Higher hemoglobin level is associated with subtle declines in renal function and presence of cardiorenal risk factors in early CKD stages

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Abstract

Background. Patients with advanced renal dysfunction have comorbidities, including anemia, as a consequence of reduced production of erythropoietin. However, little is known about the renal response to early decreases in estimated glomerular filtration rate (eGFR) before the onset of anemia. We therefore investigated the hemoglobin concentration across subtle declines in renal function stratified by cardiorenal risk factors, in subjects with eGFR ≥50 mL/min/1.73 m².

Methods. Based on the data from routine health check-ups in tertiary university hospitals during the last 15 years, 145 865 adult subjects were identified.

Results. Hemoglobin levels among eGFR Groups 2–6 (50 ≤ eGFR < 100 mL/min/1.73m²) were significantly higher compared to eGFR group ≥100 mL/min/1.73m²² (P < 0.001), and the highest level of mean hemoglobin was seen at eGFR 50–59 mL/min/1.73m². The mean hemoglobin level of subjects with eGFR 50–59 mL/min/1.73m² and eGFR ≥100 mL/min/1.73m² were 13.36 (95% confidence interval: 13.33–13.40) g/dL versus 12.92 (95% CI: 12.88–12.95) g/dL in women (P < 0.001); in men, 15.60 (95% CI: 15.57–15.63) g/dL versus 15.15 (95% CI: 15.11–15.18) g/dL (P < 0.001). Among each eGFR group, hemoglobin levels were higher in subjects with hypertension (P < 0.001 in both genders), diabetes mellitus (P < 0.001 in both genders) and components of MS (P < 0.003 in both genders) compared to subjects without these conditions.

Conclusion. Hemoglobin concentration may be slightly higher across subtle declines in renal function and the presence of cardiorenal risk factors in early CKD stages.

Keywords: cardio renal risk factor; glomerular filtration rate; hemoglobin; renal response

Introduction

Prevalence of early stages of chronic kidney disease (CKD) has been increasing [1]. According to decreases in estimated glomerular filtration rate (eGFR), metabolic derangements are developed and associated with morbidities like anemia and mortality [2, 3]. Peritubular fibroblasts of the renal cortex are known to produce erythropoietin (EPO) [4, 5]. In subjects with advanced renal dysfunction, levels of hemoglobin decrease primarily as a consequence of reduced renal production of EPO [6]. The National Health and Nutrition Examination Survey III reported that the prevalence of anemia is increased in the subjects with eGFR <60 mL/min/1.73m²² [7]. Additionally, a cohort study including subjects who had Stage 2 through Stage 5 CKD determined that the eGFR threshold level to detect complications with 90% sensitivity is 44 mL/min/1.73m²² [8]. However, little is known about the renal response to early decreases in eGFR before the onset of clinically evident complications.

Donnelly et al. [9] proposed that the kidney detects changes in tissue oxygen content for EPO production as a critmeter, a regulator of blood volume and hematocrit. When renal function decreases, the macula densa cells respond to the change in luminal delivery of chloride, leading to release of renin and angiotensin II [10]. Angiotensin II increases oxygen consumption as well as decreasing the oxygen supply to the juxta-medullary area of the kidney where EPO is produced [9, 11]. Renal dysfunction is closely related to atherosclerosis and cardiorenal risk factors [12, 13]. Atherosclerosis causes increased oxygen consumption in inflammatory cells and decrease of oxygen diffusion to tissues due to plaques thickening the blood vessel walls [14]. The kidney is exposed to hypoxia, leading to increased hypoxia-inducible factor (HIF) and EPO that subsequently increase hemoglobin [15, 16]. This response of increased hemoglobin in the early phase of renal dysfunction has not been noticed in studies of other large cohorts [7, 17, 18]. In this study, we investigated the hemoglobin concentration across subtle declines in renal function in early CKD stages. We also evaluated hemoglobin concentration under conditions of increased hypoxic stimuli such
as hypertension (HTN), diabetes mellitus (DM) and metabolic syndrome (MS).

Materials and methods

Subjects
We included 145,865 adult subjects, aged ≥ 18 years, who had a voluntary routine health checkup at Seoul National University Hospital from 1995 to 2006 and Seoul National University Bundang Hospital and Healthcare System Gangnam Center from 2003 to 2009. We analyzed data acquired during the first visit if a subject had multiple examinations. The subjects answered questions about smoking and drinking habits, medical history of renal disease, DM, HTN, angina pectoris, acute myocardial infarction and self-medication prior to the examination.

