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# Association Between the Presence of Iron Deficiency Anemia and Hemoglobin A1c in Korean Adults

## *The 2011–2012 Korea National Health and Nutrition Examination Survey*

*Jae W. Hong, Cheol R. Ku, Jung H. Noh, Kyung S. Ko, Byoung D. Rhee, and Dong-Jun Kim*

**Abstract:** Few studies have investigated the clinical effect of iron deficiency anemia (IDA) on the use of the Hemoglobin A1c (HbA1c) as a screening parameter for diabetes or prediabetes. We investigated the association between IDA and HbA1c levels in Korean adults.

Among the 11,472 adults (≥19 years of age) who participated in the 2011–2012 Korea National Health and Nutrition Examination Survey (a cross-sectional and nationally representative survey conducted by the Korean Center for Disease Control for Health Statistics), 807 patients with diabetes currently taking anti-diabetes medications were excluded from this study. We compared the weighted HbA1c levels and weighted proportion (%) of HbA1c levels of ≥5.7%, ≥6.1%, and ≥6.5% according to the range of fasting plasma glucose (FPG) levels and the presence of IDA.

Among 10,665 participants (weighted n = 35,229,108), the prevalence of anemia and IDA was 7.3% and 4.3%, respectively. The HbA1c levels were higher in participants with IDA (5.70% ± 0.02%) than in normal participants (5.59% ± 0.01%; $P < 0.001$), whereas there was no significant difference in FPG levels. In participants with an FPG level of <100 mg/dL and 100 to 125 mg/dL, the weighted HbA1c level was higher in those with IDA (5.59% ± 0.02% and 6.00% ± 0.05%) than in normal participants (5.44% ± 0.01% and 5.82% ± 0.01%) after adjusting for confounders such as age, sex, FPG level, heavy alcohol drinking, waist circumference, and smoking status as well as after exclusion of an estimated glomerular filtration rate of <60 mL/min/1.73 $m^2$ ($P < 0.001$, <0.01). The weighted proportions (%) of an HbA1c level of ≥5.7% and ≥6.1% were also higher in participants with IDA than in normal participants ($P < 0.001$, <0.05). However, the weighted HbA1c levels in individuals with an FPG level ≥126 mg/dL and a weighted proportion (%) of an HbA1c level of ≥6.5% showed no significant differences according to the presence of IDA.

In conclusion, the presence of IDA shifted the HbA1c level upward only in the normoglycemic and prediabetic ranges, not in the diabetic range. Therefore, IDA should be considered before using HbA1c as a screening test for prediabetes.

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From the Department of Internal Medicine, Ilsan-Paik Hospital, College of Medicine, Inje University, Koyang, Gyeonggi-do, Republic of Korea; (JWH, JHN, D-JK); Endocrinology, Yonsei University College of Medicine, Seoul, South Korea (CRK) and Department of Internal Medicine, Sanggye Paik Hospital, Cardiovascular and Metabolic Disease Center, College of Medicine, Inje University, Seoul, Republic of Korea (KSK, BDR).
Correspondence: Dong-Jun Kim, Department of Internal Medicine, Ilsan-Paik Hospital, 2240 Daehwa-dong, Ilsanseoku, Koyang City, Gyonggi-do, 411-706, Republic of Korea (e-mail: djkim@paik.ac.kr).
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**Abbreviations**: ADA = The American Diabetes Association, FPG = fasting plasma glucose, IDA = iron deficiency anemia, KNHANES = Korea National Health and Nutrition Examination Survey.

## INTRODUCTION

Hemoglobin A1c (HbA1c) is formed by glycation of the $NH_2$-terminal valine residue of the β-chain of hemoglobin (Hb). It is commonly used as a marker of glucose control when monitored over 3 months, and provides information on the risk of long-term complications in patients with diabetes. HbA1c is also used to diagnose diabetes and to identify individuals that are at high risk for developing diabetes.[1] The American Diabetes Association (ADA) has suggested that an HbA1c level of ≥6.5% is the diagnostic cutoff point for diabetes and that a level of 5.7% to 6.4% is the threshold for prediabetes.[2] Measurement of HbA1c levels to screen for diabetes or prediabetes has many advantages over measurement of the fasting plasma glucose (FPG) level or performance with the 75-g oral glucose tolerance test (OGTT). However, HbA1c levels can be influenced by a variety of factors, including age, ethnicity, smoking, and conditions that alter red cell turnover and glucose homeostasis.[3–6]

One condition that affects erythrocyte turnover is anemia. Anemia may be associated with more rapid erythrocyte turnover, which decreases the HbA1c level, or with slower turnover of or changes in the 3-dimensional configuration of Hb, which elevates the HbA1c level.[7] Iron and vitamin B12 deficiency, renal failure, and bone marrow suppression in alcoholism inhibit erythropoiesis and increase the mean survival duration of erythrocyte, leading to increase HbA1c. However, hemolytic anemia, chronic liver disease, and increased hemolysis from splenomegaly increase reticulocyte and decrease the mean age of erythrocyte, which can decrease HbA1c level.[7] Furthermore, numerous hemoglobinopathies, including HbAS, HbAC, HbE, and HbD, can also influence HbA1c level.

