentages in Relation to Hemoglobin Levels**

| | Hemoglobin quartiles | | | | |
|---|---|---|---|---|---|
| | Q1 (low) | Q2 | Q3 | Q4 (high) | p |
| Men | | | | | |
| Median hemoglobin (Hb) level, g/dL | 13.6 | 14.4 | 15.0 | 15.9 | |
| No. at risk | 304 | 274 | 298 | 315 | |
| Age, years | 66.3 ± 8.8 | 63.3 ± 9.4 | 62.1 ± 9.8 | 62.2 ± 10.1 | |
| Systolic blood pressure, mmHg | 139 | 139 | 144 | 145 | <0.001 |
| Diastolic blood pressure, mmHg | 83 | 84 | 87 | 88 | <0.001 |
| Antihypertensive medication use, % | 23.1 | 24.7 | 29.4 | 29.3 | 0.172 |
| History of cardiovascular disease, % | 8.3 | 11.0 | 7.3 | 7.5 | 0.355 |
| Body mass index, kg/m$^2$ | 23.1 | 23.8 | 24.2 | 24.8 | <0.001 |
| Current drinker, % | 50 | 53 | 54 | 55 | 0.650 |
| Current smoker, % | 22 | 26 | 26 | 31 | 0.063 |
| Diabetes, % | 9.6 | 9.5 | 10.2 | 9.9 | 0.995 |
| Serum triglycerides (TGs), mg/dL | 112 | 125 | 136 | 153 | <0.001 |
| Serum alanine aminotransferase (ALT), IU/L | 22 | 24 | 25 | 28 | <0.001 |
| Serum γ-glutamyltranspeptidase (γGTP), IU/L | 39 | 43 | 50 | 54 | 0.005 |
| Serum creatinine, mg/dL | 0.89 | 0.89 | 0.87 | 0.89 | 0.218 |
| Glomerular filtration rate (GFR), mL/min/1.73m$^2$ | 71.0 | 70.5 | 72.2 | 70.3 | 0.422 |
| Women | | | | | |
| Median hemoglobin (Hb) level, g/dL | 12.3 | 12.9 | 13.4 | 14.2 | |
| No. at risk | 481 | 482 | 529 | 520 | |
| Age, years | 62.5 ± 10.1 | 62.0 ± 10.3 | 62.4 ± 9.5 | 62.4 ± 9.9 | |
| Systolic blood pressure, mmHg | 136 | 138 | 141 | 143 | <0.001 |
| Diastolic blood pressure, mmHg | 80 | 82 | 84 | 85 | <0.001 |
| Antihypertensive medication use, % | 27.0 | 26.2 | 30.1 | 31.8 | 0.127 |
| History of cardiovascular disease, % | 6.8 | 4.3 | 5.1 | 4.6 | 0.271 |
| Body mass index, kg/m$^2$ | 22.6 | 22.8 | 23.4 | 23.7 | <0.001 |
| Current drinker, % | 11.7 | 10.6 | 13.8 | 12.2 | 0.453 |
| Current smoker, % | 4.8 | 3.7 | 3.8 | 5.8 | 0.321 |
| Diabetes, % | 4.3 | 6.9 | 4.5 | 7.1 | 0.093 |
| Serum triglycerides (TGs), mg/dL | 116 | 117 | 123 | 127 | 0.053 |
| Serum alanine aminotransferase(ALT), IU/L | 18 | 19 | 20 | 22 | <0.001 |
| Serum γ-glutamyltranspeptidase (γGTP), IU/L | 27 | 24 | 26 | 27 | 0.276 |
| Serum creatinine, mg/dL | 0.69 | 0.69 | 0.71 | 0.70 | 0.017 |
| Glomerular filtration rate (GFR), mL/min/1.73m$^2$ | 70.4 | 70.4 | 67.3 | 68.3 | 0.003 |

Age: mean ± standard deviation. p: p factor. Hemoglobin level quartiles: 13.0-14.0g/dL, 14.1-14.6g/dL, 14.7-15.3g/dL, and >15.3g/dL for men, and 12.0-12.6g/dL, 12.7-13.1g/dL, 13.2-13.7g/dL, and >13.7g/dL for women.

moglobin levels and GFR (Table 1).

