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ORIGINAL ARTICLE

Association of fasting glucose and glycated hemoglobin with the long-term risk of incident metabolic syndrome: Korean Genome and Epidemiology Study (KoGES)

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Abstract

Aims Previous studies have proposed potential benefit of glycated hemoglobin (HbA1c) supplementary to fasting glucose in detecting metabolic syndrome (MetS). This study was to investigate an association of incident MetS with levels of HbA1c and fasting glucose.

Methods In a cohort of Korean Genome and Epidemiology Study, 5515 non-diabetic adults were grouped by the levels of baseline fasting glucose and HbA1c, and followed-up for 10 years. Using multivariate Cox proportional hazards assumption, hazards ratios (HRs) and 95% confidence interval (CI) for incident MetS (adjusted HRs [95% CI]) were calculated according to baseline fasting glucose and HbA1c. In individuals with normal fasting glucose, subgroup analysis was conducted to evaluate an association of HbA1c levels with MetS.

Results The risk for MetS significantly increased proportionally to fasting glucose ≥ 80 mg/dL and HbA1c ≥ 5.5%, compared with fating glucose < 80 mg/dL and HbA1c < 5.3%, respectively. In subgroups of normal fasting glucose, HbA1c ≥ 5.7% had the increased risk of MetS in fasting glucose < 80 mg/dL (5.7–5.9%: 1.41 [1.07–1.86] and 6.0–6.4%: 2.20 [1.40–2.92]), and HbA1c ≥ 5.5% had the increased risk of MetS in fasting glucose of 80–99 mg/dL (5.5–5.6%: 1.33 [1.08–1.64], 5.7–5.9%: 1.57 (1.27–1.93), and 6.0–6.4%: 2.37 [1.87–3.00]).

Conclusions Both elevated fasting glucose and HbA1c were significantly associated with the increased risk of MetS even within normal range. HbA1c is effective in identifying high-risk group for MetS in individuals with normal fasting glucose.

Keywords Fasting glucose · Glycated hemoglobin · Metabolic syndrome

Introduction

Metabolic syndrome (MetS) is diagnosed in individuals with at least three of metabolic components including abdominal obesity, impaired fasting glucose (IFG), elevated blood pressure, and dyslipidemia in triglyceride and high-density

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lipoprotein (HDL) cholesterol [1]. The growing prevalence of obesity has contributed to marked increase in the prevalence of MetS [2], and the expected rising rate of obesity heralds the great burden of public health related to MetS.

Insulin resistance (IR) is an underlying mechanism for MetS [3], linking to each metabolic component. IFG is an indicator of IR, and abdominal obesity is an aggravating factor for IR [4]. In addition, it has been demonstrated that IR contributes to the elevation of blood pressure and dyslipidemia [5]. Considering association among IR, IFG, and MetS, MetS-free individuals with IFG may have the elevated risk of MetS in future. However, not all individuals with MetS have IFG, and MetS can be present in individuals with normal fasting glucose. Although high normal fasting glucose is generally believed to accompany the high risk of MetS, evidence is still insufficient to establish the predictive ability of fasting glucose level within normal range on MetS.

In the last decades, accumulating evidence has indicated the clinical usefulness of glycated hemoglobin (HbA1c) in predicting cardiometabolic disease [6–8]. HbA1c is easily accessible by one time blood exam, representing the higher reproducibility and lower individual variability than fasting glucose [9]. Measurement of HbA1c has been standardized and recommended in diagnosing diabetes mellitus (DM) as well as determining high-risk group of DM. In addition, some studies have proposed the potential availability of HbA1c as a diagnostic criterion of MetS [10–12]. Thus, it is postulated that HbA1c may become a useful surrogate marker in predicting MetS. However, there is only limited information about predictive ability of fasting glucose and HbA1c for long-term risk of MetS.

Using data from a cohort of Korean Genome Epidemiology study (KoGES), we evaluated the risk of incident MetS according to fasting glucose and HbA1c levels. In addition, we investigated the predictive ability of HbA1c for MetS in normal rage of fasting glucose.

Research design and methods

Study population

All study subjects were participants of KoGES, which was a state-run and population-based cohort study conducted in rural (Ansung) and urban (Ansan) area of South Korea. Aim of KoEGS is to investigate public health and disease epidemiology in community-based Korean population living in rural (Ansung) and urban (Ansan) area. Detailed methods and study population of the present study are described in a previous study [13].