The prevalence of anemia is estimated about 10% to 30% in patients with diabetes.[8] Approximately one-third of patients with anemia exhibit iron deficiency.[9,10] Previous studies have shown that iron deficiency elevates HbA1c levels independent of glycemia.[11,12] Koga et al.[13] showed that the HbA1c levels in subjects with iron deficiency anemia (IDA) were higher than those of subjects with normal iron levels. Shanti et al[14] also showed that iron deficiency was associated with higher proportions of HbA1c in subjects without diabetes. However, because these studies were performed mostly in subjects without diabetes, they could not conclude whether the presence of IDA affected the HbA1c level in diabetic or pre-diabetic patients.

Although IDA is a commonly encountered disease in clinical practice, few studies have investigated the clinical effect of IDA on the use of the HbA1c level as a screening parameter for diabetes or prediabetes.

In the current study, we performed a cross-sectional analysis to investigate the association between IDA and HbA1c levels in Korean adults based on the 2011–2012 Korea National Health and Nutrition Examination Survey (KNHANES).

## METHODS

### Study Population and Data Collection

This study used data from the 2011–2012 KNHANES, a cross-sectional and nationally representative survey conducted by the Korean Center for Disease Control for Health Statistics. The KNHANES has been performed periodically since 1998 to assess the health and nutritional status of the civilian, non-institutionalized Korean population. Participants were selected using proportional allocation systematic sampling with multi-stage stratification. A standardized interview was conducted in the homes of the participants to collect information regarding demographic variables, family history, medical history, medications used, and a variety of other health-related variables. The health interview included well-established questions to determine the demographic and socioeconomic characteristics of the subjects, including questions concerning age, education level, occupation, income, marital status, smoking habits, alcohol consumption, exercise, previous and current diseases, and family disease history.

The subjects were asked whether they exercised with an intensity that caused slight breathing difficulty and sweating. Those who exercised regularly at moderate intensity were asked about the frequency at which they exercised per week and the length of time per exercise session. Regular exercise was defined as $\geq$5 exercise sessions per week. Alcohol consumption was assessed by questioning the subjects about their drinking behavior during the month prior to the interview. Heavy alcohol drinking was categorized as drinking $\geq$4 times per week. Diabetes was defined as a FPG level of $\geq$126 mg/dL (7.0 mmol/L), an HbA1c level of $\geq$6.5%, current use of anti-diabetes medication, or a previous diagnosis of diabetes by a physician. Obesity was defined as a body mass index (BMI) of $\geq$25 kg/m$^2$ according to the Asia-Pacific obesity classification.[15]

Height and weight were obtained using standardized techniques and equipment. Height was measured to the nearest 0.1 cm using a portable stadiometer (Seriter, Bismarck, ND). Weight was measured to the nearest 0.1 kg using a Giant-150N calibrated balance-beam scale (Hana, Seoul, Korea). BMI was calculated by dividing the weight by the square of the height (kg/m$^2$).

### Laboratory Methods

Blood samples were collected in the morning after the subjects had fasted for at least 8 h. The FPG and serum creatinine levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney

**TABLE 1.** Demographic and Clinical Characteristics of Korean Population Without Current Anti-diabetes Medication, Aged 19 Years and Older, in 2011–2012 Korea National Health and Nutrition Examination Survey

| **Number (Unweighted/Weighted)** | **10665/35229108** |
|---|---|
| Age, years | 44.4 (43.8–44.9) |
| Women (%) | 50.1 (49.1–51.1) |
| College graduation (%) (unweighted N = 10,241) | 32.0 (30.4–33.7) |
| Heavy alcohol drinking (%) (unweighted N = 10,364) | 7.0 (6.4–7.7) |
| Regular exercise (%) (unweighted N = 10,364) | 7.5 (6.8–8.2) |
| Current smoking (%) (unweighted N = 10,364) | 25.6 (24.4–26.7) |
| Waist circumference, cm (unweighted N = 10,653) | 80.8 (80.5–81.2) |
| BMI, kg/m$^2$ (unweighted N = 10,621) | 23.7 (23.6–23.8) |
| Obesity (%) (unweighted N = 10621) | 31.6 (30.4–32.8) |
| FPG, mg/dL | 94.7 (94.2–95.1) |
| 100 $\leq$ FPG (mg/dL) $\leq$ 125 (%) | 19.4 (18.3–20.4) |
| FPG $\geq$126 mg/dL (%) | 3.2 (2.9–3.6) |
| HbA1c (%) | 5.59 (5.58–5.61) |
| HbA1c, mmol/mol | 37.6 (37.5–37.8) |
| Diabetes (%) | 5.1 (4.7–5.7) |
| eGFR (mL/min/1.73m$^2$) | 97.5 (97.0–98.0) |
| eGFR <60 (%), mL/min/1.73m$^2$ | 1.8 (1.6–2.2) |
| Cancer history (%) (unweighted N = 10,364) | 2.3 (2.0–2.6) |
| Hemoglobin, g/dL | 14.2 (14.2–14.3) |
| Hematocrit (%) | 42.3 (42.2–42.4) |
| Anemia (%) | 7.3 (6.7–7.9) |
| Iron deficiency anemia (%) | 4.3 (3.9–4.8) |

Data are expressed as mean with 95% confidence interval. Heavy alcohol drinking, $\geq\times$4 alcoholic drinks/week. Regular exercise, $\geq\times$5 exercise/week; obesity, BMI $\geq$25 kg/m$^2$ or more; diabetes, FPG $\geq$126 mg/dL, or HbA1c $\geq$6.5%; anemia, Hb <13 g/dL in men and Hb <12 g/dL in women; iron deficiency anemia, anemia with either transferrin saturation of <10% or a serum ferritin level of <15 μg/L. BMI = body mass index, FPG = fasting plasma glucose, eGFR = estimated glomerular filtration rate by using the Chronic Kidney Disease Epidemiology Collaboration equation.