### Association between the hemoglobin levels and hypertension among the total subjects

As shown in Table 2, the hemoglobin levels were positively associated with the risk of hypertension in both men and women; the multivariable-adjusted ORs and 95%CIs for hypertension of a one SD increment in hemoglobin were 1.21 (95%CI: 1.05-1.40) for men and 1.25 (95%CI: 1.13-1.39) for women.

### Association between the hemoglobin levels and hypertension in relation to BMI

Another analysis was performed to evaluate the association between BMI on the one hand and the hemoglobin levels and hypertension on the other. We found that BMI was positively associated with both the hemoglobin levels and hypertension. The results of the age-adjusted linear regression analysis of the hemoglobin levels and hypertension per one SD increment in BMI (3.1 kg/m$^2$ for men and 3.4 kg/m$^2$ for women) were, respectively: regression coefficient β=0.23 (95%CI: 0.16, 0.29; p<0.001) and β=0.54 (95%CI: 0.42, 0.65; p<0.001) for men, and β=0.17 (95%CI: 0.12, 0.23; p<0.0001) and β=0.51 (95%CI: 0.42, 0.61; p<0.001) for women. While a similar association was observed for participants with a BMI of <25 kg/m$^2$, for participants with a BMI of ≥25 kg/m$^2$, the association between BMI and the hemoglobin levels was no longer significant. For participants with a BMI of <25 kg/m$^2$, the adjusted linear regression analysis of the hemoglobin levels and hypertension per one SD increment in BMI yielded β=0.12 (95%CI: 0.07, 0.17; p<0.001) and β=0.26 (95%CI: 0.17, 0.34; p<0.001) for men and β=0.07 (95%CI: 0.04, 0.11; p<0.001) and β=0.20 (95% CI: 0.13, 0.27; p<0.001) for women. For participants with a BMI of ≥25 kg/m$^2$, the corresponding values were β=0.04 (95%CI: -0.04, 0.13; p=0.334) and β=0.20 (95%CI: 0.04, 0.35; p=0.013) for men and β=0.07 (95%CI: -0.004, 0.14; p=0.066) and β=0.21 (95%CI: 0.07, 0.34; p=0.003) for women.

### Association between the hemoglobin levels and BMI status

We also investigated the association between the hemoglobin levels and BMI status. Compared with the reference group of BMI<25 kg/m$^2$, we detected significantly higher hemoglobin levels in both men and women with a BMI of ≥25 kg/m$^2$. The age-adjusted hemoglobin level for men was 14.6 g/dL for a BMI of <25 kg/m$^2$ and 15.0 g/dL for a BMI

**Table 2. Sex-specific Odd Ratios (OR) and 95% Confidence Intervals (CI) for Hypertension in Relation to Hemoglobin Levels for All Subjects**

| | Hemoglobin quartiles | | | | | Per 1 SD increment in hemoglobin |
|---|---|---|---|---|---|---|
| | Q1 (low) | Q2 | Q3 | Q4 (high) | p for trend | |
| All subjects | | | | | | |
| Men | | | | | | |
| No. at risk | 304 | 274 | 298 | 315 | | |
| No. of cases (percentage) | 174 (57.2) | 150 (54.7) | 201 (67.4) | 215 (68.3) | | |
| Age-adjusted ORs | 1.00 | 1.09 (0.77-1.53) | 2.11 (1.48-3.01) | 2.19 (1.54-3.11) | <0.001 | 1.38 (1.21-1.58) |
| Multivariable ORs | 1.00 | 0.94 (0.65-1.34) | 1.72 (1.18-2.49) | 1.54 (1.05-2.25) | <0.001 | 1.21 (1.05-1.40) |
| Women | | | | | | |
| No. at risk | 481 | 482 | 529 | 520 | | |
| No. of cases (percentage) | 251 (52.2) | 254 (52.7) | 319 (60.3) | 334 (64.2) | | |
| Age-adjusted ORs | 1.00 | 1.07 (0.81-1.42) | 1.50 (1.14-1.97) | 1.83 (1.39-2.42) | <0.001 | 1.32 (1.19-1.46) |
| Multivariable ORs | 1.00 | 1.06 (0.79-1.41) | 1.34 (1.01-1.78) | 1.62 (1.21-2.17) | <0.001 | 1.25 (1.13-1.39) |