Measurements and definitions
The subjects arrived to the hospitals after an overnight fast of at least 12 h, completed the questionnaires and underwent blood and urine tests. Serum creatinine was measured by Jaffe reaction with an automatic analyzer (TBA-200FR; Toshiba, Tokyo, Japan) in three hospitals except for Seoul National University Hospital from 1995 to 1999 (Hitachi 747; Hitachi Co., Nagashi, Japan). The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation [19]. Proteinuria was determined by urine dipstick test and defined as being protein ≥ 1+. HTN was defined as systolic blood pressure (SBP) of ≥ 140 mmHg, diastolic blood pressure of 90 mmHg or greater, a self-reported history of HTN or use of antihypertension medications. DM was defined as a fasting glucose of ≥ 126 mg/dL, a self-reported history of angina or acute myocardial infarction. Body mass index was calculated based on weight and height [weight (kg)/height (m²)]. The components of MS were defined by the National Cholesterol Education Program ATP III [20]. We classified subjects into seven groups according to eGFR: Group 1, eGFR ≥ 100; Group 2, eGFR 90–99; Group 3, eGFR 80–89; Group 4, eGFR 70–79; Group 5, eGFR 60–69; Group 6, eGFR 50–59 and Group 7, eGFR < 50 mL/min/1.73m².

Statistical analyses
All analyses were performed using SPSS (SPSS version 15.0, Chicago, IL). Data were presented as the mean ± SD for continuous variables and as proportions for categorical variables. Differences in continuous variables were analyzed by one-way analysis of variance tests and by chi-square tests in categorical variables. We analyzed independent factors related to hemoglobin levels by multiple linear regression analysis. Analysis of co-variance (ANCOVA) was used for adjusting independent factors related to hemoglobin. P-values were reported with 0.05 taken as the level of statistical significance. To detect intragroup differences in hemoglobin levels among eGFR groups we used Bonferroni’s correction for significant level of P-value (P < 0.001), DM (P < 0.001), antihypertensive medication (P < 0.001) and a history of smoking (P < 0.001) and eGFR (P < 0.001) by multiple linear regression analysis.

The hemoglobin levels among eGFR groups

The hemoglobin levels of eGFR Groups 2–6 were higher compared to Group 1 (P < 0.001) using ANCOVA adjusted by age, SBP, total cholesterol, antihypertensive medication, DM and smoking history in both genders.

Among women, the mean hemoglobin in eGFR Group 1 was 12.92 g/dL [95% confidence interval (CI): 12.88–12.95]; Group 6, 13.36 g/dL (95% CI: 13.33–13.40). In men, the mean hemoglobin of eGFR Group 1 was 15.15 g/dL (95% CI: 15.11–15.18); Group 6, 15.60 g/dL (95% CI: 15.57–15.64). The mean value of hemoglobin maximized in Group 6. The difference in mean hemoglobin levels between Groups 1 and 6 was 0.4465 g/dL (95% CI: 0.4439–0.4491) in women and 0.4589 g/dL (95% CI: 0.4588–0.4590) g/dL in men (Figure 1).

P for trend was analyzed in eGFR Groups 1–6 in both genders (P < 0.001) (Table 1).

The hemoglobin levels according to SBP in each eGFR group

We divided the subjects into five groups according to levels of SBP (Group A: < 110 mmHg; Group B: 110–119 mmHg; Group C: 120–129 mmHg; Group D: 130–139 mmHg and Group E: ≥ 140 mmHg). The hemoglobin values in SBP Groups B–E were significantly higher compared to SBP group A in each eGFR group among women (P < 0.001) and men (P ≤ 0.002) with the criteria of P-value by Bonferroni’s correction.

