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Framingham Risk Score Assessment in Subjects with Pre-diabetes and Diabetes: A Cross-Sectional Study in Korea

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Background: This study aimed to evaluate cardiovascular risk in subjects with pre-diabetes and diabetes in Korea.

Methods: In this pan-Korean, non-interventional, cross-sectional study, data were collected from medical records of 10 hospitals between November 2013 and June 2014. Subjects (aged ≥40 years) with medical records of dysglycemia and documentation of total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, and smoking status in the past 6 months were included. The primary endpoint was to determine the Framingham risk score (FRS). The relationships between FRS and cardiovascular risk factors, glycated hemoglobin, and insulin usage were determined by multiple linear regression analyses.

Results: Data from 1,537 subjects with pre-diabetes (n=1,025) and diabetes (n=512) were analyzed. The mean FRS (mean±standard deviation) in subjects with pre-diabetes/diabetes was 13.72±8.77. FRS was higher in subjects with diabetes than pre-diabetes ($P<0.001$). FRS in men with pre-diabetes was comparable to that in women with diabetes (13.80±7.37 vs. 13.35±7.13). FRS was elevated in subjects who consumed alcohol (2.66, $P=0.033$) and with obesity-class II (6.10, $P=0.015$) among subjects with diabetes (n=199), and was elevated in patients with left ventricular hypertrophy (11.10, $P=0.005$), those who consumed alcohol (3.06, $P=0.000$), were pre-obese (3.21, $P=0.002$), or were obesity-class I (2.89, $P=0.002$) among subjects with pre-diabetes (n=306) in comparison to subjects without these coexisting risk factors.

Conclusion: Overall, Korean subjects with pre-diabetes and diabetes have an increased cardiovascular risk, which is significantly higher in those subjects with diabetes than with pre-diabetes. The present data can be used to develop measures to prevent and manage cardiovascular complications in Koreans with impaired glucose metabolism.

Key words: Cardiovascular diseases, Diabetes mellitus, Risk assessment

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INTRODUCTION

In the last few decades, there has been a global increase in the prevalence of pre-diabetes and diabetes.[1] In 2019, the worldwide prevalence of pre-diabetes among adults aged 20–79 years was 7.5% while that of diabetes was 9.3%; these values have been projected to increase to 8.6% and 10.9%, respectively, by 2045.[1] Contribution of the Western Pacific region to the total global diabetes disease burden is approximately 35%.[1] Among countries in the Western Pacific region, the prevalence of diabetes in Korea increased from 12.4% in 2011 to 14.4% in 2016 and was higher in men (15.8%) than in women (13.0%).[2] This increase was attributed to an aging population, westernized lifestyle, and other socioeconomic factors.[3]

Complications due to diabetes are associated with increased medical costs and reduced life expectancy. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in subjects with diabetes, and the risk of developing CVD is almost double that in individuals with diabetes compared to those without.[1] CVD is known to be associated with fasting plasma glucose (FPG); postprandial plasma glucose (PPG) is also an important determinant of CVD burden.[4-6] Pre-diabetes increases the risk of CVD and all-cause mortality, and the risk appears to be present in subjects with an FPG as low as 100 mg/dL and glycated hemoglobin (HbA1c) of 5.7%.[7]

International guidelines established by the American Diabetes Association and the European Association for the Study of Diabetes recommend a reduction in diabetes complications and CVD risk as the primary goal in the management of diabetes.[8] In agreement with the international guidelines, the Korean Diabetes Association also emphasizes the evaluation and prevention of CVD while managing diabetes.[9] Cardiovascular (CV) risk should be assessed quantitatively to prevent and effectively manage CV complications in subjects with diabetes. Various algorithms have been devised for CV risk assessment, but their suitability for assessing risk in subjects with diabetes is unclear.[10-13] The Framingham risk score (FRS) is one of the most useful CV risk calculators used globally in clinical practice to identify and treat high-risk populations as well as to communicate risk effectively.[14,15]

In Korea, the prevalence of pre-diabetes and diabetes is increasing, but information on associated CV risk is limited. In view of this, the OCARINA (a cross-sectional study to evaluate cardiovascular risk in prediabetic and diabetic patients) study was undertaken to investigate the relationship between FRS and CV risk factors (myocardial infarction [MI], stroke, history of CV revascularization, history of angina, left ventricular hypertrophy [LVH], coronary artery stenosis > 50%, and carotid stenosis > 50%) in subjects with pre-diabetes and diabetes in Korea.