The initial enrollment for study subjects and baseline survey on them were performed between 2001 and 2002, and follow-up had been conducted every 2 years from time of baseline survey to finish of follow-up between 2011 and 2012. Initially, a total of 10,038 subjects aged 40–69 participated in the study. 5018 participants were recruited by cluster-sampling method stratified by age, sex, and residential district in Ansung community (rural area), and 5020 participants were selected by random sampling method in Ansan (urban area).

Exclusion criteria were the presence of baseline DM or MetS and missing values in metabolic components including fasting glucose, HbA1c, lipid profile, and waist circumference (WC).

In baseline analysis, 3284 participants with DM or MetS and 611 participants with missing values in fasting glucose, HbA1c, lipid profile, and WC were excluded from study participants. During a 10 year follow-up, 628 participants were further excluded due to follow-up loss or incomplete follow-up data. Finally, 5515 participants were enrolled in the present study. Participation in the study was voluntary, and informed consent was obtained from all participants in each baseline survey and follow-up survey. Ethics approvals for the study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital.

Clinical and biochemical measurements

Study data include a medical history and sociodemographic information provided by a self-administered questionnaire, anthropometric measurements, and laboratory biochemical measurements. All study participants were also asked to respond to a health-related behavior questionnaire, which includes the topics of alcohol consumption, smoking and exercise. Physical activity divided two categories: regular exercise (≥ 90 min exercise per week, at least moderate intensity) or inactive group. The questions about alcohol intake include the frequency of alcohol consumption on a weekly basis and typical amount that was consumed on a daily basis (g/day). Smoking status are divided into three categories: never, former, and current smoker.

The presence of DM was defined as one of the following conditions: fasting glucose level ≥ 126 mg/dL, HbA1c level of ≥ 6.5%, 2 h glucose ≥ 200 mg/dL in oral glucose tolerance test (OGTT) and history of diagnosed DM [14]. Hypertension was defined in participants with history of diagnosed hypertension, or a measured blood pressure ≥ 140/90 mmHg at the initial examinations. Blood pressure was measured on both arms in sitting position after at least 10 min' relaxation. Blood pressure measurement was done twice, and 5 min' resting exist between each measurement. Arithmetic mean value of blood pressure was used to define systolic and diastolic blood pressure. Height, weight, body mass index (BMI), and WC were also measured in all the participants.

After fasting overnight for 12 h, plasma concentrations of glucose, total cholesterol, triglyceride, and HDL cholesterol were measured enzymatically using a HITACHI Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). In the baseline and follow-up examinations, the study participants underwent OGTT. HbA1C was measured by high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA).

Inter-assay and intra-assay for the coefficients of variation (CV) in the measurement of biochemical parameters were conducted.

According to the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention [1], the presence of MetS was made in case that three or more of the following five criteria are met: blood pressure ≥ 130/85 mmHg, fasting glucose ≥ 100 mg/dL, WC ≥ 90 cm in men and ≥ 85 cm in women [15], triglyceride ≥ 150 mg/dl, and HDL cholesterol < 40 mg/dL in men and < 50 mg in women.

Statistical analysis

All participants were grouped by the levels of fasting glucose (< 80, 80–89, 90–99, 100–125 mg/dL) and HbA1c (< 5.3, 5.3–5.4, 5.5–5.6, 5.7–5.9, and 6.0–6.4%), respectively. Data are presented as means ± standard deviation for continuous variables and as proportions for categorical variables within each study group. The linear trends of variables among study groups were calculated by linear regression model for continuous variables and Cochran–Armitage trend test for categorical variables.

The unadjusted and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CI) for MetS were estimated by Cox proportional hazards model (fully adjusted HRs [95% CI]). The covariates of multivariable model were selected from variables presenting statistically significant differences in baseline mean values among groups. Adjusting covariates included age, sex, study area (Ansung and Ansan community), regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI. Incidence cases of MetS and incidence density (incidence cases per 1000 person-years) was calculated in each study group.

In subgroups of participants with normal fasting glucose (< 80 mg/dL and 80–99 mg/dL), adjusted HRs and 95% CI for MetS were calculated according to the levels of HbA1c (< 5.3, 5.3–5.4, 5.5–5.6, 5.7–5.9, and 6.0–6.4%). In addition, the generalized addictive model (GAM) analysis was performed in subgroups of normal fasting glucose to characterize a pattern of relationship among HbA1c, fasting glucose, and incidence of MetS.

All statistical analyses were performed using R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and a value of $P < 0.05$ was considered statistically significant in all analyses.

Result

A total of 5515 participants were enrolled in the study (2726 men and 2789 women). The overall incidence of MetS was 29.8% ($n = 1591$), and mean age of study participants was 50.7 ± 8.6. The final follow-up examination was done in 2011–2012.