Fig. 1. The distribution of hemoglobin level among eGFR groups in each gender. *Hemoglobin levels among eGFR Groups 2–6 were significantly higher compared to eGFR Group 1 (P < 0.001), mean hemoglobin values were not significantly different only between eGFR Groups 5 and 6 among men. **Hemoglobin levels among eGFR Groups 2–6 were significantly higher compared to eGFR Group 1 (P < 0.001); mean hemoglobin values were not significantly different only between eGFR Groups 2 and 3 among women. The hemoglobin value is adjusted by age, SBP, serum total cholesterol, antihypertensive medication, DM and smoking history using co-variance (ANCOVA) analysis. Error bars show the SEM. eGFR, calculated glomerular filtration rate by modified MDRD equation (mL/min/1.73m²).
Elevated hemoglobin associated with subtle decrease of GFR

**Table 1.** Mean hemoglobin level among eGFR groups in each gender

<table>
<thead>
<tr>
<th>eGFR group, mL/min/1.73m²</th>
<th>Group 1 (≥100)</th>
<th>Group 2 (90–99)</th>
<th>Group 3 (80–89)</th>
<th>Group 4 (70–79)</th>
<th>Group 5 (60–69)</th>
<th>Group 6 (50–59)</th>
<th>P for trend</th>
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<tr>
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<td>6445</td>
<td>12 181</td>
<td>19 267</td>
<td>14 931</td>
<td>3470</td>
<td></td>
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<tr>
<td>Estimated mean of hemoglobin</td>
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<td>12.98</td>
<td>12.98</td>
<td>13.16</td>
<td>13.32</td>
<td>13.41</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Men</strong></td>
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<td></td>
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<tr>
<td>N</td>
<td>3232</td>
<td>6798</td>
<td>16 894</td>
<td>23 752</td>
<td>14 582</td>
<td>3011</td>
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<tr>
<td>Estimated mean of hemoglobin</td>
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<td>15.25</td>
<td>15.34</td>
<td>15.46</td>
<td>15.59</td>
<td>15.62</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The hemoglobin value is adjusted by age, SBP, serum total cholesterol, antihypertensive medication and smoking history using co-variance (ANCOVA) analysis.

Among women, the highest level of mean hemoglobin was found in eGFR Group 6 in each SBP group (13.29 ± 1.07, 13.39 ± 1.04, 13.40 ± 1.02, 13.54 ± 0.98 and 13.56 ± 1.07 g/dL in SBP Groups A, B, C, D and E, respectively). The differences in mean hemoglobin levels between eGFR Groups 1 and 6 were 0.53 ± 0.05, 0.46 ± 0.03, 0.44 ± 0.14, 0.56 ± 0.31 and 0.44 ± 0.08 g/dL in SBP Groups A, B, C, D and E, respectively. The hemoglobin levels of eGFR Groups 3–6 were higher compared to eGFR Group 1 among SBP Group A (P < 0.001) and eGFR Groups 4–6 were higher compared to eGFR Group 1 in SBP Groups B, C, D and E (P < 0.001) (Figure 2A). Among men, the highest level of mean hemoglobin was recorded in eGFR Group 5 (15.41 ± 1.07, 15.54 ± 1.07, 15.59 ± 1.06, 15.59 ± 1.11 and 15.55 ± 1.15 g/dL in SBP Groups A, B, C, D and E, respectively). The differences in mean hemoglobin between eGFR Groups 1 and 5 were 0.40 ± 0.05, 0.35 ± 0.09, 0.30 ± 0.04, 0.34 ± 0.00 and 0.27 ± 0.05 g/dL in SBP Groups A, B, C, D and E, respectively. The hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in SBP Groups A, B and D (P < 0.05); eGFR Groups 3–5 were higher compared to eGFR Group 1 in SBP Group C (P < 0.001) and eGFR Groups 2–5 were higher compared to eGFR Group 1 in SBP Group E (P < 0.05) (Figure 2B).

The hemoglobin levels according to the presence of HTN in each eGFR group

The hemoglobin level in subjects with HTN was significantly higher compared to subjects without HTN (P ≤ 0.001), even with the criteria of P-value by Bonferroni’s correction in eGFR Groups 1–6 in women and eGFR Groups 1–5 in men. Compared to the hemoglobin level of eGFR Group 1 among women, eGFR Groups 3–6 of normotensive subjects showed higher hemoglobin levels (P ≤ 0.005) and along with of hypertensive subjects in eGFR Groups 4–6 (P < 0.001). Among eGFR groups, the highest value of mean hemoglobin was found in eGFR Group 6 (13.37 ± 1.02 g/dL in normotensive women and 13.52 ± 1.08 g/dL in hypertensive women). The differences in mean hemoglobin between eGFR Groups 1 and 6 were 0.52 ± 0.11 g/dL in normotensive women and 0.39 ± 0.11 g/dL in hypertensive women (Figure 3A).