METHODS

Study design

OCARINA was a pan-Korea, multicenter, non-interventional, cross-sectional study conducted in compliance with good epidemiologic practice.[16] Physicians from 10 general hospitals in Korea, who managed and treated subjects with diabetes based on health system and expertise, participated in the study as investigators. The study period was from November 2013 to June 2014.

Study population

Subjects with pre-diabetes or diabetes aged ≥ 40 years who visited outpatient departments at the ten medical institutions during the participating physicians' duty schedules were enrolled based on the availability of their case records. Type 2 diabetes mellitus (T2DM) was diagnosed based on plasma glucose (PG), FPG of ≥ 126 mg/dL or 2-hour PG of ≥ 200 mg/dL during a 75-g oral glucose tolerance test (OGTT), or HbA1c level ≥ 6.5%.[17-19] Pre-diabetes was diagnosed based on the presence of impaired fasting glucose (IFG) with FPG ranging from 100 to 125 mg/dL and/or impaired glucose tolerance with a 2-hour PG of 140 to 199 mg/dL during a 75-g OGTT, and/or HbA1c of 5.7% to 6.4%.[17-19] Subjects with documented total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) values, systolic blood pressure (SBP), and smoking status within the previous 6 months were included in the study. Subjects that were receiving any investigational drug; those with a history of MI, stroke, or major surgery; or those with a reported use of systemic glucocorticoids for a week within the 3 months preceding enrollment were excluded from the study.

Data collection and verification

Data from medical records were entered in electronic case report

forms. Data included demographics, pharmacotherapy in the previous 6 months, record of CV risk factors, FPG, PPG, HbA1c, TC, HDL-C, antihyperlipidemic therapy, SBP, diastolic blood pressure (DBP), antihypertensive therapy, and smoking status.

Study endpoints

The primary endpoint of the study was to determine the FRS. Framingham equations for general CV risk were used to calculate the CV risk for the FRS using an online calculator (https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/). Secondary endpoints included the percentage of subjects with high CV risk, the relationship between FRS and HbA1c level and insulin usage, and the relationship between high CV risk and HbA1c level and insulin usage.

High CV risk in subjects was defined as having at least one of the following underlying CV risk factors: MI, history of stroke, prior revascularization, history of angina, urine albumin creatinine ratio (UACR) > 30 μg/mg, history of LVH, or stenosis of the coronary arteries.

Statistical analysis

Data collected from subjects were analyzed using descriptive statistics. Qualitative data were summarized as frequencies and percentages, while quantitative data were summarized using descriptive statistics (mean, standard deviation [SD], median, and range). Multiple linear regression was performed to investigate the relationship between FRS and CV risk factors, as well as FRS according to HbA1c level and insulin use. The association between presence of CV risk factors and HbA1c level and insulin usage was assessed by multiple logistic regression analysis. SAS versions 9.2 or higher (SAS Institute Inc., Cary, NC, USA) were used to perform all analyses.

Ethical considerations

This non-interventional, retrospective study protocol was approved by local ethics review committees with informed consent form exemption. Institutional review board approval numbers from the 10 hospitals that participated in this study are as follows: Konkuk University Medical Center (KUH1010518), Gangdong Kyung Hee University Hospital (2013-0077), Ulsan University Hospital (2013096), Chonbuk National University Hospital (CUH 2013-10-021), Seoul National University Bundang Hospital (B-1310/222-112), Daegu Catholic University Hospital (CR-13-085-L), The Catholic University of Korea, Yeouido St. Mary's Hospital (XC13RSMI0125S), The Catholic University of Korea, St. Vincent's Hospital (XC13RSMI0125V), Hallym University Kangnam Sacred Heart Hospital (2013-11-91), and Hanyang University Hospital (HYUH 2013-11-015).

RESULTS

Population demographics and clinical characteristics

Out of 1,540 subjects screened, data from 1,537 subjects were included in the analysis; one subject was excluded because his/her medical record did not confirm dysglycemia at enrollment, and two other subjects were excluded as baseline data (TC, HDL-C, SBP, and smoking status) within 6 months before enrollment were missing.