The baseline clinical characteristics of fasting glucose groups and HbA1c groups are presented in Tables 1 and 2, respectively. The groups with higher fasting glucose and HbA1c tended to have the worse metabolic profiles, compared to the groups with lower fasting glucose and HbA1c. In an association with metabolic components, baseline fasting glucose showed a proportional relationship with WC and prevalence of hypertension. Regarding HbA1c, triglyceride, WC, and prevalence of hypertension increased proportionally to baseline levels of HbA1c.

Supplementary Table 1 shows the inter- and intra-assay for CV in the measurement of biochemical parameters.

Table 3 shows the HRs and their 95% CI for MetS according to the levels of fasting glucose and HbA1c. Compared to group with fasting glucose < 80 mg/dL, the fully adjusted HRs for MetS significantly increased proportionally to the level of fasting glucose ≥ 80 mg/dL (80–89 mg/dL: 1.42 [1.27–1.60], 90–99 mg/dL: 1.95 [1.69–2.25], and 100–125 mg/dL: 2.52 [1.86–3.40]). This association was similarly observed in the groups of HbA1c (reference: < 5.3%, 5.3–5.4%: 1.13 [0.95–1.34], 5.5–5.6%: 1.37 [1.36–1.61], 5.7–5.9%: 1.65 [1.41–1.94], and 6.0–6.4%: 2.48 [2.05–3.00]).

In subgroup analyses for individuals with normal fasting glucose (Table 4), the HRs and their 95% CI for MetS significantly increased proportionally to the HbA1c above 5.7% in fasting glucose < 80 mg/dL (reference: < 5.3%, 5.3–5.4%: 1.10 (0.84–1.45), 5.5–5.6%: 1.18 [0.90–1.54], 5.7–5.9%: 1.41 [1.07–1.86] and 6.0–6.4%: 2.20 [1.40–2.92]) and HbA1c above 5.5% in fasting glucose of 80–99 mg/dL (reference: < 5.3%, 5.3–5.4%: 1.04 (0.83–1.31), 5.5–5.6%: 1.33 [1.08–1.64], 5.7–5.9%: 1.57 (1.27–1.93), and 6.0–6.4%: 2.37 [1.87–3.00]).

Figure 1 shows the GAM graph indicating a pattern of relationship between incident MetS and HbA1c across three ranges of fasting glucose ≤ 125 mg/dL (1a), < 80 mg/dL (1b) and 80–99 mg/dL (1c). Dose-dependent relationship was found between incident MetS and HbA1c above the specific levels in three ranges of fasting glucose.

Table 1 Baseline clinical characteristics according to the fasting glucose level

Fasting glucose	< 80 mg/dl (n = 2198)	80–89 mg/dl (n = 2366)	90–99 mg/dl (n = 831)	100–125 mg/dl (n = 120)	P for Trend
Male sex [n, (%)]	878 (39.9%)	1209 (51.1%)	549 (66.1%)	90 (75.0%)	< 0.001
Age (year)	50.9 ± 8.7	50.5 ± 8.5	50.8 ± 8.6	49.8 ± 9.3	0.286
HbA1c (%)	5.4 ± 0.3	5.5 ± 0.3	5.6 ± 0.3	5.7 ± 0.3	< 0.001
Fasting glucose (mg/dL)	74.7 ± 3.5	83.7 ± 2.7	93.5 ± 2.7	105.9 ± 5.8	< 0.001
Total cholesterol (mg/dL)	180.9 ± 32.2	189.4 ± 33.9	199.5 ± 35.8	199.3 ± 37.3	< 0.001
HDL cholesterol (mg/dL)	46.5 ± 10.1	46.8 ± 10.0	48.1 ± 10.4	51.4 ± 10.9	< 0.001
Triglyceride (mg/dL)	127.8 ± 64.1	136.0 ± 90.3	138.5 ± 83.1	120.0 ± 57.8	0.005
Average alcohol use (g/day)	6.6 ± 19.1	9.2 ± 20.8	14.6 ± 24.6	21.0 ± 28.7	< 0.001
Current smoking (%)	25.1%	25.3%	32.0%	30.8%	< 0.001
Regular exercise (%)	39.9%	39.0%	40.0%	35.0%	0.534
BMI (kg/m^2)	23.4 ± 2.8	23.9 ± 2.8	24.3 ± 2.9	23.6 ± 2.6	< 0.001
Waist circumference (cm)	78.4 ± 7.7	79.9 ± 7.5	81.7 ± 7.4	80.7 ± 6.7	< 0.001
Hypertension (%)	15.2%	19.4%	24.3%	21.7%	< 0.001
Incidence of MetS [n, (%)]	481 (21.9%)	724 (30.6%)	339 (40.8%)	47 (39.2%)	< 0.001