Among men, the hemoglobin levels of eGFR Groups 2–6 were higher compared to Group 1 in normotensive subjects (P < 0.001) and eGFR Groups 3–5 in hypertensive subjects (P ≤ 0.001). The peak level of mean hemoglobin was found in eGFR Group 5 (15.51 ± 1.07 g/dL in normotensive men and 15.58 ± 1.12 g/dL in hypertensive men). The differences in mean hemoglobin between eGFR Groups 1 and 5 were 0.37 ± 0.06 g/dL in normotensive subjects and 0.22 ± 0.02 g/dL in hypertensive subjects (Figure 3B).

The hemoglobin levels according to the presence of DM in each eGFR group

The hemoglobin level in the DM group was higher compared to that of the non-DM group in eGFR Groups 1–5 among women (P ≤ 0.001) and eGFR Groups 1–3, 5 and 6 among men (P ≤ 0.001) with P-value criteria of Bonferroni’s correction. Among women, the mean hemoglobin level reached its peak in eGFR Group 6 of the non-DM group (13.42 ± 1.02 g/dL) and in eGFR Group 5 of the DM group (13.54 ± 1.05 g/dL). The differences in mean hemoglobin levels between eGFR Groups 1 and 6 were 0.56 ± 0.10 g/dL in the non-DM group but the differences of it between eGFR Groups 1 and 5 were only 0.09 ± 0.26 g/dL in DM group (Figure 4A).

Among men, the highest level of mean hemoglobin was found in eGFR Group 5 of the non-DM group (15.54 ± 1.07 g/dL) and in eGFR Group 3 of the DM group (15.50 ± 1.11 g/dL). The differences in mean hemoglobin between peak level and that of eGFR Group 1 were 0.37 ± 0.07 g/dL in the non-DM group and 0.13 ± 0.04 g/dL in the DM group (Figure 4B).

The hemoglobin levels according to the number of components of MS in each eGFR group

We divided subjects according to the number of MS components (0, 1, 2 and ≥3) into four groups (MS 0, 1, 2 and 3, respectively). Compared to the hemoglobin levels of MS Group 0, that of MS Groups 2–3 were higher among eGFR Groups 2–6 (P ≤ 0.003) among both genders, and hemoglobin levels of MS Group 1 were higher among eGFR Groups 4–5 among women (P < 0.001) and eGFR Groups 2–6 among men (P ≤ 0.003), with P-value criteria of Bonferroni’s correction. Among women, the highest level of mean hemoglobin was found in eGFR Group 6 (13.29 ± 1.01, 13.41 ± 1.06, 13.45 ± 1.04 and 13.64 ± 1.05 g/dL in MS Groups 0, 1, 2 and 3, respectively). The differences in
mean hemoglobin between the peak value and that of eGFR Group 1 were $0.48 \pm 0.07$, $0.58 \pm 0.10$, $0.46 \pm 0.15$ and $0.37 \pm 0.16$ g/dL in MS Group 0, 1, 2 and 3, respectively. The hemoglobin levels of eGFR Groups 4–6 were higher compared to eGFR Group 1 in MS Groups 0, 2 and 3 ($P < 0.001$) and eGFR Groups 3–6 in MS Group 1 ($P < 0.05$) (Figure 5A).

Among men, the highest level of mean hemoglobin was recorded in eGFR Group 5 (15.30 ± 1.04, 15.47 ± 1.07, 15.61 ± 1.06 and 15.76 ± 1.14 g/dL in MS Group 0, 1, 2 and 3, respectively).