About one-third (33%, 512/1,537) of analyzed subjects had diabetes, while the remainder (n = 1,025) had pre-diabetes. More than half (60.0%, 922/1,537) of the subjects were men; the mean ± SD age and body mass index of the study subjects was 56.2 ± 8.8 years and 24.9 ± 3.2 kg/m^2, respectively. The Mean ± SD of SBP and DBP were 125.5 ± 14.2 mmHg and 75.7 ± 9.6 mmHg, respectively. About one-fifth (19.5%, 299/1,537) of subjects were active smokers. Fewer than half (45.8%, 522/1,139) of subjects were alcohol consumers. The proportion of subjects who received antihypertensive and antihyperlipidemic therapy was 34.1% (430/1,261) and 49.7% (573/1,154), respectively (Table 1).

FRS in subjects with diabetes and pre-diabetes

In subjects whose records had all the data required for calculation of FRS (n = 1,261), the mean ± SD FRS was 13.72 ± 8.77 (Fig. 1). Through assumption of either "yes" or "no" when data for the parameter "treatment with antihypertensive drugs" was unavailable, the FRS score was 13.88 ± 8.71 and 13.30 ± 8.66, respectively (Supplementary Table 1).

Subjects with diabetes had a higher FRS (18.99 ± 8.79) than those with pre-diabetes (10.74 ± 7.23) (P < 0.001) (Fig. 1). FRS in men with pre-diabetes was comparable to that in women with diabetes (13.80 ± 7.37 and 13.35 ± 7.13, respectively) (Fig. 2).

Table 1. Demographics of the study subjects

Variable	Diabetes (n=512)	Pre-diabetes (n=1,025)	Total (n=1,537)	*P*
Anthropometrics				
Age (yr)	57.2±9.1	55.7±8.6	56.2±8.8	0.001*
Sex				
Male	314 (61.3)	608 (59.3)	922 (60.0)	0.448†
Female	198 (38.7)	417 (40.7)	615 (40.0)	0.448†
Height (cm)	163.7±8.4	163.2±9.1	163.4±8.9	0.369*
Weight (kg)	68.4±11.6	67.2±11.7	67.6±11.7	0.115*
BMI (kg/m^2)	25.2±3.4	24.7±3.1	24.9±3.2	0.012*
Waist circumference (cm)	88.2±10.1	83.4±9.3	84.4±9.6	<0.001*
SBP (mmHg)	126.6±3.6	125.0±14.5	125.5±14.2	0.037*
DBP (mmHg)	75.6±9.4	75.7±9.6	75.7±9.6	0.848*
Lifestyle practice				
Smoking				
Yes	117 (22.9)	182 (17.8)	299 (19.5)	0.017†
Alcohol consumption (n=1,139)				
Yes	150 (44.4)	372 (46.4)	522 (45.8)	<0.001†
Exercise (n=854)				
Yes	115 (51.8)	377 (59.7)	492 (57.6)	0.042†
Current pharmacotherapy				
Antihypertensive (n=1,261)				
Yes	203 (44.5)	227 (28.2)	430 (34.1)	<0.001†
Antihyperlipidemic (n=1,154)				
Yes	230 (59.4)	343 (44.7)	573 (49.7)	<0.001†

Values are presented as mean± standard deviation or number (%). Denominator of the percentage is the number of subjects. Subjects with unknown information were not included: height: 563 subjects, weight: 375 subjects, alcohol consumption: 398 subjects, exercise status: 683 subjects, treatment with antihypertensive drugs: 276 subjects, and treatment with antihyperlipidemic drugs: 341 subjects (missing data in 42 subjects).
*t-test; †Chi-square test.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

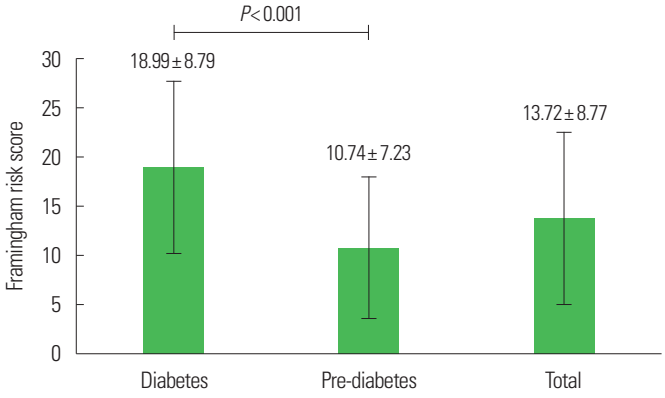

Figure 1. Comparison of Framingham risk score between diabetes and pre-diabetes.Values are presented as mean±standard deviation. Framingham risk score comparison between diabetes vs. pre-diabetes by t-test.