Multivariable ORs: adjusted further for age, body mass index, smoking, alcohol intake, history of cardiovascular disease, diabetes, serum triglycerides (TGs), serum alanine aminotransferase(ALT), serum γ-glutamyltranspeptidase (γGTP) and glomerular filtration rate (GFR). Hemoglobin level quartiles: 13.0-14.0g/dL, 14.1-14.6g/dL, 14.7-15.3g/dL, and >15.3g/dL for men, and 12.0-12.6g/dL, 12.7-13.1g/dL, 13.2-13.7g/dL, and >13.7g/dL for women.

**Table 3. Sex-specific Odd Ratios (OR) and 95% Confidence Intervals (CI) for Hypertension in Relation to Hemoglobin Levels Stratified by BMI**

| | Hemoglobin quartiles | | | | | Per 1 SD increment in hemoglobin |
|---|---|---|---|---|---|---|
| | Q1 (low) | Q2 | Q3 | Q4 (high) | p for trend | |
| BMI<25kg/m$^2$ | | | | | | |
| Men | | | | | | |
| No. at risk | 230 | 179 | 193 | 168 | | |
| No. of cases (percentage) | 115 (50.0) | 90 (50.3) | 120 (62.2) | 107 (63.7) | | |
| Age-adjusted ORs | 1.00 | 1.20 (0.80-1.80) | 2.23 (1.47-3.38) | 2.33 (1.51-3.60) | <0.001 | 1.44 (1.22-1.69) |
| Multivariable ORs | 1.00 | 1.05 (0.68-1.63) | 1.90 (1.22-2.96) | 1.96 (1.23-3.13) | <0.001 | 1.34 (1.12-1.60) |
| Women | | | | | | |
| No. at risk | 377 | 375 | 364 | 353 | | |
| No. of cases (percentage) | 169 (50.1) | 182 (48.5) | 200 (54.9) | 203 (57.5) | | |
| Age-adjusted ORs | 1.00 | 1.20 (0.87-1.64) | 1.61 (1.17-2.21) | 1.93 (1.40-2.67) | <0.001 | 1.33 (1.18-1.49) |
| Multivariable ORs | 1.00 | 1.19 (0.87-1.65) | 1.52 (1.10-2.10) | 1.88 (1.35-2.62) | <0.001 | 1.31 (1.16-1.47) |
| BMI ≥25kg/m$^2$ | | | | | | |
| Men | | | | | | |
| No. at risk | 74 | 95 | 105 | 147 | | |
| No. of cases (percentage) | 59 (79.9) | 60 (63.2) | 81 (77.1) | 108 (73.5) | | |
| Age-adjusted ORs | 1.00 | 0.55 (0.26-1.14) | 1.22 (0.57-2.63) | 1.00 (0.49-2.02) | 0.319 | 1.08 (0.86-1.36) |
| Multivariable ORs | 1.00 | 0.65 (0.31-1.38) | 1.27 (0.58-2.78) | 0.95 (0.46-1.97) | 0.572 | 1.01 (0.79-1.30) |
| Women | | | | | | |
| No. at risk | 104 | 107 | 165 | 167 | | |
| No. of cases (percentage) | 82 (78.8) | 72 (67.3) | 119 (72.1) | 131 (78.4) | | |
| Age-adjusted ORs | 1.00 | 0.61 (0.32-1.18) | 0.76 (0.41-1.42) | 0.99 (0.53-1.87) | 0.651 | 1.12 (0.90-1.39) |
| Multivariable ORs | 1.00 | 0.61 (0.31-1.21) | 0.81 (0.43-1.53) | 0.94 (0.49-1.80) | 0.786 | 1.09 (0.87-1.37) |

Multivariable ORs: adjusted further for age, body mass index, smoking, alcohol intake, history of cardiovascular disease, diabetes, serum triglycerides (TGs), serum alanine aminotransferase(ALT), serum γ-glutamyltranspeptidase (γGTP) and glomerular filtration rate (GFR). Hemoglobin level quartiles: 13.0-14.0g/dL, 14.1-14.6g/dL, 14.7-15.3g/dL, and >15.3g/dL for men, and 12.0-12.6g/dL, 12.7-13.1g/dL, 13.2-13.7g/dL, and >13.7g/dL for women.

of ≥25 kg/m$^2$ (p<0.001). For women, the corresponding values were 13.2 g/dL and 13.4 g/dL, respectively (p=0.009).