Disease Epidemiology Collaboration equation: GFR = 141 × min(Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.209}$ × 0.993$^{Age}$ × 1.018 (if female) × 1.159 (if black), where Scr is the serum creatinine level in mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.[16]

The HbA1c level was measured using high-performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan). The detailed methods of comparing and verifying the validity and reliability of each survey were described previously.[17] The Hb level was measured via the cyanide-free sodium lauryl sulphate Hb detection method, and the hematocrit was measured via cumulative pulse height detection using an XE-2100D hematology analyzer (Sysmex, Kobe, Japan). Serum ferritin levels were measured by an immunoradiometric assay method with a 1470 WIZARD gamma counter (PerkinElmer, Waltham, MA).

## Definitions

Anemia was defined in accordance with the World Health Organization criteria: Hb <13 g/dL in men and Hb <12 g/dL in women.[18] Iron deficiency was defined as either transferrin saturation of <10% or a serum ferritin level of <15 μg/L. IDA was defined as anemia with iron deficiency, and non-IDA was defined as anemia without iron deficiency. Prediabetes was defined as the FPG level between 100 and 125 mg/dL.

## Ethics Statement

The institutional review board of Ilsan Paik Hospital, Republic of Korea approved this study. After approval of the study proposal, the KNHANES dataset was made available at the request of the investigator. Because the dataset did not include any personal information and participant consent had already been given for the KNHANES, our study was exempt from participant consent requirements.

## Statistical Analyses

Participants in the KNHANES were not sampled randomly. Specifically, the KNHANES was designed using a complex, stratified, multistage probability-sampling model. Thus, each participant does not have the same power in his or her representation of the whole Korean population. Accurate

**TABLE 2.** Weighted Age, Sex, and Age- and Sex-adjusted Demographic and Clinical Characteristics of Korean Population Without Current Anti-diabetes Medication, Aged 19 Years and Older, in 2011–2012 Korea National Health and Nutrition Examination Survey by the Presence of Anemia

| | No Anemia | Non-iron Deficiency Anemia | Iron Deficiency Anemia | |
|---|---|---|---|---|
| **Number (Unweighted/Weighted)** | **9775/32,659,660** | **414/104,7601** | **476/1,521,846** | ***P*** |
| Age, years | 44.1 ± 0.3 | 56.7 ± 1.3 | 41.2 ± 0.7*** | <0.001 |
| Women (%) | 47.0 ± 0.5 | 72.0 ± 2.9 | 93.0 ± 1.5*** | <0.001 |
| College graduation (%) | 31.8 ± 0.8 | 31.8 ± 2.4 | 35.8 ± 2.7 | 0.297 |
| Heavy alcohol drinking (%) | 7.2 ± 0.4 | 3.0 ± 1.1 | 5.8 ± 0.6* | <0.001 |
| Regular exercise (%) | 7.5 ± 0.3 | 7.5 ± 1.8 | 8.1 ± 1.8 | 0.927 |
| Current smoking (%) | 25.6 ± 0.6 | 22.1 ± 2.0 | 19.3 ± 1.4*** | <0.001 |
| Waist circumference, cm | 81.0 ± 0.2 | 76.7 ± 0.6 | 79.0 ± 0.5*** | <0.001 |
| BMI, kg/m$^2$ | 23.8 ± 0.1 | 22.2 ± 0.2 | 23.1 ± 0.2*** | <0.001 |
| Obesity (%) | 32.3 ± 0.7 | 18.6 ± 2.4 | 25.3 ± 2.2* | <0.001 |
| FPG, mg/dL | 94.8 ± 0.2 | 89.9 ± 0.7 | 94.9 ± 0.7 | <0.001 |
| 100 ≤ FPG (mg/dL) ≤ 125 (%) | 19.7 ± 0.5 | 10.1 ± 1.9 | 17.8 ± 1.9 | <0.001 |
| FPG ≥126 mg/dL (%) | 3.3 ± 0.2 | 1.5 ± 1.0 | 2.7 ± 0.7 | 0.242 |
| HbA1c (%) | 5.59 ± 0.01 | 5.44 ± 0.03 | 5.70 ± 0.02*** | <0.001 |
| HbA1c, mmol/mol | 37.6 ± 0.11 | 36.0 ± 0.11 | 38.8 ± 0.22*** | <0.001 |
| Diabetes (%) | 5.0 ± 0.2 | 3.0 ± 1.4 | 5.0 ± 0.8 | 0.251 |
| eGFR, mL/min/1.73m$^2$ | 97.5 ± 0.2 | 95.4 ± 0.9 | 98.7 ± 0.7 | 0.016 |
| eGFR <60 (%), mL/min/1.73m$^2$ | 1.5 ± 1.3 | 11.0 ± 1.6 | 2.7 ± 0.7 | <0.001 |
| Cancer history (%) | 2.2 ± 0.2 | 3.8 ± 1.1 | 2.7 ± 0.7 | 0.361 |
| Hemoglobin, g/dL | 14.4 ± 0.1 | 12.3 ± 0.1 | 11.5 ± 0.1*** | <0.001 |
| Hematocrit (%) | 42.7 ± 0.1 | 37.1 ± 0.1 | 36.1 ± 0.2*** | <0.001 |
| Serum ferritin, ng/mL | 90.4 ± 1.3 | 88.8 ± 4.8 | 42.7 ± 1.8*** | <0.001 |
| Serum ferritin <15 (%), ng/mL | 9.3 ± 0.4 | 0.0 ± 0.0 | 89.6 ± 1.1*** | <0.001 |
| Transferrin saturation (%) | 38.9 ± 0.2 | 35.3 ± 0.9 | 15.3 ± 0.5*** | <0.001 |
| Transferrin saturation (%) <10 (%) | 0.1 ± 0.1 | 0.1 ± 0.1 | 54.5 ± 2.7*** | <0.001 |