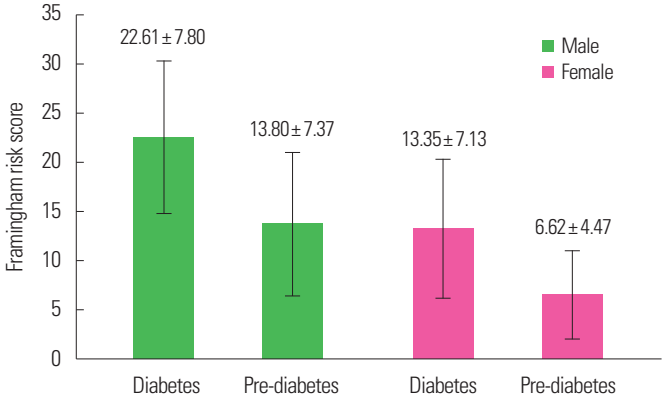

Figure 2. Comparison of Framingham risk score within pre-diabetes and diabetes populations by sex. Values are presented as mean±standard deviation. Sex comparisons within pre-diabetes and diabetes population by analysis of variance. Multiple comparisons by Duncan's test. Male diabetes>male pre-diabetes=female diabetes>female pre-diabetes (*P*<0.001).

Subjects with high CV risk and associated FRS

Among 132 subjects whose high-risk status could be ascertained, 81 (61.4%; 95% confidence interval [CI], 53.06–69.67) presented with at least one risk factor (thus falling in the high CV risk category). The most prevalent CV risk factor was angina, reported in 28 subjects (2.72%), followed by stroke (n=17, 1.66%), ankle-brachial index <0.9 (n=15, 7.77%), UACR >30 μg/mg (n=10, 3.46%), LVH (n=9, 1.02%), MI (n=6, 0.58%), prior revascularization (n=6, 0.60%), and ≥50% stenosis of coronary arteries (n=2, 0.22%). No subject had ≥50% stenosis of the lower extremity or carotid arteries.

In subjects with high CV risk (presence of ≥1 CV risk factors), the mean±SD of FRS was 17.86±8.86; in comparison, the FRS in those without any coexistent CV risk factor was 14.58±8.54 (*P*=0.048). FRS was higher in subjects with stroke (Δ=4.49, *P*=0.032), angina (Δ=6.58, *P*=0.000), LVH (Δ=9.21, *P*=0.003), alcohol consumption (Δ=3.66, *P*<0.001), higher BMI (Δ=0.3 [underweight vs. normal], Δ=2.14 [pre-obesity vs. normal], and Δ=3.14 [obesity vs. normal]; *P*<0.001), and higher HbA1c (Δ=3.48 [tertile 2 vs. 1], Δ=6.83 [tertile 3 vs. 1]; *P*<0.001) than in those without these coexisting risk factors. FRS was substantially elevated in patients with angina (Δ=4.57; *P*=0.019) and those who consumed alcohol (Δ=3.96, *P*=0.000) among subjects with diabetes and in those with stroke (Δ=5.1, *P*=0.031), LVH (Δ=11.76, *P*=0.005), alcohol consumption (Δ=3.62, *P*<0.001), higher BMI (Δ=−4.19 [underweight vs. normal], Δ=1.74 [pre-obesity vs. normal], and Δ=2.06 [obesity vs. normal]; *P*=0.000), and higher HbA1c (Δ=

