

Is There a Difference in Cardiovascular Disease Risk Between Newly Diagnosed Male and Female Korean Diabetes Subjects?: Korea National Health and Nutrition Examination Survey

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Abstract- In the general population, males show increased cardiovascular disease prevalence compared to females of similar age. However, evidence suggests women with diabetes might show similar or even increased risk for cardiovascular disease (CVD) compared to diabetic males of similar age. The aim of this study was to demonstrate if future CVD risk gender differences exist at the time of diabetes diagnosis, and to examine which CVD risk factors contribute to increased CVD risk in Korean women with diabetes compared to men with incident diabetes. CVD gender risk factor differences were investigated in subjects from the Korea National Health and Nutrition Surveys (KNHANES), 2007-2010, CVD risks were estimated using the Framingham risk prediction model, and the relative attribution power of CVD risk factors were analyzed by gender and risk groups. 402 subjects (1.8%) were drawn from 33,829 population-based subjects newly diagnosed with diabetes. There were no significant gender differences for 10-year coronary heart disease (CHD) and CVD risk at the time of diabetes diagnosis. Hypercholesterolemia, high LDL-cholesterol, low HDL-cholesterol and abdominal obesity prevalence were higher in newly diagnosed diabetic women than men in the CHD risk groups. The odds ratio for increased CHD risk for abdominal obesity was 4.656, higher LDL-cholesterol was 2.837, lower HDL-cholesterol was 2.958 and hypercholesterolemia was 1.940 in newly diagnosed diabetic women compared to men.

In conclusion, abdominal obesity and dyslipidemia control can be the most important treatment strategy to reduce future CVD risk in newly diagnosed Korean diabetic women.

Index Terms— cardiovascular disease, gender difference, newly diagnosed diabetes.

I. INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death in many countries. Diabetes is a powerful risk factor related to increased CVD [1], [2]. CVD is less prevalent in Korea compared to Western countries, however recent increases in obesity and diabetes have resulted in CVD becoming the second most important cause of death in Korea [3]. In the general population, women show lower risk for cardiovascular disease compared to men of similar age [4]-[6], however this female protection seems to be absent when women are diabetics [7]-[9]. Evidence shows that women with diabetes are at greater risk for CVD and higher

all-cause mortality compared to men [10], [11]. However, this evidence was based on study results from western populations. Although CVD risk factors were related to CVD occurrence across all ethnic groups, many reports suggest that CVD risk factor distribution and clinical characteristics correlate with ethnicity [12]-[15]. Moreover, there is no data on gender-associated CVD risk differences in newly diagnosed Korean diabetes patients. Therefore, we investigated if gender difference for future cardiovascular disease risk exist in adult Korean women and men at diabetes diagnosis, and asked what different kinds of cardiovascular risk factors were associated with increased CVD risk in women with diabetes compared to men in newly diagnosed Korean diabetic patients

II. SUBJECTS AND METHOD

A. Study subjects

Data from the Korea National Health and Nutrition Examination Survey (KNHANES) collected by the Korea Centers for Disease Control and Prevention and the Korean Ministry of Health and Welfare from 2007 to 2010 were analyzed in this study. A total of 33,829 subjects aged 20 to 85 were studied. The KNHANES survey included a health interview, a health examination, and a nutrition survey. KNHANES was a nationwide study of the healthy population and used a stratified and multistage probability sampling design with a rolling survey-sampling model. Well-trained staff conducted in person interviews with structured questionnaires. Subjects who had histories of taking steroids and high risk groups for steroid use including bronchial asthma, allergic disease and autoimmune disease were excluded. Subjects with a history of malignant disease, recent pregnancy, infectious disease such as tuberculosis and pneumonia were also excluded. Subjects with a creatinine level over 1.5 mg/dL, serum bilirubin over 2.0 mg/dL and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) over 100 U/L were also excluded. After these exclusions, a total of 21,797 subjects remained, and new onset diabetes subjects were selected. New onset diabetes diagnosis was defined as plasma glucose greater than 126 mg/dL without a reported diabetes history. A total of 402 subjects (208 men and 109 women) from the original 33,829 were selected for analysis in this study. The database contained no identifiable information and all subjects provided written consent. Submit your manuscript

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electronically for review.