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**Fig. 2.** The distributions of hemoglobin levels according to SBP in each eGFR group. (A) Women: *$P < 0.003$, hemoglobin levels of GFR Groups 3–6 were higher compared to GFR Group 1 in patients with SBP $< 110$ mmHg. **$P < 0.001$, hemoglobin levels of GFR Groups 4–6 were higher compared to GFR Group 1 in patients with SBP 110–119 mmHg. ††$P < 0.001$, hemoglobin levels of GFR Groups 4–6 were higher compared to GFR Group 1 in patients with SBP 120–129 mmHg. †$P < 0.001$, hemoglobin levels of GFR Groups 4–6 were higher compared to GFR Group 1 in patients with SBP 130–139 mmHg. ‡‡$P < 0.001$, hemoglobin levels of GFR Groups 4–6 were higher compared to GFR Group 1 in patients with SBP $\geq 140$ mmHg. §Hemoglobin levels of SBP 110–119 were higher compared to SBP $< 110$ mmHg in GFR Groups 2, 4 and 5 ($P < 0.001$); hemoglobin levels of SBP 120–129 were higher compared to SBP $< 110$ mmHg in GFR Groups 2–6 ($P < 0.001$); hemoglobin levels of SBP $\geq 140$ mmHg were higher compared to SBP $< 110$ mmHg in GFR Groups 1–6 ($P < 0.001$). (B) Men: *$P < 0.005$, hemoglobin levels of GFR Groups 2–6 were higher compared to GFR Group 1 in patients with SBP $< 110$ mmHg. **$P < 0.05$, hemoglobin levels of GFR Groups 2–6 were higher compared to GFR Group 1 in patients with SBP 110–119 mmHg. ††$P < 0.001$, hemoglobin levels of GFR Groups 3–5 were higher compared to GFR Group 1 in patients with SBP 120–129 mmHg. †††$P < 0.05$, hemoglobin levels of GFR Groups 2–5 were higher compared to GFR Group 1 in patients with SBP $\geq 140$ mmHg. §Hemoglobin levels of SBP 110–119 mmHg were higher compared to SBP $< 110$ mmHg in GFR Groups 2–6 ($P < 0.001$); hemoglobin levels of SBP 120–129 mmHg were higher compared to SBP $< 110$ mmHg in GFR Groups 1–5 ($P < 0.001$); hemoglobin levels of SBP $\geq 140$ mmHg were higher compared to SBP $< 110$ mmHg in GFR Groups 1–5 ($P < 0.001$). Error bars show the SEM. eGFR, calculated glomerular filtration rate by modified MDRD equation (ml/min/1.73m²).
The differences in mean hemoglobin between the peak value and that of eGFR Group 1 were 0.34 \(\pm\) 0.05, 0.39 \(\pm\) 0.10, 0.32 \(\pm\) 0.08, and 0.20 \(\pm\) 0.09 g/dL in MS Group 0, 1, 2, and 3, respectively. The hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients with HTN. *P < 0.001, hemoglobin levels of eGFR Groups 3–6 were higher compared to eGFR Group 1 in patients with HTN. †Hemoglobin levels in HTN groups were higher compared to no HTN groups within the same eGFR group (P < 0.001), except for eGFR Group 7. (B) Men: *P < 0.001, hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients without HTN. **P \(\leq\) 0.001, hemoglobin levels of eGFR Groups 3–5 were higher compared to eGFR Group 1 in patients with HTN. †Hemoglobin levels in HTN groups were higher compared to no HTN groups within the same eGFR group (P \(\leq\) 0.001), except for eGFR Groups 6 and 7. Error bars show the SEM. eGFR, calculated glomerular filtration rate by modified MDRD equation (mL/min/1.73m\(^2\)).

**Discussion**

We observed elevation of hemoglobin across subtle decline in renal function before the emergence of anaemia. We also noticed that hemoglobin levels were higher along with SBP elevation, increased number of MS components and with HTN and DM. However, the difference between the peak level of mean hemoglobin and that of eGFR Group 1 was blunted when cardiovascular risk factors were present. These observations suggested some possibilities that pre-existing conditions might exist before subtle declines in renal function in subjects with cardiorenal risk factors. This might result from an increase in tissue hypoxia seen in early diabetic kidney and angiotensin II-related HTN [21, 22].

The kidney receives 20–25% of the cardiac output but is prone to hypoxia partly because of its peculiar capillary system and high rate of oxygen consumption per gram of tissue [23, 24]. Donnelly et al. [9] found that the kidney senses red blood cells mass and relative plasma volume through tissue oxygen content. More than 80% of oxygen consumption in the kidney is needed for sodium reabsorption in normal kidney and is directly linked to glomerular filtration rate (GFR). However, in animal models of early
CKD, GFR was reduced to 62% of baseline value and oxygen consumption factored by sodium reabsorption was increased. These data imply that there may be an increase of ‘work’ other than sodium reabsorption [11]. Renin–angiotensin system (RAS) could be related to increased work of kidney because oxygen consumption and hypoxic insult improve through blocking RAS [11, 25–28]. When GFR starts to decrease, the macula densa cells respond to reduced luminal delivery of chloride, leading to release of renin, and angiotensin II is activated by its release [10]. Angiotensin II increases oxygen consumption and decreases oxygen supply through constriction of vasa recta [9]. As a result, RAS activation due to decreased GFR leads to a shortage of oxygen in the kidney. After the kidney is exposed to hypoxia, protein levels of HIF are increased and induce transcription of EPO and other cellular processes to compensate for the hypoxia [15, 16].