Table 2. Effect of cardiovascular risk factors on the Framingham risk score

Variable	Parameter estimate (SE)	*P**
Overall (n = 469)†		
Stroke presence (vs. none)	3.28 (3.11)	0.291
Angina presence (vs. none)	1.65 (3.10)	0.594
LVH presence (vs. none)	10.75 (3.34)	0.001
Alcohol consumption presence (vs. none)	3.22 (0.75)	<0.001
HbA1c tertile 2 (vs. tertile 1)	3.31 (0.93)	<0.001
HbA1c tertile 3 (vs. tertile 1)	7.22 (0.88)	<0.001
BMI underweight (vs. normal weight)	9.02 (4.05)	0.026
BMI pre-obesity (vs. normal weight)	2.92 (1.04)	0.005
BMI obesity-class I (vs. normal weight)	3.21 (0.90)	<0.001
BMI obesity-class II (vs. normal weight)	4.00 (1.80)	0.027
BMI obesity-class III (vs. normal weight)	1.28 (4.05)	0.751
Diabetes (n = 199)†		
Angina presence (vs. none)	4.98 (2.96)	0.094
Alcohol consumption presence (vs. none)	2.66 (1.24)	0.033
BMI underweight (vs. normal weight)	3.49 (4.49)	0.437
BMI pre-obesity (vs. normal weight)	1.93 (1.80)	0.285
BMI obesity-class I (vs. normal weight)	2.70 (1.56)	0.085
BMI obesity-class II (vs. normal weight)	6.10 (2.49)	0.015
BMI obesity-class III (vs. normal weight)	0.91 (5.12)	0.859
Pre-diabetes (n = 306)†		
Stroke presence (vs. none)	4.40 (2.82)	0.119
LVH presence (vs. none)	11.10 (3.94)	0.005
Alcohol consumption presence (vs. none)	3.06 (0.78)	<0.001
HbA1c tertile 2 (vs. tertile 1)	1.02 (0.90)	0.257
HbA1c tertile 3 (vs. tertile 1)	1.86 (0.96)	0.054
BMI underweight (vs. normal weight)	NA	NA
BMI pre-obesity (vs. normal weight)	3.21 (1.05)	0.002
BMI obesity-class I (vs. normal weight)	2.89 (0.90)	0.002
BMI obesity-class II (vs. normal weight)	–0.11 (2.11)	0.958
BMI obesity-class III (vs. normal weight)	3.65 (4.71)	0.439

HbA1c was subdivided into tertiles: HbA1c ≤5.9% (tertile 1), >5.9% to ≤6.3% (tertile 2), and >6.3% (tertile 3) for the overall population, HbA1c ≤6.4% (tertile 1), >6.4% to ≤7.0% (tertile 2), and >7.0% (tertile 3) for the diabetes population; and HbA1c ≤5.7% (tertile 1), >5.7% to ≤6.0% (tertile 2), and >6.0% (tertile 3) for the pre-diabetes population; Underweight: BMI <18.5 kg/m^2, normal weight: BMI 18.5–22.9 kg/m^2, pre-obesity: BMI 23.0–24.9 kg/m^2, obesity-class I: BMI 25.0–29.9 kg/m^2, obesity-class II: BMI 30.0–34.9 kg/m^2, and obesity-class III: BMI ≥35 kg/m^2.
*Multivariable analysis of the relationship between risk factors and the Framingham risk score (multiple linear regression); †Number of observations with missing values: overall, 1,068; diabetes, 313; and pre-diabetes, 719.
SE, standard error; LVH, left ventricular hypertrophy; HbA1c, glycated hemoglobin; BMI, body mass index; NA, not applicable.

1.00 [tertile 2 vs. 1] and Δ = 2.24 [tertile 3 vs. 1]; *P* = 0.010) among subjects with pre-diabetes in comparison to those without these coexisting CV risk factors (Supplementary Table 2).

Multivariate analysis that included factors with statistical significance (*P* < 0.005) in the univariate analysis was performed to identify significant CV risk factors (Table 2). FRS was elevated in diabetic subjects (n = 199) who consumed alcohol (2.66, *P* = 0.033) and fell in the obesity-class II category (6.10, *P* = 0.015) while it was elevated in pre-diabetic subjects (n = 306) with LVH (11.10, *P* = 0.005), alcohol consumption (3.06, *P* < 0.001), pre-obesity (3.21, *P* = 0.002), and obesity-class I (2.89, *P* = 0.002) in comparison to subjects without these coexisting risk factors (Table 2).