B. Anthropometric measurements

A well-trained staff measured the subjects by predefined methods. Heights and weights were measured while patients wore light clothing with shoes off in centimeters and kilograms, respectively. Waist circumference (WC) was measured at the end of inspiration at the horizontal middle line between the lower costal margin and iliac crest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained with a mercury sphygmomanometer (Baumanometer; W. A. Baum Co., Inc., Copiague, NY, USA) three times for each subject after seated resting for at least 5 minutes before measurement. Average BP values obtained during the second and third measurements were used for analysis. Total body fat (%) was measured by whole body dual-energy X-ray absorptiometry (DXA) using a QDR Discovery fan beam densitometer (Hologic Discovery, Hologic, USA).

C. Biochemical measurement

Blood was sampled after a minimum of eight hours after last food intake. Fasting blood glucose (FBG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), gamma glutamyltransferase (γ GTP) and creatinine levels were measured enzymatically using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) by the Central Testing Institute in Seoul, Korea.

Complete blood count (CBC) was measured using XE-2100D (Sysmax, Japan). HbA1C levels were measured with high performance liquid chromatography using HLC-723G7 (Tosoh, Japan). Serum 25(OH)D3 levels were measured with radioimmunoassay using the 1470 Wizard Gamma Counter (PerkinElmer, Finland). Serum ferritin levels were measured with immunoradiometric assay using a 1470 Wizard Gamma Counter (PerkinElmer, Finland).

D. Cardiovascular risk assessment

Several prospective cohort studies have utilized risk scoring systems to predict future CVD [16]-[18]. The Framingham risk model for coronary heart disease (CHD) and CVD prediction is based on results from the Framingham Heart Study and has been validated in the US population, both in men and women [19]. Although the Framingham Risk Score (FRS) can overestimate CVD risk in populations other than the US population [20]-[22], it is considered one of the best predictive scoring systems for future CVD [23]. Moreover, there is no well-recognized and validated CVD risk prediction tool specified for Korean people, so FRS was used to estimate future CHD and CVD risk in this study. Overweight and obesity was defined as a body mass index (BMI) over 23 kg/m² and abdominal obesity was defined by WC over 90cm in men and 85cm in women respectively. Systolic and diastolic hypertension were defined as 140/85mmHg and over. Hypercholesterolemia was defined as a cholesterol level 200 mg/dL or greater,

Table 1. Study Subject baseline characteristics

Variables	Men (n=208)	Women (n=194)	P value
Age, yrs	55.14 ± 14.12	58.51 ± 14.36	0.019
Smoking	60 (29.7%)	61 (33.0%)	0.511
SBP, mmHg	129.6 ± 15.70	130.3 ± 19.31	0.715
DBP, mmHg)	82.98 ± 10.15	80.16 ± 10.5	0.006
Total cholesterol, mg/dL	199.39 ± 40.01	215.06 ± 38.42	0.000
HDL cholesterol, mg/dL	44.89 ± 1 0.40	49.75 ± 11.64	0.000
Triglyceride, mg/dL	224.99 ± 179.81	170.20 ± 116.81	0.000
LDL cholesterol, mg/dL	115.35 ± 36.95	135.41 ± 35.52	0.000
non_HDL cholesterol, mg/dL	154.50 ± 39.30	165.31 ± 38.32	0.006
AST , U/L	28.56 ± 16.05	24.70 ± 11.45	0.006
ALT , U/L	31.85 ± 17.44	25.46 ± 14.07	0.000
rGTP, U/L	58.59 ± 42.45	42.53 ± 44.65	0.072
Creatinine, mg/dL	0.97 ± 0.16	0.76 ± 0.15	0.000
WBC, ×10 ³ /μL	7.06 ± 1.85	6.60 ± 1.87	0.014
Platelet, ×10 ³ /μL	250.47 ± 51.87	272.05 ± 63.15	0.066
Fasting glucose, mg/dL	152.22 ± 35.24	157.26 ± 43.15	0.198
HbA1C, %	7.16 ± 1.60	7.27 ± 1.66	0.505
BMI, kg/m ²	25.07 ± 3 .57	26.19 ± 3.68	0.002
Waist circumferences, cm	88.09 ± 9.18	87.71 ± 10.20	0.694
Whole body fat, %	23.41 ± 4.69	35.84 ± 5.15	0.000
25(OH)D ₃ , ng/dL	20.22 ± 7.30	17.82 ± 7.042	0.324
Ferritin, ng/mL	181.23 ± 196.63	78.52 ± 60.84	0.000
HOMA-IR	5.42 ± 4.92	7.22 ± 10.56	0.028