Data are expressed as mean with SEM. Heavy alcohol drinking, ≥×4 alcoholic drinks/week. Regular exercise, ≥×5 exercise/week; obesity, BMI ≥25 kg/m$^2$ or more; diabetes, FPG ≥126 mg/dL, or HbA1c ≥6.5%; anemia, Hb <13 g/dL in men and Hb <12 g/dL in women; iron deficiency anemia, anemia with either transferrin saturation of <10% or a serum ferritin level of <15 μg/L. BMI = body mass index, FPG = fasting plasma glucose, eGFR = estimated glomerular filtration rate by using the Chronic Kidney Disease Epidemiology Collaboration equation. Significance of the difference between no anemia and iron deficiency anemia in post hoc analyses

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

presentation of a certain prevalence in the whole Korean population using the KNHANES dataset requires consideration of how much power each participant has for representation (sample weight) of the whole Korean population.

After the Korean Center for Disease Control approved the investigator's proposal of this study, the Center provided a survey dataset including information about the survey location; strata by age, sex, and other factors, and sample weights for each participant to the investigator. Survey sample weights, calculated by taking the sampling rate, response rate, and age/sex proportions of the reference population (2005 Korean National Census Registry) into consideration, were used in all analyses to produce estimates representative of the non-institutionalized Korean civilian population. All statistical analyses were performed using SPSS software (ver. 21.0 for Windows; SPSS, Chicago, IL).

The demographic and clinical characteristics among groups were compared according to the presence of anemia and iron deficiency. Age was evaluated by analysis of variance, and the percentage of women was evaluated by the $\chi^2$ test. Analysis of covariance with the Bonferroni post hoc test was used to adjust for age and sex (Table 2). General linear models were used to assess weighted HbA1c levels (Table 3) and the weighted proportion (%) of an HbA1c level of $\geq$5.7%, $\geq$6.1%, and $\geq$6.5% (Table 4) according to the presence of anemia and iron deficiency before (Model 1) and after (Models 2–4) adjustment for confounders. Age (years), sex (men/women), and FPG level (mmol/L) were adjusted in Model 2. In Model 3, heavy alcohol drinking ($\geq$4 or <<<4 alcoholic drinks/week), waist circumference (cm), and smoking history (never, past, or current) as well as age, sex, and FPG level were adjusted for the analysis. Heavy alcohol drinking, waist circumference, and smoking were independently associated with the HbA1c level in previous study.[6,19–21] Adjustment for confounding factors in Model 3 was performed after exclusion of an eGFR of <60 mL/min/1.73 $m^2$ in Model 4 because renal insufficiency is also known to shorten erythrocyte survival and lower the HbA1c level.[22]

As shown in Table 4, the HbA1c cutoff value of 6.1% was selected because a recent Korean study showed that an HbA1c cutoff level of 6.1% was the optimal corresponding value for diagnosing diabetes, with the criteria of an FPG level of $\geq$7.0 mmol/L and/or a 2-h FPG level of $\geq$11.1 mmol/L on the 75-g OGTT (63.8% sensitivity and 88.1% specificity).[23] An HbA1c threshold of 5.7% had reasonable sensitivity (48.6%) and specificity (65.7%) for identification of prediabetes.[23] All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

## RESULTS

### Demographic and Clinical Characteristics of the Study Population

The demographic and clinical characteristics of the study population are shown in Table 1. Among the 16,576 participants who participated in the health interviews of the 2011–2012 KNHANES, 12,859 adult participants ($\geq$19 years of age) were analyzed. Among them, 11,472 subjects completed laboratory examinations. Eight hundred seven patients with diabetes