Table 3. Framingham risk score according to HbA1c

Variable	n*	Parameter estimate	Standard error	*P*
Total	980			
Overall HbA1c†		2.41	0.26	<0.001
HbA1c (%)‡				
≥5 to <6	367	1.47	5.96	0.806
≥6 to <6.5	322	5.03	5.96	0.398
≥6.5 to <7	125	7.07	5.99	0.238
≥7	164	10.14	5.98	0.090

*The number of subjects included in the analysis; †Analysis for the relationship between HbA1c and FRS (linear regression analysis); ‡Analysis for the relationship between HbA1c classification and FRS (linear regression analysis).
HbA1c, glycated hemoglobin; FRS, Framingham risk score.

HbA1c, insulin usage, and association with FRS and CV risk

Overall, the mean ± SD HbA1c was 6.34% ± 1.03% (n = 1,154); HbA1c was 8.29% ± 2.06% in insulin users (n = 18) and 6.30% ± 0.98% in non-insulin users (n = 1,136), and a significant increase in FRS was noted with an increase in HbA1c (2.41, *P* < 0.001). Further, with each 0.5% to 1% increase in HbA1c from 5% to 7%, there was a directly proportional but statistically insignificant increase in the FRS (Table 3). HbA1c ≥7% was associated with a higher CV risk than an HbA1c <7% (odds ratio, 3.43; *P* = 0.026). Insulin usage, however, did not have a statistically significant association with the FRS. An increase in BMI tended to be associated with an increase in FRS. In particular, a J-shaped curve was observed in men with diabetes as the FRS was high for those men with a BMI <18.5 kg/m^2 (Fig. 3).

DISCUSSION

In this study, about 33% of subjects had diabetes, while the remaining subjects had pre-diabetes. Evaluation of CV risk using the

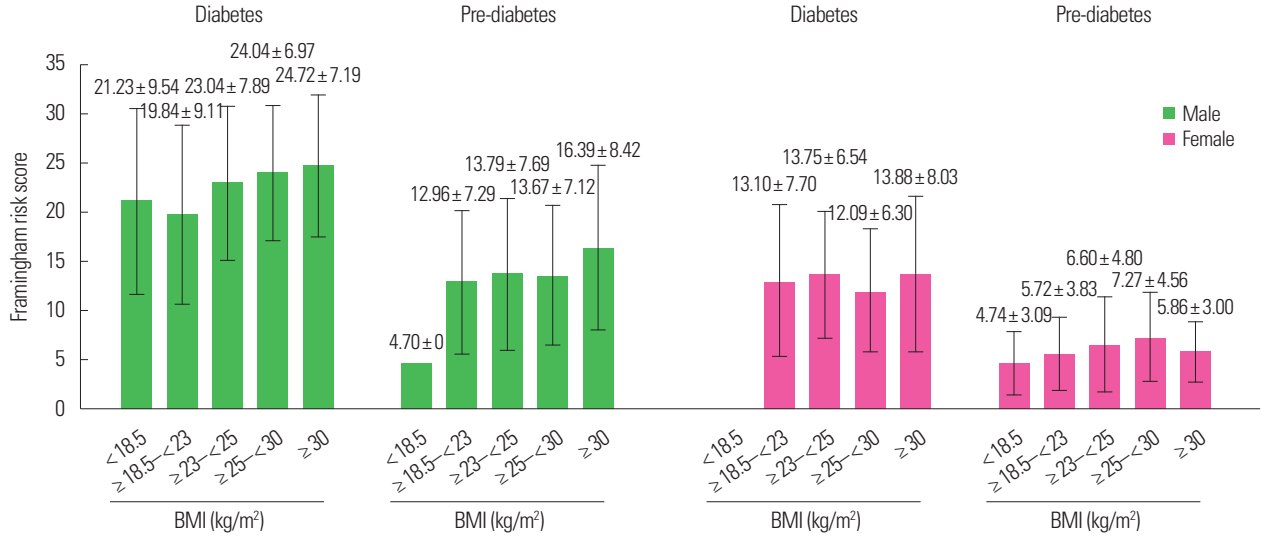

Figure 3. Comparison of Framingham risk score according to body mass index (BMI). Values are presented as mean ± standard deviation.