Values are presented as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGTP, gamma glutamyltransferase; WBC, white blood cell; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

hypertriglyceridemia was defined as triglyceride level 200 mg/dL or over. High LDL-cholesterol was defined as LDL-C

140 mg/dL or over and low HDL-cholesterol was defined as an HDL-C level less than 40 mg/dL in men, and 50 mg/dL in

women respectively.

A. Statistical analysis

Data are presented as mean ± standard deviation (SD) or standard errors (SE). In order to compare baseline clinical characteristics, a t-test was used. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare variables and risk factors between men and women in different cardiovascular risk groups. Future CHD and CVD risks were driven by the FRS risk scoring system and subjects were divided into three groups: low risk, high risk or very high risk groups. These were considered as less than 10%, between 10 to 20% and over 20% for CHD-FRS risk and less than 20%, between 20 to 40% and over 40% for CVD-FRS risks respectively for categorization in the ANOVA and ANCOVA. The Cochran-Mantel-Haenszel Chi-square test was used to analyze variables that contributed to increased 10-year CHD risk in women compared to men, and increased CHD risk groups were defined as high or very high FRS CHD risk groups. All Statistical tests were two tailed. A P-value of less than 0.05 was considered statistically significant. 95% confidence intervals for each variable were calculated. Data was analyzed with the Statistical Package for Social Science version 18.0 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

A. Subject characteristics

402 subjects (1.8%) with newly diagnosed type 2 diabetes drawn from 33,829 population-based standard subjects of KNHANES were included. 208 men (51.7%) and 194 women

(48.3%) were included respectively. Newly diagnosed diabetes patients baseline characteristics by gender are presented in Table 1. Mean age for new-onset diabetes women was 58.5 years and 55.1 for men (p=0.019). Mean body mass index (BMI), whole body fat, total cholesterol, triglyceride, LDL-cholesterol, non-HDL cholesterol, white blood cell count and diastolic pressure were significantly different between men and women. But, mean value for waist circumference, systolic blood pressure, fasting blood glucose and HbA1C were not different between men and women. Decreased ferritin level in women was observed and thought to be associated with menstruation in premenopausal women.

B. CHD and CVD risk in women and men with incident diabetes

Future CHD and CVD risks predicted by the Framingham model were similar between women and men in newly diagnosed diabetic Korean patients and the risk was significantly increased by age for both genders (Fig. 1). After controlling for age, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, non-HDL cholesterol and triglyceride were different between different CHD risk groups for both genders. Whole body fat was statistically significant only in men (Table 2). BMI, WC and LDL-cholesterol were not statistically difference between the CHD risk groups after adjustment for age. Similar results were observed for the different CVD risk groups except systolic blood pressure was not significantly different between men and WC was significantly different between women (Table 2).

Table 2. Age-adjusted mean values for parameters between different cardiovascular risk groups by gender.

