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Silent coronary artery disease and incidence of cardiovascular and mortality events at different levels of glucose regulation; results of greater than a decade follow-up ☆

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ABSTRACT

Background: To determine the impact of silent coronary artery disease (CAD), in different levels of glucose regulation at baseline, i.e., those with normal fasting glucose/normal glucose tolerance (NFG/NGT), pre-diabetic and newly diagnosed diabetes mellitus (NDM), on cardiovascular disease (CVD) and total mortality in Iranian populations.

Methods: The study population included 1809 individuals, aged ≥50 years, free of CVD at baseline with a median follow-up of 12.1 years. To explore the risk of CVD and mortality associated with the presence of silent CAD (as defined by Minnesota coding criteria for baseline electrocardiogram (ECG) in the absence of a history of CVD) in each of the glucose regulation categories, multivariate adjusted hazard ratios (HRs) were calculated for the presence of silent CAD, compared to the corresponding non-silent CAD counterpart, as reference.

Results: During follow-up 382 CVD (321 coronary heart disease) and 208 deaths (91 CVD mortality) occurred. Among the female population, the presence of silent CAD, independent of traditional risk factors, significantly increased the risk of CVD for population with NFG/NGT [2.40 (1.33–4.35)] and pre-diabetes [HR: 2.04 (1.14–3.63)]; however, in the male population the risk was significant for CVD [3.04 (1.53–6.05)] and mortality events [2.60 (1.22–5.56)] in the NDM population and marginally significant for mortality events in NFG/NGT.

Conclusion: Different strategies should be considered for silent CAD in males and females with different levels of glucose regulation. It might be justified that screening ECG for prevention of CVD events should be considered mainly among non-diabetic women and men with NDM.

1. Introduction

Silent myocardial ischemia, first described by Stern [1], is defined as an ischemic episode documented by any objective method of diagnosis without having related symptoms [2]. Despite the increasing attention given to ischemic heart disease during recent decades, coronary heart disease (CHD) remains the first cause of mortality in many countries. One of the proposed reasons might arise from the fact that about 70–80% of ischemic episodes detected by Holter monitoring remain silent [3,4] and only some of these episodes present with angina or ischemic associated symptoms.

On the other hand studies report higher incidences of cardiovascular complications among diabetic and pre-diabetic patients [5,6]. Asymptomatic diabetic persons experience higher rate of cardiovascular complications associated with silent coronary artery disease (CAD) and have a poorer prognosis compared to non-diabetic individuals [7]. It was also recently shown that in newly diagnosed diabetic mellitus (NDM) patients, evidence of silent myocardial infarction (MI) increased the risk of fatal MI and all-cause mortality [8]. Furthermore, the status of silent ischemia and its prognosis among pre-diabetic individuals have been poorly evaluated (i.e., those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both) [9]. To the best of our knowledge, only one study has so far assessed cardiovascular morbidities of patients with IFG, but they did not use oral glucose tolerance test (OGTT) to exclude cases of NDM [10].

The public health burden of diabetes mellitus (DM) is growing globally, especially in the Middle Eastern region [11,12]. It was determined that about one third of Tehranian adults, aged ≥20 years were affected by some degrees of hyperglycemia, including impaired glucose tolerance or DM [13]. Furthermore, it was shown that the impact of DM

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and pre-diabetes status on cardiovascular disease (CVD) among females was stronger than in their male counterparts [14,15].

This study was conducted in a large community based cohort of the Tehran Lipid and Glucose Study (TLGS), to determine the impact of silent CAD in different glucose tolerance statuses i.e., those with normal fasting glucose/normal glucose tolerance (NFG/NGT), prediabetic and NDM patients, on CVD/CHD events and total mortality in Iranians, which could facilitate designing of appropriate health strategies.