Continuous variables are expressed as mean (± SD), and categorical variables are expressed as number (percentage (%))

HbA1c glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *BMI* body mass index, *MetS* metabolic syndrome

Table 2 Baseline clinical characteristics according to the HbA1c level

HbA1c level (%)	< 5.3 (N = 1197)	5.3–5.4 (N = 1235)	5.5–5.6 (N = 1323)	5.7–5.9 (N = 1273)	6.0–6.4 (N = 487)	P for trend
Male sex [n, (%)]	536 (44.8%)	611 (49.5%)	663 (50.1%)	660 (51.8%)	256 (52.6%)	< 0.001
Age (year)	48.4 ± 7.8	49.2 ± 8.1	51.1 ± 8.7	52.5 ± 9.0	54.2 ± 8.4	< 0.001
HbA1c (%)	5.1 ± 0.2	5.4 ± 0.0	5.5 ± 0.0	5.8 ± 0.1	6.1 ± 0.1	< 0.001
Fasting glucose (mg/dL)	79.9 ± 7.4	81.1 ± 7.5	82.1 ± 7.7	83.6 ± 8.2	86.1 ± 9.0	< 0.001
Total cholesterol (mg/dL)	180.6 ± 32.8	184.6 ± 33.5	188.9 ± 34.0	192.2 ± 34.4	198.7 ± 35.2	< 0.001
HDL cholesterol (mg/dL)	47.6 ± 10.2	47.0 ± 10.2	46.5 ± 9.8	47.1 ± 10.2	46.4 ± 10.2	0.041
Triglyceride (mg/dL)	122.1 ± 72.3	127.2 ± 69.9	133.7 ± 78.0	139.6 ± 85.6	152.3 ± 96.3	< 0.001
Average alcohol use (g/day)	9.4 ± 22.9	9.7 ± 21.5	8.4 ± 18.6	9.1 ± 20.0	10.4 ± 25.4	0.921
Current smoking (%)	20.0%	24.9%	27.4%	30.4%	32.0%	< 0.001
Regular exercise (%)	34.8%	36.4%	40.5%	42.7%	47.0%	< 0.001
BMI (kg/m^2)	23.4 ± 2.7	23.6 ± 2.7	23.8 ± 2.8	23.9 ± 3.0	24.4 ± 2.9	< 0.001
Waist circumference (cm)	78.2 ± 7.5	78.7 ± 7.6	80.0 ± 7.4	80.2 ± 7.6	82.2 ± 7.5	< 0.001
Hypertension (%)	16.2%	17.5%	18.7%	21.2%	19.1%	0.003
Incidence of MetS [n, (%)]	239 (20.0%)	292 (23.6%)	405 (30.6%)	432 (33.9%)	223 (45.8%)	< 0.001

Continuous variables are expressed as mean (± SD), and categorical variables are expressed as number (percentage (%))

HbA1c glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *BMI* body mass index, *MetS* metabolic syndrome

Discussion

In a cohort of middle-aged Korean population, individuals with elevated fasting glucose or HbA1c tended to have the relatively worse metabolic profiles, which links to the increased incidence of MetS. The risk of MetS significantly increased proportionally to the level of fasting glucose ≥ 80 mg/dL and HbA1c ≥ 5.5%, compared to fasting glucose < 80 mg/dL and HbA1c < 5.3%, respectively. It is of note that proportional relationship was consistently observed in the normal range of fasting glucose (< 100 mg/dL) and HbA1c (< 6.0%). Our results suggest that both elevated fasting glucose and HbA1c associate with aggravation of metabolic condition, describing the increased risk of MetS across normal and prediabetic range of fasting glucose and HbA1c.