Increased production of EPO could result in increases in hemoglobin values as indicated by the results of our study, showing that higher hemoglobin levels were observed across subtle decline of eGFR.

National Health and Nutrition Examination Survey (NHANES) III showed slight elevation of blood hemoglobin in 60 < eGFR < 90 mL/min/1.73m² in a graph of

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**Fig. 4.** The mean values of hemoglobin among eGFR groups in patients with and without DM. (A) Women: *P ≤ 0.001, hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients without DM. **P ≤ 0.001, hemoglobin levels of eGFR Group 7 were significantly different compared to eGFR Group 1 in patients with DM. Hemoglobin levels were significantly different between no DM and DM groups within the same eGFR group (P ≤ 0.001), except for eGFR Groups 6 and 7. (B) Men: *P ≤ 0.001, hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients without DM. **P ≤ 0.001, hemoglobin levels of eGFR Group 7 were significantly different compared to eGFR Group 1 in patients with DM. Hemoglobin levels were significantly different between no DM and DM groups within the same eGFR group (P ≤ 0.001), except for eGFR Group 4. Error bars show the SEM. eGFR, calculated glomerular filtration rate by modified MDRD equation (mL/min/1.73m²).
Elevated hemoglobin associated with subtle decrease of GFR

hemoglobin percentile by GFR adjusted to age of 60 years [7]. In the data of Kidney Early Evaluation Program and NHANES 1999–2004, serum hemoglobin was 13.5, 13.7 and 13.5 g/dL in CKD Stages 1, 2 and 3, respectively [17]. In Atherosclerosis Risk in Communities study, hemoglobin concentration was 13.1 g/dL in eGFR ≥90 mL/min/1.73m², 13.3 g/dL in 75–89 mL/min/1.73m² and 13.1 g/dL in 60–74 mL/min/1.73m² [18]. Although subtle elevations of hemoglobin concentration were shown constantly, these findings have not received the attention. In this study, we noted the significance on the higher hemoglobin concentration across subtle declines in renal function.

A few studies reported that cardiovascular risk factors are associated with elevated hemoglobin. Hemoglobin levels in patients with Type 1 DM are higher than those of the

![Graph A](image)

**Fig. 5.** The hemoglobin levels among eGFR groups according to number of MS components. (A) Women: *P < 0.001, hemoglobin levels of eGFR Groups 4–6 were higher compared to eGFR Group 1 in patients with no components of MS. **P < 0.05, hemoglobin levels of eGFR Groups 3–6 were higher compared to eGFR Group 1 in patients with one component of MS. †P < 0.001, hemoglobin levels of eGFR Groups 4–6 were higher compared to eGFR Group 1 in patients with two components of MS. ‡P < 0.001, hemoglobin levels of eGFR Groups 4–6 were higher compared to eGFR Group 1 in patients with more than three components of MS. §Hemoglobin levels in individuals with three components of MS were higher compared to ones with no components within eGFR Groups 1–6 (P < 0.001); hemoglobin levels in patients with one component of MS were higher compared to ones with two components of MS within eGFR Groups 4–6 (P < 0.001); hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients with no components of MS. *P < 0.001, hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients with one component of MS. **P < 0.001, hemoglobin levels of eGFR Groups 2–6 were higher compared to eGFR Group 1 in patients with two components of MS. †P < 0.003, hemoglobin levels in patients with one component of MS were higher compared to ones with no components within eGFR Groups 2–6 (P ≤ 0.003). Error bars show the SEM. eGFR, calculated glomerular filtration rate by the modified MDRD equation (mL/min/1.73m²). Numbers of abnormalities among MS components was defined by the National Cholesterol Education Program ATP III as described in Materials and Methods section.
general population [29]. Diabetic subjects with stroke had higher plasma hematocrit than other diabetic subjects [30]. Atherosclerosis is one of the fundamental pathophysiological mechanisms underlying cardiovascular disease. As the number of cardiovascular risk factors increase, the severity of atherosclerosis is also increased [31]. Atherosclerosis induces hypoxia and is also caused by hypoxia [9, 32, 33].