Variables	Men (n=208)			P value	Women (n=192)			P value
	<10%	10~20%	≥20%		<10%	10~20%	≥20%	
CHD-FRS								
Numbers (%)	67 (32.2%)	83 (39.9%)	58 (27.9%)		66 (34.4%)	73 (39.1%)	51 (26.6%)	
Age, year	41.9±8.1	55.8±9.6	69.5±10.0	0.000	44.9±11.1	63.48±10.9	68.75±8.6	0.000
BMI, kg/m ²	24.1±1.6	25.5±0.3	26.2±0.6	0.77	25.9±0.7	25.9±0.5	26.7±0.8	0.639
WC, cm	86.1±1.6	88.5±1.0	90.5±1.7	0.264	85.7±2.14	88.0±1.5	88.9±2.2	0.631
WBF, %	21.4±0.9	23.6±0.6	25.2±1.0	0.043	37.4±1.1	35.1±0.7	35.4±1.1	0.259
sBP, mmHg	119±2.7	129±1.7	145±2.9	0.000	120±3.1	135±2.2	139±3.2	0.000
dBp, mmHg	79±1.7	85±1.1	88±1.9	0.008	75±1.9	83±1.3	86±2.0	0.001
T-chol, mg/dL	186±7.6	192±4.7	227±8.19	0.001	200±7.0	213±4.9	236±7.3	0.004
HDL-C, mg/dL	55.5±1.9	45±1.2	37±2.0	0.000	59.0±2.26	51.1±1.6	41±2.35	0.000
LDL-C, mg/dL	102.2±9.5	110±7.9	127±12.5	0.367	122.5±10.5	130±9.0	138±11.1	0.677
non HDL-C, mg/dL	131±7.04	147±4.4	189±7.6	0.000	141±6.6	161±4.6	195±6.9	0.000
TG, mg/dL	138±36	232±23	369±39	0.001	129±25.3	174±17.7	266±26.3	0.002
HOMA-IR	3.8±0.5	4.8±0.3	4.5±0.6	0.291	6.1±2.2	7.2±1.5	4.1±2.2	0.484
CVD-FRS								
Numbers (%)	84(40.4%)	82(39.4%)	42(20.2%)		77(40.1%)	70(36.5%)	45(23.4%)	
Age, year s	42.8±7.9	59.5±9.6	71.3±9.1	0.000	45.4±8.8	63.2±8.8	73.6±9.0	0.000
BMI, kg/m ²	24.4±0.5	25.4±0.4	26.9±0.7	0.052	25.6±0.7	26.2±0.5	26.4±0.9	0.832
WC, cm	85.6±1.4	88.7±1.1	93.0±2.0	0.038	85.6±2.1	88.3±1.6	88.8±2.5	0.640
WBF, %	22.3±0.8	23.5±0.6	25.6±1.1	0.197	36.4±1.1	35.4±0.8	35.8±1.3	0.761
sBP, mmHg	117.6±2.3	133.6±1.8	151.0±3.2	0.000	120.0±3.1	136.8±2.3	141.5±3.7	0.681
dBp, mmHg	79.1±1.5	86.3±1.2	91.2±2.1	0.000	75.2±1.9	84.1±1.4	87.3±2.27	0.000
T-chol, mg/dL	197.6±6.9	191.1±5.4	221±9.6	0.011	198.8±7.1	217.6±5.3	237.3±8.5	0.016
HDL-C, mg/dL	52.2±1.8	44.7±1.4	36.7±2.4	0.000	60.1±2.4	50.1±1.7	42.6±2.8	0.003
LDL-C, mg/dL	110.3±9.8	111.1±8.6	113.3±14.2	0.987	121.2±9.3	133.8±8.3	141.5±13.4	0.562
Non HDL-C, mg/dL	145.3±6.6	146.4±5.1	184.7±9.1	0.001	140.9±6.9	167.5±5.1	194.7±8.2	0.000
TG, mg/dL	184.6±32.6	221.1±25.4	399.8±45.3	0.001	110.8±25.1	194.1±18.5	276.4±29.9	0.002
HOMA-IR	4.3±0.5	4.6±0.4	4.4±0.7	0.914	6.7±2.1	6.7±1.6	4.3±2.5	0.681

Values are presented as mean ± standard error. CHD-FRS, Framingham risk score for coronary heart disease ; CVD-FRS, Framingham risk score for cardiovascular disease, BMI, body mass index; WC, Waist circumference; WBF, whole body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Non HDL-C, non-high density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance.