Given that MetS links to the elevated risk of cardiovascular disease (CVD), our results are corresponding to the previous studies investigating an association of cardiovascular

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of metabolic syndrome according to the fasting glucose and HbA1c

Characteristics	Unadjusted HR	Adjusted HR	Incidence cases	Incidence density
Fasting glucose				
< 80 mg/dL (*n* = 2198)	1.00 (Reference)	1.00 (Reference)	481	28.7
80–89 mg/dL (*n* = 2366)	1.47 (1.31–1.65)	1.42 (1.27–1.60)	724	41.5
90–99 mg/dL (*n* = 831)	2.24 (1.95–2.58)	1.95 (1.69–2.25)	339	60.5
100–125 mg/dL (*n* = 120)	2.38 (1.77–3.22)	2.52 (1.86–3.40)	47	60.8
HbA1c (%)				
< 5.3 (*n* = 1197)	1.00 (Reference)	1.00 (Reference)	239	26.2
5.3–5.4 (*n* = 1235)	1.20 (1.01–1.42)	1.13 (0.95–1.34)	292	31.0
5.5–5.6 (*n* = 1323)	1.59 (1.35–1.86)	1.37 (1.16–1.61)	405	40.6
5.7–5.9 (*n* = 1273)	1.95 (1.67–2.29)	1.65 (1.41–1.94)	432	47.9
6.0–6.4 (*n* = 487)	3.19 (2.65–3.83)	2.48 (2.05–3.00)	223	73.3

Adjusted for age, sex, area, regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI

Incidence density: incidence cases per 1000 person-years

Table 4 Hazard ratios (HRs) and 95% confidence intervals (CI) for incident metabolic syndrome according to HbA1c in subgroups with normal level of fasting glucose

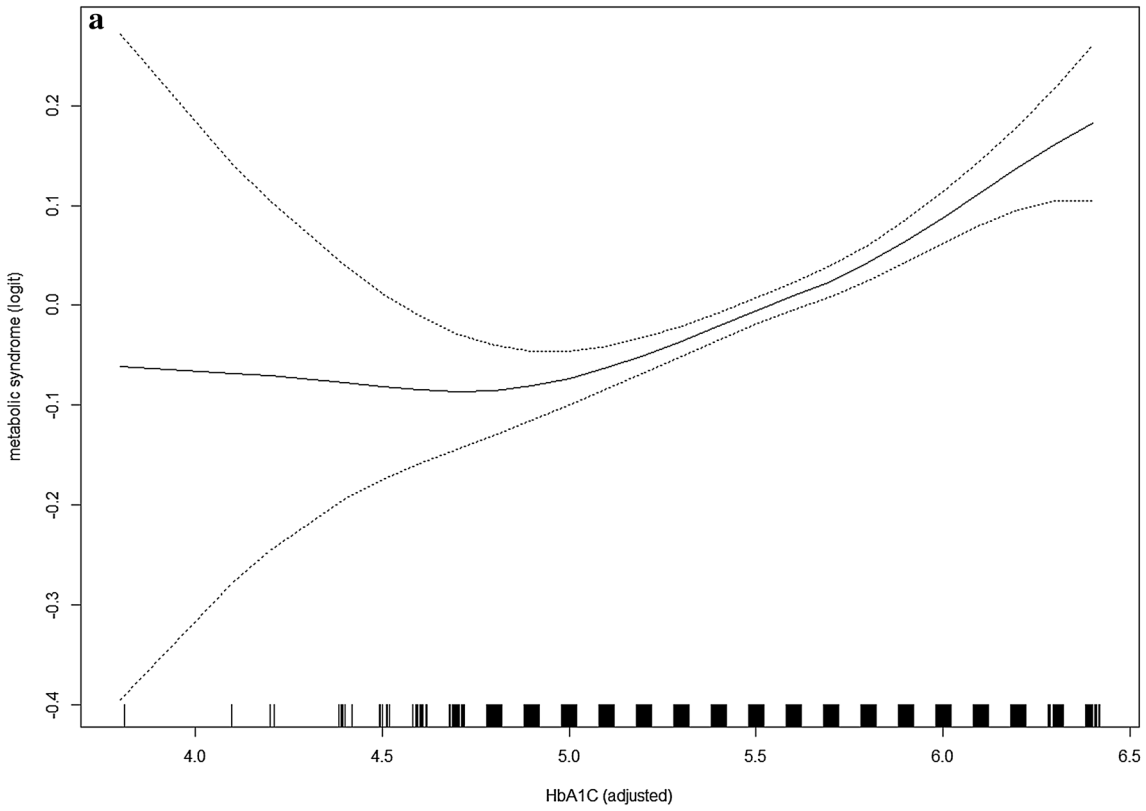
Characteristics	Unadjusted HR	Adjusted HR	Incidence cases	Incidence density
Fasting glucose < 80 mg/dL				
Level of HbA1c				
< 5.3% (*n* = 630)	1.00 (Reference)	1.00 (Reference)	107	22.2
5.3–5.4% (*n* = 544)	1.13 (0.86–1.48)	1.10 (0.84–1.45)	104	24.7
5.5–5.6% (*n* = 493)	1.40 (1.08–1.82)	1.18 (0.90–1.54)	118	30.6
5.7–5.9% (*n* = 416)	1.65 (1.26–2.16)	1.41 (1.07–1.86)	107	34.7
6.0–6.4% (*n* = 115)	2.93 (2.07–4.16)	2.02 (1.40–2.92)	45	57.6
Fasting glucose 80–99 mg/dL				
Level of HbA1c				
< 5.3% (*n* = 555)	1.00 (Reference)	1.00 (Reference)	131	31.0
5.3–5.4% (*n* = 672)	1.15 (0.92–1.45)	1.04 (0.83–1.31)	181	35.7
5.5–5.6% (*n* = 803)	1.53 (1.24–1.89)	1.33 (1.08–1.64)	275	46.3
5.7–5.9% (*n* = 820)	1.86 (1.51–2.28)	1.57 (1.27–1.93)	309	54.0
6.0–6.4% (*n* = 347)	2.92 (2.32–3.67)	2.37 (1.87–3.00)	167	79.5