### *Association between the hemoglobin levels and hypertension stratified by the BMI status*

Table 3 shows the ORs and 95% CIs for hypertension according to the hemoglobin levels in relation to the BMI status. For both men and women, a significant positive association was observed for participants with a BMI of <25 kg/m$^2$, while no significant associations were observed for those with a BMI of ≥25 kg/m$^2$. For participants with a BMI of <25 kg/m$^2$, the multivariable-adjusted ORs and 95%CIs for hypertension of a one SD increment in hemoglobin were 1.34 (95%CI: 1.12-1.60) for men and 1.31 (95%CI: 1.16-1.47) for women. For participants with a BMI of ≥25 kg/m$^2$, the corresponding values were 1.01 (95%CI: 0.79-1.30) and 1.09 (95%CI: 0.87-1.37), respectively.

To eliminate the influence of menstrual bleeding, we investigated the association between a one SD increment in hemoglobin and the risk of hypertension in elderly women (≥60 years) only and found essentially the same association as for all women: the multivariable ORs and 95%CIs for hypertension for the former group with a BMI of <25 kg/m$^2$ and a BMI of ≥25 kg/m$^2$ were 1.35 (95%CI: 1.16-1.58) and 1.10 (95%CI: 0.82-1.46), respectively.

We also investigated the effects on hypertension of the relationship between the hemoglobin levels and BMI category, that is, a BMI of <25 kg/m$^2$ or a BMI of ≥25 kg/m$^2$. While we found no significant relationships between the hemoglobin levels and BMI category in men, in both all and elderly women (≥60 years), significant association was observed: the multivariable-adjusted p value of this relationship for hypertension was 0.300 for men, 0.028 for all women and 0.004 for elderly women.

## Discussion

The major finding of the present study is that the hemoglobin levels are independently associated with hypertension in both non-anemic Japanese men and women. Moreover, this association was observed only among the participants with a BMI of <25 kg/m$^2$.

A Dutch study of 691,107 voluntary blood donors reported that the hemoglobin levels are positively associated with both systolic and diastolic blood pressure (7). A Germany study of 1,013 unselected persons showed a significant correlation between the hemoglobin levels and blood pressure and a statistically significant correlation between the mean (as well as systolic and diastolic) arterial blood pressure and hemoglobin concentration (r=0.29; p< 0.0001) (4). Our present study found further evidence that these positive associations were confined to participants, both men and women, with a BMI of <25 kg/m$^2$.

It has been reported that elevation of the hemoglobin levels increases blood viscosity and that this augmented viscosity, through its effect on blood pressure, may worsen the cardiovascular function (14). Previous studies of patients with hypertension have provided support for the role of heightened blood viscosity in raising blood pressure (15), but not so in healthy individuals (14). Since our study demonstrated that the significant positive association was confined to the participants with a BMI of <25 kg/m$^2$, the mechanisms underlying this association remain controversial. Further studies of blood viscosity data are therefore needed. Another study reported that treatment with erythropoiesis-stimulating proteins used to treat anemia in hemodialysis patients is related to elevated blood pressure (6). Endothelial dysfunction is recognized to be one of the initial mechanisms and may lead to glomerular injury (16) and atherosclerosis, thus constituting an important link between hemodialysis and atherosclerosis. Vasodilation and vasoconstriction are restricted in the arteries of atherosclerotic individuals, and these functions are important for blood pressure management. Blood pressure may therefore increase with the improvement of anemia. These mechanisms may then explain the positive association between the hemoglobin levels and hypertension, especially in patients with atherosclerosis. A Japanese study of 120 men and 223 women reported that slightly low hemoglobin levels had a beneficial effect on arterial stiffness in community-dwelling women but not men (5). That study partly supports the concept that higher hemoglobin levels indicate the presence of both hypertension and atherosclerosis. As part of our study, we conducted a further investigation of CAVI (Cardio Ankle Vascular Index) data for 1,176 men and 1,994 women, which showed a significant association between the hemoglobin levels and increased arterial stiffness (CAVI ≥9.0), also limited to participants with a BMI of <25 kg/m$^2$. The multivariable-adjusted ORs and 95%CIs for increased arterial stiffness of a one SD increment in hemoglobin for participants with a BMI of <25 kg/m$^2$ and those with a BMI of ≥25 kg/m$^2$ were 1.34 (95%CI: 1.10-1.64) and 0.92 (95%CI: 0.72-1.17) for men and 1.29 (95%CI: 1.10-1.51) and 1.23 (95%CI: 0.95-1.58) for women, respectively. The renin-angiotensin-aldosterone system may also have an effect on the association between the hemoglobin levels and the risk of hypertension. One study reported that subjects with a deficient sympathetic nervous system had erythropoietin-responsive anemia (17), while another study found that angiotensin II may play a role in erythropoietin production (18). Since the sympathetic nervous system regulates the renin-angiotensin-aldosterone system, which is known to affect erythropoietin production, both hemoglobin and blood pressure may be related to this system.