2. Methods

2.1. Study population

In brief, TLGS is a prospective population-based cohort study carried out on 15,005 people, aged ≥3 years, living in district 13 of Tehran, to ascertain the risk factors for non-communicable diseases and to develop population-based measures to develop healthy lifestyles to prevent the growing trends in non-communicable disease risk factors. Age and sex distributions of the population in the district were representative of the overall population of Tehran at the time of the baseline examination [16]. From the overall general population those aged ≥50 years at the baseline TLGS examination (February 1999–August 2001) entered the study (n = 3394). Participants who were treated by antidiabetic medications (n = 460), with history of CVD (n = 443) and those with missing data on fasting plasma glucose (FPG) or 2 hour post load glucose (2 h-PLG) or electrocardiogram (ECG) data (n = 501) were excluded, leaving 1990 participants of which 1809 (female = 957) participants were followed up until 20th March 2012, a median of 12.1 years (Fig. 1).

All participants provided written, informed consent. The protocol of the present study was designed in accordance with the principles of the Helsinki declaration, and was approved by the Research Council of Research Institute of Endocrine Sciences of Shahid Beheshti University.

2.2. Clinical, anthropometric, and laboratory measurements

The details of data gathering have been described elsewhere [16]. Using pretested questionnaires which included demographic data, age, past medical history of CVD, drug consumption and smoking behavior, subjects were interviewed privately, face-to-face by trained interviewers. Weight, height, waist circumference (WC), and blood pressure were measured according to the standard methods [16]. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). A 12-lead resting ECG was recorded by two trained technicians according to a standard recording protocol developed by the School of Public Health, University of Minnesota [17] using a PC-ECG 1200 machine. Two trained physicians coded the ECGs independently according to the Minnesota codes using a measuring loupe specially manufactured by the University of Minnesota [18]. For assurance of quality, a third trained physician recoded 10% of ECGs and all the data were doubly entered and rechecked.

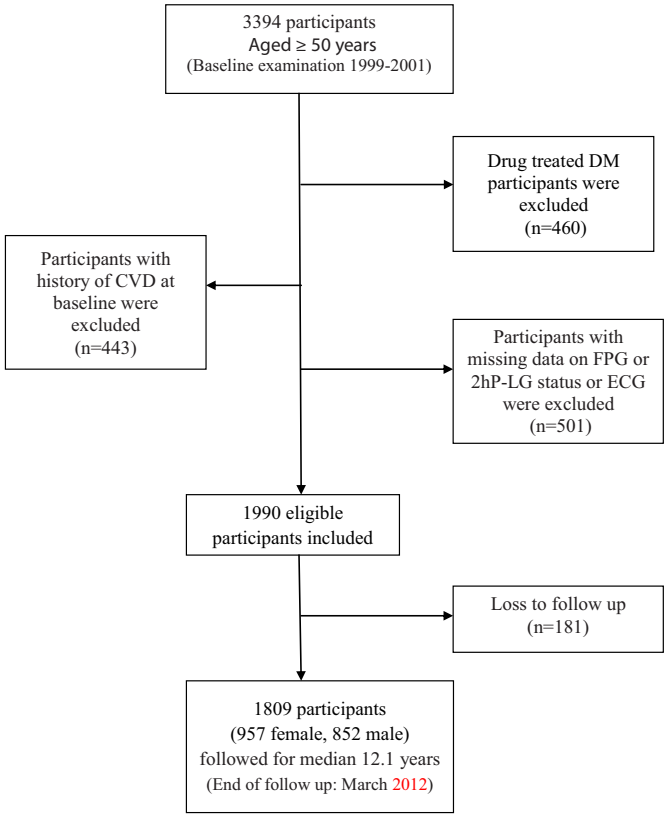

Fig. 1. Flow chart of study population. DM, diabetes mellitus; CVD, cardiovascular disease; FPG, fasting plasma glucose; 2 h-PLG, 2 hour post load glucose; ECG, electrocardiogram.

A blood sample was taken after 12–14 h overnight fasting at the TLGS research laboratory. Details for measurements of FPG, 2 h-PLG and total cholesterol (TC) have been reported elsewhere [16].