Adjusted for age, sex, area, regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI

Incidence density: incidence cases per 1000 person-years

risk with the non-diabetic ranges of fasting glucose and HbA1c [16–18]. IFG was significantly associated with an increased long-term risk of CVD including coronary heart disease and ischemic stroke [16, 17]. Even within category of IFG, fasting glucose between 110 and 125 mg/dL had the higher cardiovascular risk than fasting glucose between 100 and 109 mg/dL [18]. Although it is less certain whether this association is present in normal range of fasting glucose, some studies have suggested the potential correlation between high normal blood glucose and the increased risk of cardiometabolic diseases such as CVD and DM [19, 20]. In addition, observational studies have suggested a potential relationship between high normal glucose level and MetS. A cross-sectional study for 323 Italian obese children and adolescent found a proportional relationship between fasting glucose level and the prevalence of MetS [21]. In studies for Taiwanese, individuals with high normal fasting glucose (90–99 mg/dL) had the higher risk of MetS than low normal fasting glucose [22, 23]. In contrast, some studies have shown the relatively weak association between non-diabetic range of fasting glucose and cardiometabolic risk [24–26].

The previous studies have reported that HbA1c was superior to fasting glucose in predicting cardiovascular risk and mortality in non-diabetic population [28–30]. In particular,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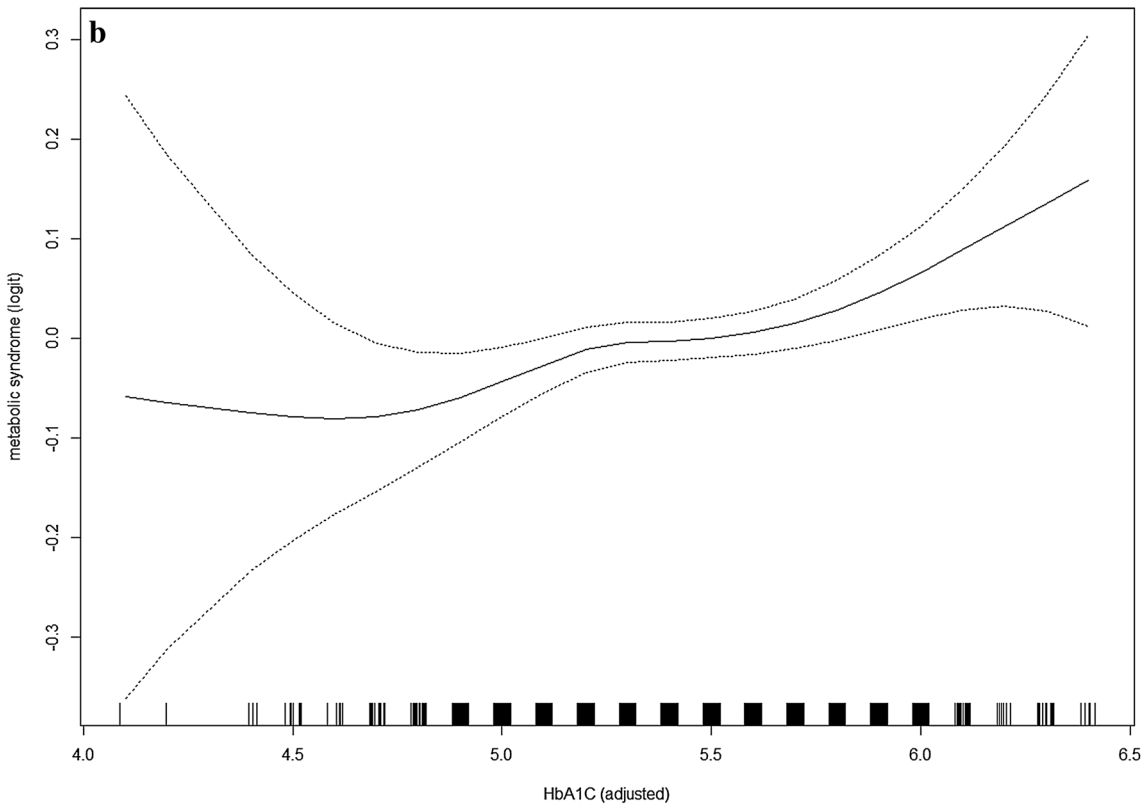
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◀ **Fig. 1** **a** The Generalized Additive Models graph for HbA1c and Metabolic syndrome in all study participants (fasting glucose ≤ 125 mg/dL) (adjusted for age, sex, area, regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI). **b** The Generalized Additive Models graph for HbA1c and Metabolic syndrome in a subgroup of normal fasting glucose (< 80 mg/dL) (adjusted for age, sex, area, regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI). **c** The Generalized Additive Models graph for HbA1c and Metabolic syndrome in a subgroup of normal fasting glucose (80–99 mg/dL) (adjusted for age, sex, area, regular exercise, hypertension, smoking, alcohol intake, total cholesterol, and BMI)