Angiotensin-converting enzyme (ACE) inhibitors (19) and angiotensin receptor antagonists (20) are commonly employed to suppress hemoglobin production. Since angiotensin II has been demonstrated to be a crucial mediator of the development of atherosclerotic lesions (21), the hemoglobin levels may serve as an indicator of the effects of these medications not only on hypertension, but also on atherosclerosis. For verify this hypothesis, further studies using detailed information on antihypertensive medications are needed.

On the other hand, several other studies have suggested that reduced adipose tissue oxygenation and cellular hypoxia may be underlying causes of adipose tissue dysfunction (22-24). Other studies have also reported that, compared to normal-weight subjects, obese participants exhibit reduced adipose tissue oxygenation (22, 25). These studies also reported that erythropoietin gene transcription stimulating factors, such as hypoxia inducible factor-1 (HIF-1), are overexpressed in the adipose tissue of obese subjects. Since hypoxia is known to be a stimulator of hemoglobin production and erythropoietin is known to be a stimulator of hemoglobin synthesis (26), the BMI may well be associated with the hemoglobin levels. In our study, we found, in fact, that both men and women participants with a BMI of ≥25 kg/m$^2$ had significantly higher hemoglobin levels than those with a BMI of <25 kg/m$^2$. Furthermore, we found that the BMI, which is associated with hypertension in both men and women, is positively associated with the hemoglobin levels for a BMI of <25 kg/m$^2$, but not for a BMI of ≥25 kg/m$^2$. Human production of hemoglobin may therefore have reached its maximal level in subjects with a higher BMI, which results in a BMI of ≥25 kg/m$^2$ acting as a confounding factor with respect to the association between the hemoglobin levels and hypertension.

In addition to these findings, our study showed that the significant positive association between the hemoglobin levels and hypertension for participants with a BMI of <25 kg/m$^2$ was independent from classical cardiovascular risks factors, including BMI. This finding may explain the previously mentioned mechanisms.

Some potential limitations of this study warrant consideration. First, the effect of hypertension on the relationship between the hemoglobin levels and BMI categories was significant for women but not for men. However, our analysis of the association between the hemoglobin levels and hypertension stratified by the BMI status showed a similar association for both men and women. This indicates that further investigations with larger numbers of participants are needed. Second, we were unable to adjust for the effects of menstrual bleeding, which may act as a confounding factor with respect to the usual hemoglobin levels. However, limiting our analysis to elderly women (≥60 years) showed essentially the same significant associations. Finally, because this is a cross-sectional study, causal relationships could not be established.

In conclusion, an independent positive association between the hemoglobin levels and the risk of hypertension was observed in both non-anemic Japanese men and women, confined to participants with a BMI of <25 kg/m$^2$. The hemoglobin levels may function as an important tool for evaluating the risk of hypertension in non-overweight participants.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

This work was financially supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (No. 22370090).