**TABLE 3.** Weighted HbA1c (%) of Korean Adult Population Without Current Anti-diabetes Medication by the Presence of Anemia

| | No Anemia | Non-iron Deficiency Anemia | Iron Deficiency Anemia | *P* for difference |
|---|---|---|---|---|
| Total number (unweighted/weighted) | 9775/32,659,660 | 414/104,7601 | 476/1,521,846 | |
| Model 1 | 5.59 ± 0.01 | 5.57 ± 0.03 | 5.64 ± 0.03 | 0.175 |
| Model 2 | 5.59 ± 0.01 | 5.57 ± 0.03 | 5.70 ± 0.02*** | <0.001 |
| Model 3 | 5.59 ± 0.01 | 5.57 ± 0.03 | 5.70 ± 0.02*** | <0.001 |
| Model 4 | 5.58 ± 0.01 | 5.55 ± 0.03 | 5.70 ± 0.02*** | <0.001 |
| FPG <100 mg/dL, number (unweighted/weighted) | 7279/25,105,606 | 322/854,004 | 407/1,306,671 | |
| Model 1 | 5.44 ± 0.01 | 5.48 ± 0.03 | 5.57 ± 0.02*** | <0.001 |
| Model 2 | 5.44 ± 0.01 | 5.41 ± 0.03 | 5.58 ± 0.02*** | <0.001 |
| Model 3 | 5.44 ± 0.01 | 5.42 ± 0.03 | 5.59 ± 0.02*** | <0.001 |
| Model 4 | 5.44 ± 0.01 | 5.40 ± 0.03 | 5.59 ± 0.02*** | <0.001 |
| 100 ≤ FPG <126 mg/dL, number (unweighted/weighted) | 2141/6,460,423 | 81/1,65,828 | 63/1,92,594 | |
| Model 1 | 5.83 ± 0.01 | 5.95 ± 0.08 | 5.93 ± 0.04* | 0.059 |
| Model 2 | 5.84 ± 0.01 | 5.80 ± 0.07 | 5.94 ± 0.04* | 0.039 |
| Model 3 | 5.83 ± 0.01 | 5.81 ± 0.07 | 5.98 ± 0.05** | 0.008 |
| Model 4 | 5.82 ± 0.01 | 5.75 ± 0.06 | 6.00 ± 0.05** | 0.005 |
| FPG ≥126 mg/dL, number (unweighted/weighted) | 354/1,085,325 | 11/27,769 | 6/22,581 | |
| Model 1 | 7.57 ± 0.13 | 6.32 ± 0.20 | 7.27 ± 0.66 | <0.001 |
| Model 2 | 7.56 ± 0.06 | 7.11 ± 0.23 | 6.90 ± 0.50 | 0.061 |
| Model 3 | 7.57 ± 0.06 | 7.09 ± 0.22 | 7.02 ± 0.51 | 0.045 |
| Model 4 | 7.59 ± 0.06 | 6.81 ± 0.23 | 7.40 ± 0.46 | 0.003 |

Model 1, no adjustment; Model 2, adjusted for age, sex, and fasting plasma glucose; Model 3, adjusted for heavy alcohol drinking, waist circumference, smoking history (never, past, and current smoking) and variables in Model 1; Model 4, Model 3 after exclusion of eGFR <60. Significance of the difference between no anemia and iron deficiency anemia in post hoc analyses.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

**TABLE 4.** Weighted Proportion of HbA1c ≥5.7%, ≥6.1%, and ≥6.5% (%) of Korean Adult Population Without Current Anti-diabetes Medication by the Presence of Anemia

| | No Anemia | Non-iron Deficiency Anemia | Iron Deficiency Anemia | *P* for difference |
|---|---|---|---|---|
| HbA1c ≥5.7% (%) | | | | |
| Model 1 | 34.6 ± 0.7 | 37.7 ± 2.8 | 44.7 ± 3.0** | 0.003 |
| Model 2 | 34.7 ± 0.6 | 28.3 ± 2.4 | 50.1 ± 2.7*** | <0.001 |
| Model 3 | 34.5 ± 0.6 | 30.3 ± 2.5 | 51.4 ± 2.7*** | <0.001 |
| Model 4 | 33.9 ± 0.6 | 28.9 ± 2.7 | 51.2 ± 2.8*** | <0.001 |
| HbA1c ≥6.1% (%) | | | | |
| Model 1 | 10.4 ± 0.4 | 11.4 ± 1.8 | 12.1 ± 1.7 | 0.507 |
| Model 2 | 10.4 ± 0.3 | 9.2 ± 1.7 | 14.2 ± 1.5* | 0.044 |
| Model 3 | 10.4 ± 0.3 | 9.9 ± 1.7 | 14.6 ± 1.5** | 0.024 |
| Model 4 | 10.0 ± 0.3 | 8.4 ± 1.6 | 14.0 ± 1.6* | 0.030 |
| HbA1c ≥6.5% (%) | | | | |
| Model 1 | 4.1 ± 0.2 | 4.3 ± 1.1 | 2.7 ± 0.8 | 0.185 |
| Model 2 | 4.0 ± 0.2 | 5.2 ± 1.1 | 3.6 ± 0.7 | 0.461 |
| Model 3 | 4.0 ± 0.2 | 5.3 ± 1.1 | 3.70 ± 2.7 | 0.447 |
| Model 4 | 3.9 ± 0.2 | 4.9 ± 1.0 | 3.6 ± 0.7 | 0.538 |

Model 1, no adjustment; Model 2, adjusted for age, sex, and fasting plasma glucose; Model 3, adjusted for heavy alcohol drinking, waist circumference, smoking history (never, past, and current smoking) and variables in Model 1; Model 4, Model 3 after exclusion of eGFR <60. Significance of the difference between no anemia and iron deficiency anemia in post hoc analyses.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

currently taking anti-diabetic medication were excluded. The remaining 10,665 participants (weighted n = 35,229,108) were analyzed in this study (Fig. 1).