epidemiological reports from Koreans have presented the better diagnostic accuracy of HbA1c for MetS than fasting glucose, proposing the cut-off of HbA1c corresponding to the cut-off of fasting glucose in detecting MetS [10, 11]. In a study for 7307 Koreans, using the HbA1c criterion of 5.7% instead of fasting hyperglycemia, detection rate of MetS increased up to 25.7%, and cut-off of HbA1C corresponding to cut-off of IFG was 5.65% (sensitivity 52.3% and specificity 76.7%) [10]. Sung et al. reported that HbA1c of 5.45% (sensitivity 53.7% and specificity 70%) was able to predict the presence of MetS in Korean subjects [11]. In our results, HbA1c had a proportional relationship with the more baseline metabolic components (triglyceride, WC, and prevalence of hypertension), compared with fasting glucose (WC and prevalence of hypertension), identifying the high-risk group for MetS within individuals with normal fasting glucose. Considering the baseline degree of obesity in our study participants, these results may provide novel insight to risk assessment for MetS. All of our study groups had normal range of baseline mean BMI (< 25 kg/m^2) and WC (< 85 cm), which indicates that most of our study participants were non-obese. In non-obese individuals with normal fasting glucose, it is apt to undervalue their cardiometabolic risk. Our study showed that the risk of MetS significantly increased proportionally to HbA1c ≥ 5.5% in individuals with normal fasting glucose level of 80–99 mg/dL and HbA1c ≥ 5.7% in individuals with normal fasting glucose level less than 80 mg/dL. These findings may expand to a clinical implication of HbA1c in effectively identifying the high cardiometabolic risk group in non-obese individuals with normal fasting glucose. In addition, although we did not analyze the optimal cut-off of HbA1c to predict MetS, our study suggests that the cut-off of HbA1c may vary according to fasting glucose level. While individuals with relatively low fasting glucose may have the increased risk of MetS in relatively high HbA1c, individuals with relatively high fasting glucose may have the increased risk of MetS even in the relatively low HbA1c. These results indicate the potential