2.3. Definition of terms

DM was defined as either FPG ≥7 mmol/l or if their 2 h-PLG test was ≥11.1 mmol/l, according to American Diabetes Association (ADA) criteria [19] or current use of antidiabetic drugs [20], NDM as FPG ≥7 mmol/l or, 2 h-PLG ≥11.1 mmol/l [11]; IFG as FPG of 5.6–6.9 mmol/l and IGT as 2 h-PLG of 7.8–11.0 mmol/l [9]. In the current study we defined pre-diabetes as having IFG and/or IGT. Smoking status was categorized as current smokers (regular or occasionally) versus non-smokers (past smoker or never smoker). Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the current use of antihypertensive medication based on JNC 7 [21]. Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/l or current use of lipid lowering drugs.

ECG determined CHD was defined according to the Minnesota code [22] and Whitehall criteria [23], in which subjects were categorized into three groups: Probable CHD, included major Q or QS wave (Minnesota codes 1.1, 1.2) or complete left bundle branch block (Minnesota code 7.1.1); possible CHD, included small Q or QS wave (Minnesota code 1.3); ST depression (Minnesota codes 4.1–4.3), or T-wave items (Minnesota codes 5.1–5.3) and no CHD (ECGs that had none of these criteria). We combined probable and possible groups as a single group of silent CAD. A minor ischemic ECG change was also defined as T-wave items (Minnesota codes 5.3–5.4) and minor ST depression changes (Minnesota codes 4.3–4.4).

2.4. Definition of outcome

Details of the collection of cardiovascular outcome data have been published elsewhere [24]. To go over the main points briefly, each participant was followed up by a trained nurse annually by phone calls for any medical event and then a trained physician collected complementary data regarding that event during a home visit and by acquisition of data from medical files. An outcome committee consisting of an internist, an endocrinologist, a cardiologist, an epidemiologist and other experts, when needed, evaluated the collected data to assign a specific outcome for every event. In this study, our desired events were incidence of CHD which included cases of definite MI diagnosed by ECG and biomarkers, probable MI (positive ECG findings plus cardiac symptoms or signs and biomarkers showing negative or equivocal results), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers) and angiographic proven CHD. CVD was specified as a composite measure of any CHD events, stroke, or cerebrovascular events.

2.5. Statistics

Continuous variables were reported as mean ± standard deviation (SD), values and frequencies (%) were used for categorical variables of baseline characteristics. Analyses of different baseline characteristics between categories of glucose regulation were done using Chi square tests for binary variables and ANOVA for continuous variables.

The multivariate adjusted hazard ratio (HR) for CVD/CHD incidents and total mortality was determined by Cox proportional hazard model in different glycemic statuses considering NFG/NGT as reference, similarly we calculated the HR for the different outcomes regarding baseline CAD status, considering those without silent CAD as reference. To explore the risk of CVD/CHD incidents and mortality associated with adding silent CAD to each of the glucose regulation categories, we calculated HRs in age as well as multivariate adjusted models in each glycemic status category in the presence of silent CAD, compared to the corresponding nonsilent CAD counterpart, as the reference using Cox analysis. Finally, to examine the multivariate and sex adjusted risk of different events for the population with minor ischemic change at baseline in different glucose regulation categories, we excluded those with major Q or QS wave (Minnesota codes 1.1, 1.2) or complete left bundle branch block (Minnesota code 7.1.1) from our data file and HR was calculated using the Cox model. Potential confounding factors in the multivariate analyses were age, BMI, hypertension, hypercholesterolemia, and smoking. The period between entrance to study and the end points, which were the CVD/CHD event, and total mortality was considered as the follow-up duration. The censoring time of an individual was the time from entry into the study to loss to follow-up or leaving the residence area or occurrence of CVD/CHD event or death, whichever occurred first.

Interactions between sex and different glucose regulation statuses were examined in the multivariate model. Since we found significant interaction between sex and NFG/NGT status (p = 0.016 and 0.012 regarding CVD and CHD, respectively) and also sex and prediabetes status (p = 0.005 and p = 0.003 regarding CVD and CHD outcomes, respectively), all analyses were sex-stratified. The proportional hazard assumption in the Cox model was assessed with the Schoenfeld residual test and all proportionality assumptions were

appropriate. Statistical analyses were performed using SPSS for windows version 15 and STATA version 10; p-values ≤ 0.05 were considered statistically significant.