FRS indicated that CV risk was significantly higher in subjects with diabetes than in those with pre-diabetes. When stratified by sex, men were at a higher CV risk than women, and men with pre-diabetes had a similar CV risk to that of women with diabetes. In addition, alcohol consumption and obesity were the most significant predictors of CV risk in Koreans with diabetes, while LVH, pre-obesity, and obesity were the most significant predictors of CV risk in Koreans with pre-diabetes.

The FRS estimation used in this study has been traditionally used to predict the 10-year risk of coronary heart disease (CHD) by factoring in age, smoking status, lipid profile, blood pressure, and presence or absence of diabetes.[20,21] A survey based on data obtained from the third Korea National Health and Nutrition Examination in 2005 of 5,271 non-institutionalized civilians (aged 20–79 years) in the Republic of Korea revealed that the FRS was closely associated with prediction of CHD.[22] In the current study, the mean FRS of 13.72 in subjects with pre-diabetes and diabetes indicates intermediate risk of developing CVD including stroke, peripheral artery disease, heart failure, and ischemic heart disease within 10 years. In a 10-year follow-up study of 2,775 subjects at high risk of diabetes, the mean Framingham 10-year CV risk scores were the highest in subjects with pre-diabetes (16.2%), intermediate in subjects with normal glucose regulation (15.5%), and the lowest in subjects with diabetes (14.4%) ($P < 0.05$ for all pairwise comparisons).[23] In contrast, the present study established that the FRS was higher in subjects with diabetes than in those with pre-diabetes.

Various studies have been conducted to assess the impact of sex on diabetes-associated CV risk.[24-26] In a cohort of 1,378 subjects selected from the Maracaibo City Metabolic Syndrome Prevalence Study, significantly higher coronary risk was observed in men with normoglycemia (3.28%) than women with normoglycemia (2.05%) ($P < 0.001$) and in men with IFG (4.90%) than women with IFG (2.75%) ($P < 0.001$). Although the overall risk was greater in subjects with diabetes than in subjects with normoglycemia or IFG, no sex differences were evident.[24] A meta analysis of 37 prospective cohort studies of T2DM and fatal CHD among 447,064 subjects revealed that the relative risk for fatal CHD associated with diabetes was 50% greater in women than in men.[26] However, in the present study, the FRS in men was higher than that in women in both pre-diabetes and diabetes groups, indicating a clear sex difference. Men with pre-diabetes had a CV risk similar to women with diabetes. This finding highlights the need to create awareness that men with pre-diabetes are at greater risk of developing CV complications than women with pre-diabetes.

CV risk factors including obesity, hypertension, and dyslipidemia are common among subjects with diabetes, increasing the risk for CV events. It is therefore important to target CV risk factors in subjects with diabetes to minimize long-term CV complications associated with diabetes.[27] We found that the mean FRS was notably higher in subjects with high CV risk than in subjects without high

CV risk ($P=0.048$) and confirmed that alcohol consumption (increased FRS by 2.66; standard error, 1.24; $P=0.033$) and obesity-class II[28] (increased FRS by 6.10; standard error, 2.49; $P=0.015$) were significant contributors to CV risk in subjects with diabetes in Korea. In a study conducted in Taiwan that included 439 subjects with chronic kidney disease, presence of diabetes, coronary artery disease, low albumin, low hemoglobin, low estimated glomerular filtration rate, high uric acid, proteinuria, left atrial diameter > 4.7 cm, LVH, and left ventricular ejection fraction < 50% were all significantly associated with an increase in CV events.[29] We found that LVH ($P=0.005$), alcohol consumption ($P=0.000$), pre-obesity ($P=0.002$), and obesity-class I ($P=0.002$) were significantly associated with increased FRS in subjects with pre-diabetes in Korea. In contrast, various studies have shown that moderate alcohol consumption is associated with a reduced risk of incident diabetes.[30,31] Obesity is a well-established risk factor for developing CV disease[32] consistent with our findings in this study; both obesity and pre-obesity were significant contributors to increased CV risk in subjects with pre-diabetes or diabetes.