The mean age of the population was 44.4 years, and 50.1% of the participants were female. The percentages of subjects with an FPG level of 100 to 125 mg/dL and ≥126 mg/dL were 19.4% and 3.2%, respectively. The mean HbA1c level was 5.59% and 5.1% of the subjects had diabetes. The average Hb level and hematocrit were 14.2 g/dL and 42.3%, respectively. The prevalences of anemia and IDA were 7.3% and 4.3%, respectively.

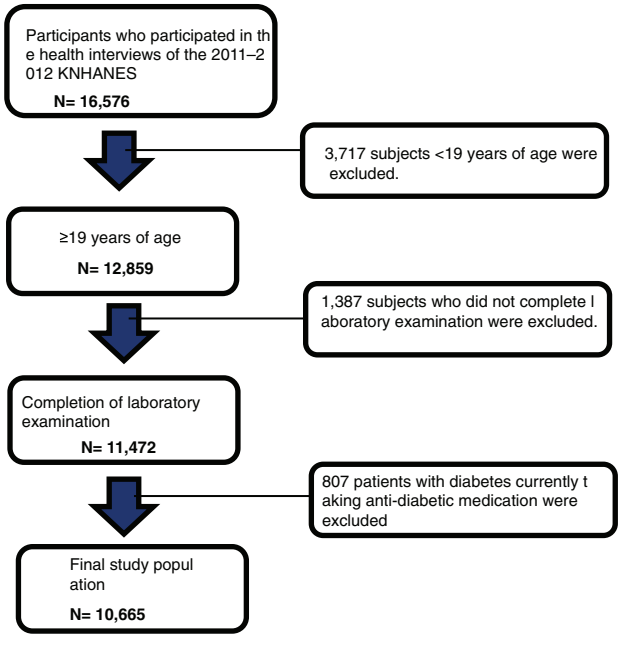


**FIGURE 1.** Flow chart of the study population.

## Weighted Age, Sex, and Age- and Sex-Adjusted Demographic and Clinical Characteristics According to the Presence of Anemia and Iron Deficiency

The participants were divided into 3 groups according to the presence of anemia and iron deficiency as follows: subjects without anemia (NL group), subjects with non-IDA (NIDA group), and subjects with IDA (IDA group) (Table 2). In the age- and sex-adjusted comparisons, the average Hb levels in the NL, NIDA, and IDA groups were 14.4 ± 0.1, 12.3 ± 0.1, and 11.5 ± 0.1 g/dL, respectively ($P < 0.001$).

The prevalence of heavy alcohol drinking, current smoking, obesity, high waist circumference, and high BMI were significantly higher in the NL than NIDA and IDA groups. There was no difference in the prevalence of diabetes or cancer history among the three groups. The prevalence of an eGFR of <60 mL/min/1.73 $m^2$ was significantly higher in the NIDA group (11.0% ± 1.6%) than in the NL group (1.5% ± 1.3%) and IDA group (2.7% ± 0.7%) ($P < 0.001$).

The HbA1c level was higher in the IDA group (5.70% ± 0.02%) than in the NL group (5.59% ± 0.01%) and NIDA group (5.44% ± 0.03%; $P < 0.001$). However, there was no difference in the FPG level, the prevalence of an FPG level of 100 to 125 mg/dL, or the prevalence of an FPG level of ≥126 mg/dL between the NL and IDA groups.

## Weighted HbA1c Levels According to Presence of Anemia and Iron Deficiency

We assessed the weighted HbA1c levels according to the range of FPG levels and the presence of anemia and iron deficiency (Table 3).

Among subjects with an FPG level of <100 mg/dL, the weighted HbA1c levels were higher in the IDA group (unweighted/weighted n = 407/1,306,671) than in the NL group (unweighted/weighted n = 7279/25,105,606) and NIDA group (unweighted/weighted n = 322/854,004) before (Model 1) and after (Models 2–4) adjustment for confounders ($P < 0.001$). After adjustment for age, sex, and FPG levels, the weighted HbA1c levels were 5.58% ± 0.02%, 5.41% ± 0.03%, and 5.44% ± 0.01% in the IDA, NIDA, and NL groups, respectively (post hoc analysis, $P < 0.001$). In Model 4, the weighted HbA1c levels were 5.59% ± 0.02%, 5.40% ± 0.03%, and 5.44% ± 0.01% in the IDA, NIDA, and NL groups, respectively (post hoc analysis, $P < 0.001$).

Among subjects with an FPG level of 100 to 125 mg/dL, the weighted HbA1c levels were also higher in the IDA group (unweighted/weighted n = 63/192,594) than in the NL group (unweighted/weighted n = 2141/6,460,423) before (Model 1) and after (Models 2–4) adjustment for confounders. In Model 4, the weighted HbA1c levels were 6.00% ± 0.05% and 5.82% ± 0.01% in the IDA and NL groups, respectively (post hoc analysis, $P = 0.003$). There was no difference in the weighted HbA1c levels between the IDA and NIDA groups in Models 1 to 3.

There was no difference in the weighted HbA1c levels between the IDA group (unweighted/weighted n = 6/22,581) and NL group (unweighted/weighted n = 354/1,085,325) or NIDA group (unweighted/weighted n = 11/27,769) in subjects with diabetes (FPG ≥126 mg/dL) before (Model 1) and after (Models 2–4) adjustment for confounders.