Our data revealed that hemoglobin values were elevated when HTN, DM and other components of MS exist. Obesity is associated with insulin resistance in peripheral tissues, often leading to Type 2 DM. Insulin resistance and adipokines can lead to vascular endothelial dysfunction, hyperlipidemia and HTN. As a result, development of atherosclerosis is promoted [34–36]. We considered the serial elevation of hemoglobin to be the most apparent with the increase in the number of metabolic syndrome components because these are more highly correlated with atherosclerosis than other cardiorenal risk factors.

However, cardiorenal risk factors did not significantly affect hemoglobin levels in men compared to women. The hemoglobin levels showed an inverse relationship with aging in men, and the differences in hemoglobin values between individuals <30 years old and ≥80 years old were 1.49 ± 0.57 mg/dL in men and 0.20 ± 0.29 mg/dL in women. Testosterone is associated with increased levels of hemoglobin [27, 37, 38]; therefore, we hypothesized that the change in testosterone levels according to age might result in differences in hemoglobin levels in men. In addition, there were significant differences in age among male subjects with HTN, DM and low SBP and ones without HTN, DM and high SBP (HTN, 54.8 ± 11.6; no HTN, 48.8 ± 11.8; DM, 57.3 ± 10.4; no DM, 49.8 ± 12.0; SBP Group A, 48.4 ± 11.2; SBP Group E, 56.7 ± 12.2 years).

In addition, menopausal status could affect hemoglobin level in women. Although menopausal status was not identified, the mean difference of hemoglobin was assessed stratified by the average age of natural menopause in Korea [39]. Mean hemoglobin of women aged ≥50 years (N = 37 369) was 13.26 ± 1.03 and aged <50 years (N = 32 117) was 12.98 ± 1.16 and this showed an opposite trend compared with men. Menopause might explain higher hemoglobin level in older women.

Thirdly, other possible explanation of hemoglobin levels among men was a higher smoking rate. Mean hemoglobin levels in current smokers were higher than those of nonsmokers or ex-smokers (15.54 versus 15.34 g/dL). The percent of smokers among men without DM was higher than that among diabetic men (33.6 versus 32.3%). Additionally, the percent of smokers was higher among normotensive men compared to hypertensive men (35.6 versus 28.4%).

Our study had several limitations. Firstly, eGFR was calculated using the MDRD study equation [19] but the accuracy of this equation has not been fully validated in the Korean population and had a limitation at near-normal range, especially. Recently, Cha et al. [40] presented the results of study designed to validate this equation in the Korean population. Based on these data, we analyzed 95% CI of systemic inulin clearance according to eGFR group. The 95% CI systemic inulin clearance of eGFR ≥ 100 mL/min/1.73m² was 86.32–97.74 mL/min/1.73m², 95% CI of 60 ≤ eGFR <70 was 48.93–61.71. We regrouped subjects based on 95% CI of systemic inulin clearance: eGFR Group A, 86.32–97.74; eGFR Group B, 48.93–61.71 mL/min/1.73m². Among women, the mean hemoglobin in eGFR Group A was 13.06 g/dL (95% CI: 13.04–13.07); Group B, 13.41 g/dL (95% CI: 13.38–13.44). In men, eGFR Group A was 15.27 g/dL (95% CI: 15.25–15.29); Group B, 15.64 g/dL (95% CI: 15.61–15.68). The difference of mean hemoglobin levels between Groups A and B was similar to that of eGFR Groups 1 and 5.

Secondly, 13.4% subjects of serum creatinine were analyzed by different types of machine in 1995–99; however, comparing data before and after 1999, the same trend was observed. Thirdly, we did not exclude nonrenal causes of anaemia. This might not affect our results because we included a large numbers of subjects in our study. Fourthly, the definition of ‘ex-smoker’ is unclear, and the extent of smoking was not verified. However, the differences of hemoglobin level among current smoker, ex-smoker and non-smoker are compatible to those of another published study [41]. Fifthly, we did not verify type or dose of antihypertensive medication. Finally, this study was not randomized.

Hemoglobin concentration was higher across subtle declines in renal function and cardiovascular risk factors were present in early CKD stages. Further investigations are needed to verify this possibility and the clinical significance of changes of hemoglobin according to eGFR.

Conflict of interest statement. None declared.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Elevated hemoglobin associated with subtle decrease of GFR


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Received for publication: 23.12.10; Accepted in revised form: 26.4.11