3. Results

A sample of 1809 participants aged ≥50 years without history of CVD at baseline of TLGS, mean (±SD) age of 59.69 (±7.14) years, (male: 60.86 (±7.62), female: 58.65 (±6.51)) were included in this study. After a median follow-up of 12.1 years, 208 deaths (male = 136) (91 death attributable to CVD events), 382 CVD incidents (male = 228) and 321 CHD incidents (male = 189) occurred.

There were significant differences in some baseline characteristics including BMI, WC, TC, systolic and diastolic blood pressures, FPG, 2 h-LPG and usage of antihypertensive drugs between glucose regulation categories in both genders. We observed no difference in prevalence of silent CAD in different glucose categories among females; however its prevalence differed significantly among males (Table 1).

Sex stratified risk of CVD/CHD incident and total mortality according to different traits of dysglycemia and the silent CAD is shown in Table 2. In the male population the presence of NDM increased the risk of CVD events to almost 50% (1.49, CI = 1.05–2.13) and for total mortality to about 240% (2.39, CI = 1.56–3.67), independent of traditional risk factors; however, the prediabetes status was not a predictor of any events. Among the female population, the presence of NDM increased the risk of CVD events about 2.3 fold (2.32, CI = 1.52–2.36); however, the risk was not significant for total mortality (1.80, CI = 0.95–3.39). Importantly the presence of pre-diabetes increased the risk of CVD events only among females to 67% (1.67, CI = 1.16–2.41). The presence of silent CAD among both genders significantly increased the risk of CVD events, compared to those without silent CAD; however this risk was significant for all-cause mortality only among male population (1.85, CI = 1.22–2.78).

Age and multivariate HRs for CVD/CHD events and deaths from all causes according to the silent CAD criteria in each of glucose tolerant categories are presented in Table 3. In NFG/NGT male population, we found 63% increased risk of CVD only in age adjusted analysis (P = 0.055) and borderline significant rise of 84% in the risk of total mortality in multivariate adjusted model (1.84, CI = 0.97–3.48, P = 0.06). In the pre-diabetic male population the presence of silent CAD had no significant effect in any outcomes; however in NDM it significantly increased the risk of all three outcomes. Among NFG/NGT and prediabetic female population the presence of silent CAD increased the risk of CVD/CHD to more than 2 fold (all $p < 0.05$), in multivariate analyses. However, in the NDM female population no significant hazard was revealed in the presence of silent CAD for any of the outcomes.

The HRs from multivariable models based on the presence or absence of minor ischemic changes in ECG, were calculated (Table 4). In these analyses there was no interaction between sex and minor ischemic changes. The HRs for incidence of CVD, CHD and total mortality in multivariate adjusted model were significantly increased to 3.43 (3.43, CI = 1.55–7.62), 4.13 (4.13, CI = 1.85–9.23) and 3.44 (3.44, CI = 1.19–9.94) respectively, among NDM patients but not among NFG/NGT or pre-diabetic population.

Finally, to reach full statistical power, we pooled NFG/NGT and prediabetes population in both genders as a single group of non-diabetic population. Accordingly, among non-diabetic population, the presence of silent CAD significantly increased the risk of CVD (2.19, CI = 1.45–4.30) in female and mortality events (1.63, CI = 0.99–2.63, P = 0.053) in male (Supplementary Table 1). Furthermore, regarding minor ischemic changes, we did not find any increased risk of outcomes due to silent CAD among non-diabetic population (Supplementary Table 2).

4. Discussion

During a long term population based study in a Middle Eastern population, we showed that gender significantly modified the impact of silent CAD in different glucose regulation categories for incidence of CVD/CHD and mortality outcomes. The presence of silent CAD, independent of traditional risk factors, among the female population, significantly increased the risk of CVD/CHD incidence for over 2 fold for those with NFG/NGT or pre-diabetes at baseline; among the male population, however, the risk was significant for CVD/CHD incidents as well as mortality events among the NDM population and marginally significant for NFG/NGT group. Importantly, in those with NDM, the presence of even minor ischemic changes significantly increased the risk to almost 3.5 fold for CVD and total mortality in multivariate sex adjusted analysis respectively.