Association between HbA1c and CV risk and mortality has been extensively investigated.[27] A systematic review (74 studies) and meta-analysis (46 studies) conducted by Cavero-Redondo et al.[33] that included observational studies established that HbA1c had a positive association with all-cause mortality and CV mortality in both subjects with diabetes and those without diabetes. A study of 34,737 subjects with T2DM reported increased microvascular and macrovascular events in subjects with diabetes and HbA1c levels ≥ 6.5% as compared to subjects with HbA1c < 6.5% for the 0- to 1-year early exposure period.[34] A retrospective study of 2,879 Korean adults aged 40 to 79 years without diabetes revealed that HbA1c levels were positively correlated with the FRS and may reflect CVD risk in subjects without diabetes.[35] In the present study, we demonstrated that an increase in HbA1c was associated with an increase in the FRS, indicating a higher probability of CV complications in subjects with uncontrolled diabetes. In subjects with high CV risk, the FRS was higher when HbA1c was ≥ 7%, alcohol was consumed, and LVH was present. HbA1c ≥ 7% was associated with higher CV risk as compared to HbA1c < 7%, emphasizing the need for HbA1c control to prevent CV complications in subjects with pre-diabetes and diabetes in Korea.

Several meta-analyses of randomized controlled trials investigating the effects of intensive glycemic control on all-cause mortality, CV death, and vascular events in T2DM have shown limited benefits of therapy and no significant effects on CV outcomes.[36-39] In this study, insulin usage did not significantly affect the FRS or high CV risk. However, the association between HbA1c and insulin usage and their cumulative effects on the FRS need to be further substantiated through future studies to assess the impact of insulin usage on the FRS and high CV risk.

BMI has been reported to be a strong predictor of future risk of CHD.[40] Positive, inverse, or U- and J-shaped associations between BMI and mortality among subjects with diabetes have been reported in different studies.[41-44] Association between BMI and CHD risk among 30,434 low-income and underinsured subjects with diabetes in the United States was positive among both men and women with T2DM at baseline and during the more than 7 years of follow-up.[45] The current study confirmed that CV risk increases with increasing BMI in subjects with diabetes, highlighting the importance of monitoring BMI to prevent CHD among subjects with diabetes.

Limitations of the study

This study assessed CV risk in subjects with pre-diabetes and diabetes based on their medical records, which is a limitation of this study, as the data may not be reliable if the required information was not noted correctly in the medical records. The period of the study over which the data were collected, i.e., 7 months may not be a representative of long-term trends. Because subjects with normal glucose levels were not included, the CV risk in subjects with pre-diabetes and diabetes could not be compared to that of non-diabetic subjects. Factors required for calculation of FRS included status of treatment with antihypertensive drugs. However, because antihypertensive treatment status was not available in 276 subjects, the FRS could not be calculated for these cases. However, an imputation method was used to account for subjects for whom antihypertensive treatment status was not available, and the mean ± SD FRS calculated using for this dataset was similar to that of the group for which data were available. Furthermore, data on the use of antihyperlipidemic drugs were missing for 341 subjects and may have impacted the FRS results. Some of the missing data, such as that on

alcohol consumption, could also have impacted the results. In addition, to determine high CV risk, previous MI, stroke, revascularization, and angina were assessed. Due to difficulty in elucidating the time sequences of these events in this cross-sectional study, we could not confidently assess correlations between the effects of current insulin use/status of HbA1c control and high CV risk. Furthermore, very few subjects were on insulin therapy. Family history of premature CV events is an important determinant of CV risk.[46] However, data on the family history of premature CV events were not collected in this study; further studies are needed to determine if family history of premature CV events affects CV risk. Finally, some researchers have suggested that the FRS may not be suitable for some populations, including Koreans.[47] Therefore, the results of this study should be verified using other CV risk scoring models. In conclusion, based on the overall distribution and characteristics of CV risk, Korean subjects with pre-diabetes and diabetes are at high risk for developing CVD, and subjects with diabetes have a significantly higher predisposition for developing CVD than those with pre-diabetes. Risk stratification based on sex, BMI, and underlying comorbidities can be used to develop measures to prevent and manage CV complications in Korean subjects with impaired glucose metabolism.

CONFLICTS OF INTEREST

Won Kim and Kyoung Hwa Lee are employees of Sanofi. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: HSK, KHS, ISN, and TSP; acquisition of data: HSK, KHS, ISN, TSP, JMY, DSK, HSS, KJA, SHC, and SHK; analysis or interpretation of data: HSK, WK, and KHL; drafting of the manuscript: HSK, KHS, and WK; critical revision of the manuscript: HSK and WK; and study supervision: ISN and TSP.

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