## Weighted Proportions (%) of HbA1c levels of ≥5.7%, ≥6.1%, and ≥6.5% According to the Presence of Anemia and Iron Deficiency

The weighted proportions (%) of an HbA1c level of ≥5.7%, ≥6.1%, and ≥6.5% according to the presence of anemia and iron deficiency are shown in Table 4 and Figure 2.

The weighted proportions (%) of an HbA1c level of ≥5.7% and ≥6.1% were higher in the IDA group than in the NL and NIDA groups after adjustment for confounders (Models 2–4).

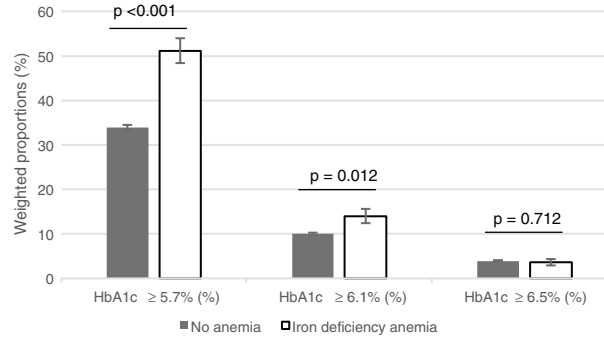


**FIGURE 2.** Weighted proportions (%) of HbA1c levels of ≥5.7%, ≥6.1%, and ≥6.5% according to the presence of iron deficiency anemia.

In Model 4, the weighted proportion of an HbA1c level of ≥5.7% was 51.2% ± 2.8% and 33.9% ± 0.6% in the IDA and NL groups, respectively ($P < 0.001$). The weighted proportion of an HbA1c level of ≥ 6.1% was 14.0% ± 1.6% and 10.0% ± 0.3% in the IDA and NL groups, respectively ($P = 0.012$). However, the weighted proportion of an HbA1c level of ≥6.5% showed no significant differences among the NL, NIDA, and IDA groups before (Model 1) or after (Models 2–4) adjustment for confounders.

## Weighted HbA1c Levels and Proportion (%) of HbA1c levels of ≥5.7%, and ≥6.5% According to the Sex and Presence of IDA

In both men and women, the weighted HbA1c levels were higher in the IDA group than in the NL group after adjustment for confounders, including age, sex, and fasting plasma glucose, heavy alcohol drinking, waist circumference, smoking history ($P < 0.001$) (Table 5). The weighted proportions (%) of an HbA1c level of ≥5.7% were higher in the IDA group than in the NL groups after adjustment for confounders in men and women. However, the weighted proportion of an HbA1c level

**TABLE 5.** Weighted HbA1c (%) and Proportion of HbA1c ≥5.7%, and ≥6.5% (%) of Korean Adult Men and Women Without Current Anti-diabetes Medication by the Presence of Iron Deficiency Anemia

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | No Anemia | Iron Deficiency Anemia | *P* | No Anemia | Iron Deficiency Anemia | *P* |
| Total number (unweighted/weighted) | 4344/17,174,586 | 38/111,169 | | 5431/15,465,371 | 438/1,410,678 | |
| HbA1c (%) | | | | | | |
| Model 1 | 5.61 ± 0.01 | 5.91 ± 0.07 | <0.001 | 5.56 ± 0.01 | 5.67 ± 0.02 | <0.001 |
| Model 2 | 5.61 ± 0.01 | 5.90 ± 0.07 | <0.001 | 5.56 ± 0.01 | 5.67 ± 0.02 | <0.001 |
| HbA1c ≥5.7% (%) | | | | | | |
| Model 1 | 35.9 ± 0.9 | 72.3 ± 8.5 | <0.001 | 33.3 ± 0.8 | 48.1 ± 2.8 | <0.001 |
| Model 2 | 35.8 ± 0.8 | 76.6 ± 8.6 | <0.001 | 33.2 ± 0.7 | 48.4 ± 2.8 | <0.001 |
| HbA1c ≥6.5% (%) | | | | | | |
| Model 1 | 4.4 ± 0.3 | 9.6 ± 5.8 | 0.373 | 3.7 ± 0.2 | 2.8 ± 0.6 | 0.087 |
| Model 2 | 4.4 ± 0.3 | 9.4 ± 5.8 | 0.385 | 3.7 ± 0.2 | 2.9 ± 0.5 | 0.196 |

Model 1, adjusted for age, sex, and fasting plasma glucose; Model 2, adjusted for heavy alcohol drinking, waist circumference, smoking history (never, past, and current smoking), and variables in Model 1.

of ≥6.5% showed no significant differences between the NL and IDA group in both men and women.

## DISCUSSION

Using the KNHANES 2011–2012 data, we found that the presence of IDA slightly increased the HbA1c level independent of the FPG level in the general adult population of Korea, even after adjustment for several confounding factors that might affect the results. This change occurred only in the normoglycemic range with an FPG level of <100 mg/dL or the prediabetic range with an FPG level of 100 to 125 mg/dL, not in the diabetic range with an FPG level of ≥126 mg/dL. Furthermore, the presence of IDA affected the HbA1c distribution with a higher weighted proportion of an HbA1c level of ≥5.7% and ≥6.1%, but not an HbA1c level of ≥6.5%.