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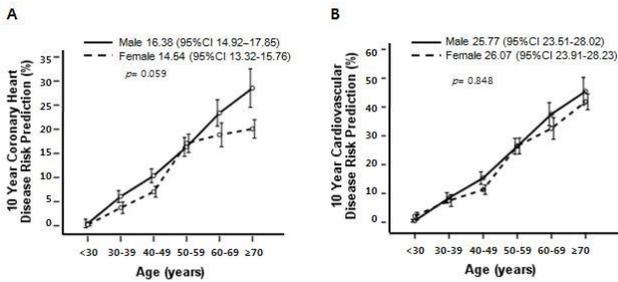


Fig. 1. Age-specific distribution for 10-year coronary heart disease risk (A) and cardiovascular disease risk (B) prediction based on the Framingham model for men and women.

There are no statistically significant differences for 10-year CHD risk (A) and CVD risk (B) by gender difference, but there are significant gradually increased risks by age for both gender groups.

C. Metabolic risk factor differences between CHD risk groups by gender.

Obesity and abdominal obesity prevalence was higher in women compared to men for all CHD groups. Hypertension prevalence was similar for both genders in all CHD risk groups (Fig. 2). Hypercholesterolemia, high LDL-cholesterol and low HDL-cholesterol prevalence were higher in women than men and men showed higher triglyceride levels than women in all CHD risk groups (Fig. 3). The odds ratio for increased 10-year CHD risk (>10%) associated with abdominal obesity was 4.656, higher LDL-cholesterol was 2.837, lower HDL-cholesterol was 2.958 and hypercholesterolemia was 1.940 in newly diagnosed diabetic women compared to men (Table 3).

I. DISCUSSION

Korean women with incident diabetes showed similar future CVD and CHD risks compared to diabetic men for all the age groups at the time of diabetes diagnosis. There is evidence to suggest that prevalence, disease progression and treatment outcomes for people with type 2 diabetes vary significantly between ethnic groups [24]-[26]. Although several reports suggested that risk factor distributions and their impacts on developing CVD and treatment outcomes for diabetes patients vary between different ethnic groups [27]-[29], our results showed an increase in CVD risk and loss of female protection for newly diagnosed Korean diabetic women similar to western mostly Caucasian women.

Unlike a similar CVD risk for incident diabetic subjects, in the Korean general population, the CVD risk for females driven by the FRS prediction for 10-year CHD was half the rate seen in males, 11.06 (95% CI 10.62-11.49), and 5.52 (95% CI 5.28-5.75) in females respectively [30]. During the transition from normoglycemia to hyperglycemia, cardiometabolic risk factor changes were more pronounced in women than men. Wannamethee et al. showed that women with diabetes gained more fat during the transition from nondiabetic to diabetic compared to men [31]. Similar results were demonstrated in the Korean population. Korean women showed higher obesity levels at the time of diabetes diagnosis [32].

In this study, women with diabetes showed worse lipid profiles. Women had higher total cholesterol, higher LDL-cholesterol and lower HDL-cholesterol levels which are known to be powerful risk factors for atherosclerosis development and progression. However, gender differences for lipid profile were not observed in the general Korean population [33]. Gouni-Berthold et al. reported that less intensive treatment for hyperlipidemia in diabetic women than men might be a possible cause for increased CVD in diabetic women [34]. However, Kanaya AM et al. demonstrated the excess CHD mortality risk in women with diabetes disappeared after controlling for classic CHD risk factors including cholesterol level [35]. If an initial worse lipid profile was combined with less intensive treatment, future CVD could be further intensified in women with diabetes.

In this study, after adjusting for gender-related confounders, abdominal obesity, high LDL-cholesterol and low HDL-cholesterol were powerful predictors for increased future CHD risk. Considering these results and others, intensive lipid management combined with abdominal obesity control along with glycemic control can form a best treatment strategy to reduce CHD and CVD in women with diabetes [34], [35]. If we compare intervention success rates, lipid management's high success rate [36] compared to the disappointing weight reduction success rate [37], lipid lowering management can be an important strategy for CVD reduction in diabetic women, although continuous efforts aimed at progressive body weight control should be maintained.