## References

1. Ezzati M, Lopez AD, Rodger A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet **360**: 1347-1360, 2002.
2. World Health Organization. The World Health Report 2002. World Health Oragnization, Geneva, 2002.
3. Lida M, Ueda K, Okayama A, et al; Nippon Data 80 Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular disease, heart disease and stroke among Japanese: 14 years follow-up of randomly selected population from Japanese - Nippon data 80. J Hum Hypertens **17**: 851-857, 2003.
4. Göbel BO, Schulte-Göbel A, Weisser B, Glänzer K, Vetter H, Düsing R. Arterial blood pressure. Correlation with erythrocyte count, hematocrit, and hemoglobin concentration. Am J Hypertens **4**: 14-19, 1991.
5. Kawamoto R, Tabara Y, Kohara K, et al. A slightly low hemoglobin levels is beneficially associated with arterial stiffness in Japanese community-dwelling women. Clin Exp Hypertens **34**: 92-98, 2012.
6. Chambers JK. Case study of the anemic patient: epoetin alfa-focus on blood pressure. ANNA J **21**: 154-157, 1994.
7. Atsma F, Veldhuizen I, de Kort W, van Kraaij M, Pasker-de Jong P, Deinum J. Hemoglobin level is positively associated with blood pressure in a large cohort of healthy individuals. Hypertension **60**: 936-941, 2012.
8. Hämäläinen P, Saltevo J, Kautiainen H, Mäntyselkä P, Vanhala M. Erythropoietin. ferritin, haptoglobin, hemoglobin and transferrin receptor in metabolic syndrome: a case control study. Cardiovasc Diabetol **11**: 116, 2012.
9. Nebeck K, Gelaye B, Lemma S, et al. Hematological parameters and metabolic syndrome: findings from an occupational cohort in Ethiopia. Diabetes Metab Syndr **6**: 22-27, 2012.
10. Imai E. Equation for estimating GFR from creatinine in Japan. Nippon Rinsho **66**: 1725-1729, 2008 (in Japanese, Abstract in English).
11. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood **107**: 1747-1750, 2006.
12. Kashiwagi A, Kasuga M, Araki E, et al. Committee on the Standardization of Diabetes Mellitus Related Laboratory Testing of Japan Diabetic Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest **3**: 39-40, 2012.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care **36**: S67-S74, 2013.
14. Vázquez BY. Blood pressure and blood viscosity are not correlated in normal healthy subjects. Vasc Health Risk Manag **8**: 1-6, 2012.
15. Devereux RB, Case DB, Alderman MH, Pickering TG, Chien S, Laragh JH. Possible role of increased blood viscosity in the hemodynamics of systemic hypertension. Am J Cardiol **85**: 1265-1268, 2000.
16. Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am Soc Nephrol **15**: 1983-1992, 2004.
17. Biaggioni I, Robertson D, Krantz S, Jones M, Haile V. The anemia of primary automatic failure and its reversal with recombinant erythropoietin. Ann Intern Med **121**: 181-186, 1994.
18. Freudenthaler SM, Schenck T, Lucht I, Gleiter CH. Fenoterol stimulates human erythropoietin production via activation of the renin angiotensin system. Br J Clin Pharmacol **48**: 631-634, 1999.
19. Azizi M, Rousseau A, Ezan E, et al. Acute angiotensin-converting enzyme inhibition increases the plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. J Clin Invest **97**: 839-844, 1996.
20. Julian BA, Brantley RR Jr, Barker CV, et al. Losartan, an angiotensinogen II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. J Am Soc Nephrol **9**: 1104-1108, 1998.
21. Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. Nature **451**: 904-913, 2008.
22. Pasarica M, Sereda OR, Redman LM, et al. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes **58**: 718-725, 2009.
23. Regazzetti C, Peraldi P, Gremeaux T, et al. Hypoxia decreases insulin signaling pathways in adipocytes. Diabetes **58**: 95-103, 2009.
24. Wood IS, de Heredia FP, Wang B, Trayhurn P. Cellular hypoxia and adipose tissue dysfunction in obesity. Proc Nutr Soc **68**: 370-377, 2009.
25. Cancello R, Henegar C, Viguerie N, et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes **54**: 2277-2286, 2005.
26. Jelkmann W. Erythropoietin: structure, control of production, and function. Physiol Rev **72**: 449-489, 1992.