Previous studies have reported similar results showing the effect of IDA on the HbA1c level in subjects without diabetes. Coban et al[24] found that the mean HbA1c level in patients with IDA was higher than that in a healthy control group without differences in the fasting or postprandial glucose levels. Furthermore, after iron treatment in patients with IDA, the HbA1c levels decreased from 7.4% ± 0.8% to 6.2% ± 0.6% ($P < 0.001$). Another study also demonstrated that HbA1c levels significantly decreased after oral iron treatment for 20 weeks, from a mean of 6.15% ± 0.62% to 5.25% ± 0.25% in subjects with IDA.[25]

A recent study based on the 1999–2006 US NHANES found that iron deficiency was associated with shifts in the HbA1c distribution from <5.5% to ≥5.5% among women without diabetes. Iron deficiency, not necessarily accompanied by anemia, was associated with a greater odds of an HbA1c level of ≥5.5% (odds ratio, 1.39; 95% confidence interval, 1.11–1.73) after adjustment among women. Similarly, Hardikar et al[26] reported an unexpectedly high prevalence of prediabetes diagnosed by the HbA1c level compared with the results of the OGTT among iron-deficient populations.

Because the above studies were performed mostly in subjects without diabetes, they could not conclude whether the presence of IDA affected the HbA1c level at the cutoff point of <6.5% vs ≥6.5%, the newly recommended diagnostic cutoff point for diabetes by the ADA. However, the present large-population study of patients with diabetes not currently taking anti-diabetes medication showed that the presence of IDA shifted the HbA1c level upward only in the normoglycemic or prediabetic range. IDA did not affect the HbA1c distribution with a weighted proportion of ≥6.5% or at an FPG level of ≥126 mg/dL.

The mechanisms leading to increased HbA1c levels in patients with IDA remain unclear. It has been suggested that the quaternary structure of the Hb molecule may be altered and that glycation of the β-globin chains occurs more readily in patients with IDA.[11,14] El-Agouza et al[25] proposed that a decrease in the Hb concentration might lead to an increase in the glycated fraction at a constant glucose level because HbA1c is measured as a percentage of total HbA. Although prolongation of erythrocyte survival in patients with IDA is known to elevate the HbA1c level,[7] some studies have shown normal or even shortened lifespans of erythrocytes in patients with IDA.[27–29] The above explanations are merely hypotheses, and further studies are needed to confirm and elucidate the exact mechanisms underlying this phenomenon.

Our study suggests that the presence of IDA shifts the HbA1c level upward at the lower end of the HbA1c spectrum. Therefore, consideration should be given to performing glucose testing for prediabetes in patients with IDA levels just below the diagnostic threshold or who are at high risk for diabetes. However, it is not likely that IDA affects the HbA1c level in patients with known diabetes or at the diagnostic cutoff point near 6.5%.

In this study, we categorized anemia into NIDA and IDA according to the iron deficiency status. In Model 4 (after excluding renal insufficiency and adjusting for confounding factors such as age, sex, FPG level, heavy alcohol drinking, waist circumference, and smoking), the IDA group had a higher weighted HbA1c level than did the NIDA group in the normoglycemic range with an FPG level of <100 mg/dL and in the prediabetic range with an FPG level of 100 to 125 mg/dL, but not in the diabetic range with an FPG level of ≥126 mg/dL, similar to the comparison of NA and IDA. Furthermore, the presence of IDA affected the HbA1c distribution with a higher weighted proportion (%) of an HbA1c level of ≥5.7% and ≥6.1%, but not ≥6.5%, compared with NIDA. These results suggest that iron deficiency itself plays an important role in elevating the HbA1c level, as identified in the recent study based on the 1999–2006 US NHANES.[12]

There are several strengths of this study. First, we examined a large, nationally representative sample of adult Koreans. Second, patients with diabetes not currently taking anti-diabetes medication were included in this study, which is distinct from the patients included in the existing studies. This allowed us to investigate the effect of IDA on the HbA1c distribution at higher levels of HbA1c (ie, <6.5% vs ≥6.5%, the diagnostic cutoff point for diabetes recommended by the ADA). Third, we adjusted for many confounding factors such as heavy alcohol drinking, waist circumference, smoking, renal insufficiency, age, sex, and FPG level.

Limitations to this study included that IDA is known to be very prevalent among women of reproductive age, especially pregnant women. However, despite the large population in this study, the number of subjects with IDA and an FPG level of ≥126 mg/dL without current anti-diabetes medication was limited. Therefore, we could not perform a subgroup analysis that included only premenopausal or pregnant women. Second, we could not examine the presence of structural hemoglobinopathies and thalassemia, which interfere with HbA1c measurement. However, because these disorders are uncommon in Korea (the carrier frequency of β-thalassemia is reportedly around 0.1% in Korea compared with 14.0% in Cyprus, the highest worldwide[30]), we believe that their impact on the HbA1c assays was minimal. Third, we could not acquire data about any conditions and medication history that could affect erythrocytes turnover rate. Fourth, this study was performed only in the Korean population. Therefore, the results should be taken cautiously in other ethnic groups.

In conclusion, the presence of IDA shifted the HbA1c level upward only in the normoglycemic or prediabetic range, but not in the diabetic range, in this nationally representative sample of Korean adults. Therefore, iron deficiency should be considered before using the HbA1c level as a screening parameter for prediabetes or for identifying patients at high risk for diabetes. It is unlikely that IDA affects the level of HbA1c in individuals with known diabetes or a higher HbA1c level of 6.5%.

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