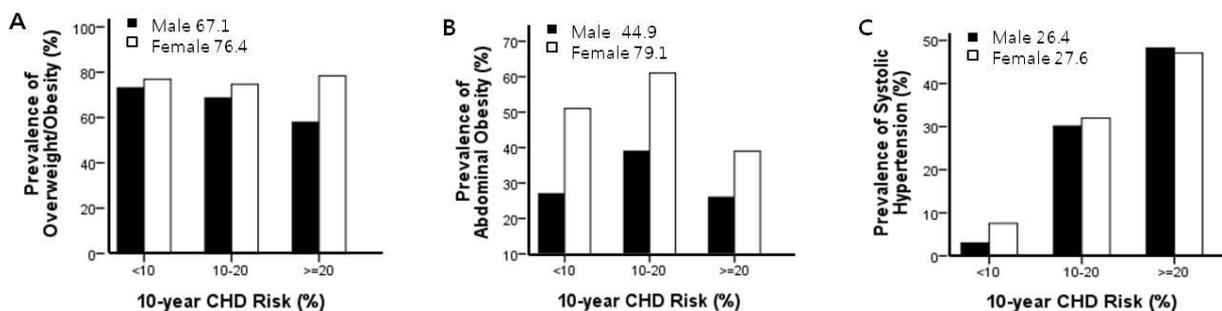


Fig. 2. Overweight/obesity (A), abdominal obesity (B), and hypertension (C) prevalence by different 10-year CHD risk for men and women.

Black squares represent male and white squares represent females. Prevalence for overweight or obesity in men (A) was 67.1% in men and 76.4% in women with increased prevalence in women between different CHD risk groups. Prevalence for abdominal obesity (B) is higher in women, however the prevalence for hypertension (C) was not different between men and women.