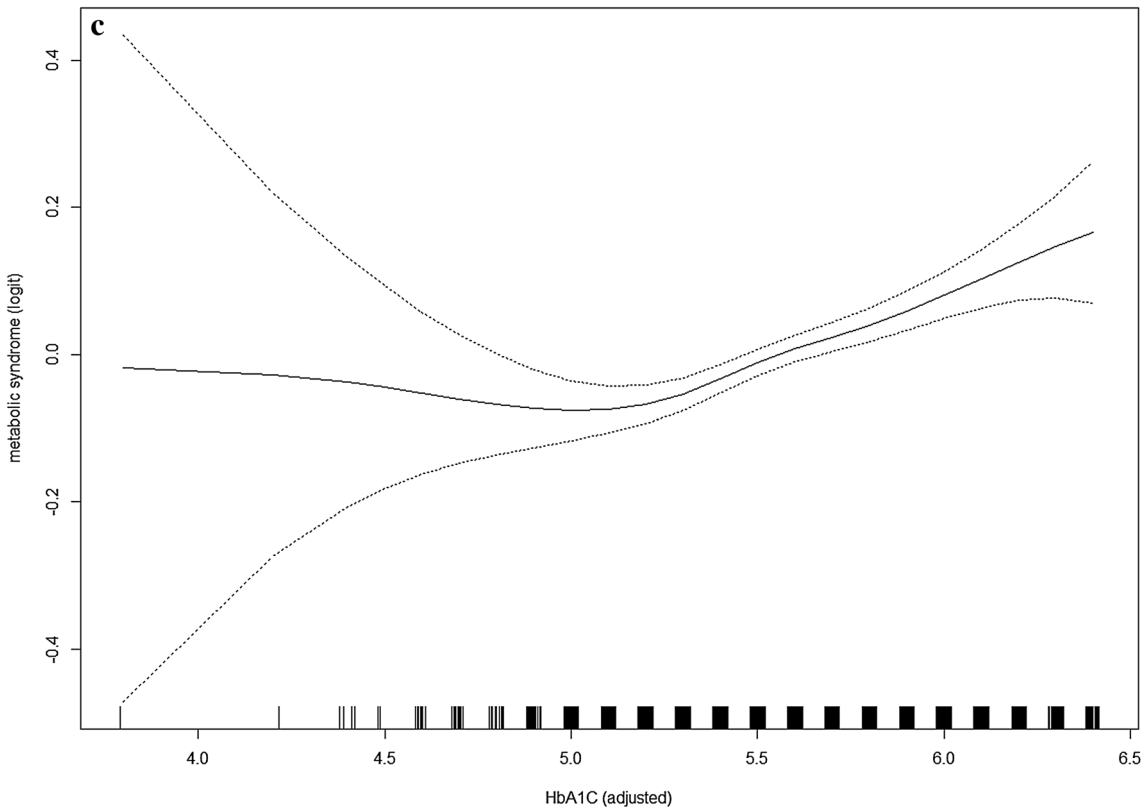

Fig. 1 (continued)

benefit of HbA1c in evaluating cardiometabolic risk, supplementary to fasting glucose.

The distinction in physiologic mechanism between fasting glucose and HbA1c may be an explanation for our findings. Fasting glucose measurement is to evaluate only fasting hyperglycemia, whereas HbA1c can reflect fasting and postprandial hyperglycemia. Despite longstanding debate on contribution of fasting and postprandial hyperglycemia to elevated HbA1c, it is evident that postprandial hyperglycemia leads to elevated HbA1c [27]. Thus, subjects with elevated HbA1c as well as normal fasting glucose may have the postprandial hyperglycemia in concurrence with fasting normoglycemia. Evidence has indicated a strong association between postprandial hyperglycemia and cardiovascular risk [28]. Moreover, individuals with both postprandial hyperglycemia and fasting normoglycemia are likely to have isolated IGT in OGTT [29]. However, the availability of OGTT is limited to test IGT in non-obese individuals with normal fasting glucose. Our results indicate a clinical usefulness of HbA1c in screening the high-risk group for MetS in non-obese individuals with normal fasting glucose.

The merits of this study are population-based longitudinal design with 10 year follow-up and identifiable medical records. These merits enable us to evaluate the risk of MetS according to the levels of fasting glucose and HbA1c across normal and prediabetic range. Nonetheless, some limitations should be acknowledged.

First, this study was conducted only in Koreans. The previous studies have demonstrated the ethnic difference of HbA1c in non-diabetic population, where HbA1c was higher in Blacks, Asians, and Latinos compared to Caucasians [30]. In addition, ethnic difference in relationship between HbA1c and blood glucose has been described [31]. Thus, our results are not likely to be generalized into the other ethnics groups.

Second, our results should be viewed in the light of longitudinal observation. Although our analysis was based on the comparison and adjustments of various baseline clinical parameters, our results cannot clarify the pathophysiological mechanism between fasting glucose, HbA1c, and incident MetS. Further study should be considered to elucidate the causative relationship among them.

In conclusion, our study demonstrated that the risk of MetS increased above the specific levels of fasting glucose and HbA1c even within normal range. Elevated HbA1c was significantly associated with the increased risk for MetS even in non-obese individuals with normal fasting glucose. These results suggest the clinical usefulness of HbA1c in screening high-risk group for MetS.

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Author Contributions Ju Young Jung coordinated the study, analyzed the data, and wrote the manuscript as a first author. Jae-Hong Ryoo and Pil-Wook Chung participated in conducting study and writing manuscript. Chang-Mo Oh played role in analyzing data and verifying the results. Joong-Myung Choi participated in English editing and reviewing manuscript. Sung Keun Park is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics approvals for the study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

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