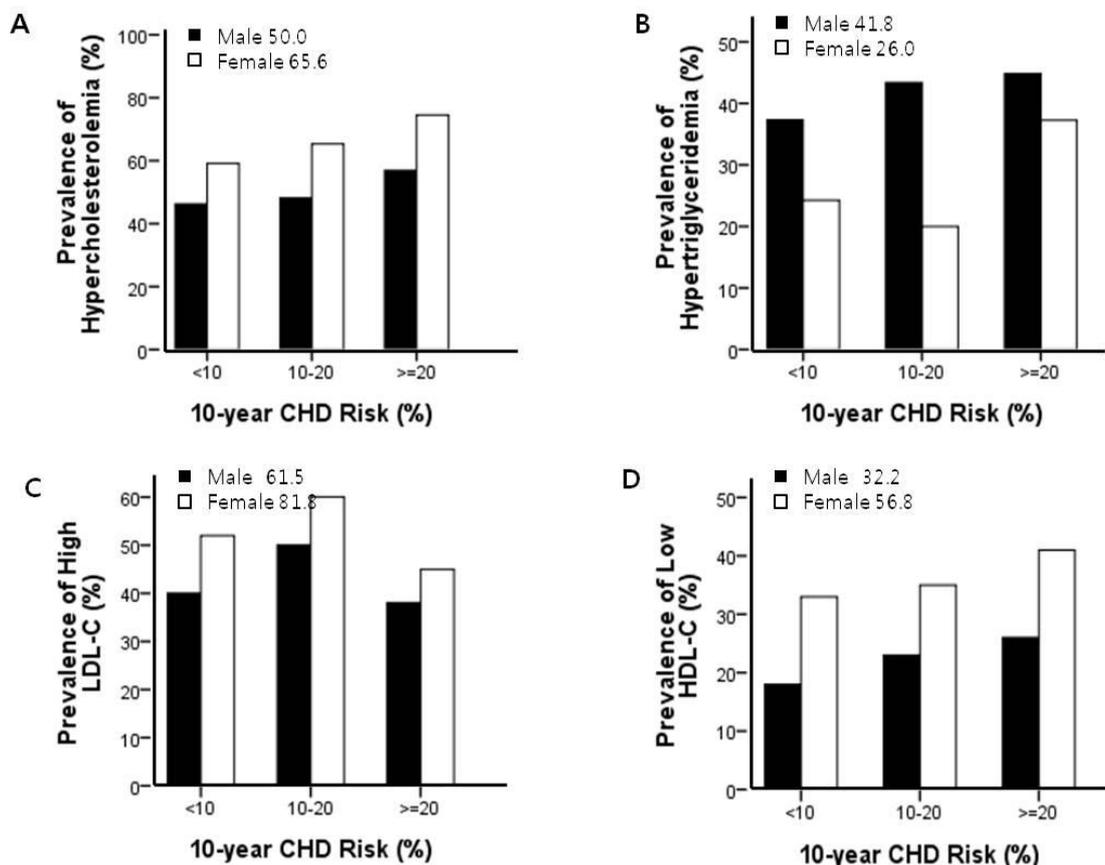


Fig. 3. 10-year CHD risk specific prevalence for dyslipidemia in men and women with incident diabetes.

Black squares represent males and white square represent females. Prevalence for hypercholesterolemia (A) was 50% in men and 65.6% in women with increased prevalence in women between different CHD risk groups. Prevalence for hypertriglyceridemia (B) was higher in men, however prevalence for LDL-cholesterol (C) and low HDL-cholesterol (D) was higher in women

Table 3. Odds ratio for risk factors contributing to increased Framingham 10-year CHD risk in newly diagnosed diabetic women compared to men.

Variables	OR	95% CI	P-value*
Overweight/obesity	1.597	1.015-2.453	0.043
Abdominal obesity	4.656	2.985-7.265	0.000
Systolic hypertension	1.122	0.696-1.808	0.637
Diastolic hypertension	0.590	0.374-0.932	0.024
Hypercholesterolemia	1.940	1.292-2.911	0.001
Hypertriglyceridemia	0.492	0.321-0.752	0.001
High LDL-C	2.837	1.786-4.507	0.000
low HDL-C	2.958	1.940-4.510	0.000
Smoking	1.148	0.728-1.811	0.552
hypertension treatment	1.261	0.757-2.251	0.432
Dyslipidemia treatment	1.694	0.616-4.655	0.307

OR, odds ratio; CHD, coronary heart disease; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. Increased Framingham 10-year coronary heart disease risk was defined as over 10%. P-values* were estimated by the Cochran-Mantel-Haenszel Chi-square test, covariate

This study has several limitations. First, the sample size is relatively small, especially for age groups older than 70 years, although subjects were selected randomly from the general population. Second, data were cross-sectional and CVD risk was estimated using the FRS. Data showing a causal relationship between CVD risk factors at the time of diabetes diagnosis and real CVD events was restricted in the Korean

population, and the FRS might overestimate CVD risk for populations other than the US [20]-[22], although it is considered to be one of the best scoring systems for predicting future CVD [23]. Therefore, further prospective studies are needed to confirm this study's results. Third, the effects of hormonal changes including menopause in women were not accounted for, although changes in estrogen levels are known to be associated with CVD risk [38]. However, the effect of hormones was not the main concern of this study and subject ages were randomly distributed between 20's to 80's.

Nevertheless, this study has several strengths. This is the first study to demonstrate a similar future CVD risk in incident Korean diabetes subjects. We also showed CVD risk was doubled in women with incident diabetes compared to women without diabetes, because CVD risk was half in women compared to men in the general Korean population. Increased abdominal obesity and elevated LDL-cholesterol with decreased HDL-cholesterol were the most powerful risk factors that predicted future CVD risks in women with diabetes. Therefore, abdominal obesity and dyslipidemia control may be the most important treatment strategy to reduce future CVD risk in newly diagnosed Korean women with diabetes.

ACKNOWLEDGMENT

No potential conflicts of interest relevant to this article were reported..

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