The Fremantle Diabetes Study (FDS) of patients with type 2 DM revealed no significant association between silent MI and CHD mortality and total mortality, which might be due to the lack of statistical power; furthermore, they did not find any interaction between sex and MI

Table 1
Baseline characteristics according to different glucose category statuses stratified by sex.

	Males				Females			
	NFG/NGT (n = 476)	PreDM (n = 247)	NDM (n = 129)	*P* value	NFG/NGT (n = 502)	PreDM (n = 313)	NDM (n = 142)	*P* value
Age (years)	60.43 ± 7.71	60.89 ± 7.32	62.41 ± 7.66	0.032	58.54 ± 6.70	58.59 ± 6.31	59.15 ± 6.26	0.606
FH of CVD (%)	11.1	11.3	12.4	0.867	16.5	20.4	23.2	0.115
Smoking (%)	22.7	15.8	20.2	0.086	3.2	2.6	0.7	0.264
BMI (kg/m^2)	25.46 ± 3.55	27.12 ± 3.82	27.80 ± 3.83	0.000	28.53 ± 4.32	29.53 ± 4.55	30.57 ± 5.01	0.000
Waist circumference (cm)	89.34 ± 9.91	93.80 ± 10.70	96.08 ± 10.52	0.000	92.73 ± 10.72	95.79 ± 10.84	100.50 ± 11.68	0.000
SBP (mm Hg)	127.59 ± 21.06	131.62 ± 19.64	138.30 ± 24.86	0.000	128.49 ± 20.69	134.69 ± 21.05	141.06 ± 20.84	0.000
DBP (mm Hg)	79.50 ± 11.87	81.52 ± 12.07	82.44 ± 14.17	0.018	81.07 ± 11.09	82.94 ± 11.39	85.69 ± 11.67	0.000
Antihypertensive drug use (%)	7.1	12.1	11.6	0.055	17.9	24.9	30.3	0.002
TC (mmol/l)	5.42 ± 0.99	5.62 ± 1.09	5.84 ± 1.11	0.000	6.31 ± 1.13	6.37 ± 1.22	6.59 ± 1.15	0.039
Triglyceride (mmol/l)	1.79 ± 1.03	2.20 ± 1.20	2.76 ± 1.83	0.000	2.10 ± 1.09	2.45 ± 1.42	2.87 ± 1.49	0.000
HDL (mmol/l)	1.03 ± 0.25	1.01 ± 0.23	1.00 ± 0.31	0.234	1.21 ± 0.29	1.16 ± 0.26	1.16 ± 0.29	0.039
Lipid-lowering drug use (%)	2.3	2.8	2.3	0.900	7.8	9.6	8.5	0.660
FPG (mmol/l)	4.89 ± 0.37	5.63 ± 0.55	8.46 ± 3.05	0.000	4.89 ± 0.37	5.59 ± 0.99	8.30 ± 3.1	0.000
2 h-PLG (mmol/l)	5.48 ± 1.23	7.85 ± 1.80	15.54 ± 5.26	0.000	5.90 ± 1.10	7.95 ± 1.48	15.18 ± 5.09	0.000
CVD 1st (%)	122(25.6)	60(24.3)	46(35.6)	0.043	57(11.3)	60(19.2)	37(26.1)	0.000
CHD 1st (%)	101(21)	48(19.4)	40(31)	0.028	47(9.4)	54(17.2)	31(21.8)	0.000
Total mortality (%)	67(14.1)	33(13.4)	36(27.9)	0.000	32(6.4)	25(8)	15(10.6)	0.230
Silent CAD (%)	49(10.3)	39(15.8)	23(17.8)	0.024	74(14.7)	53(16.9)	31(21.8)	0.129
Minor ischemic changes in ECG (%)	7(1.5)	6(2.4)	6(4.7)	0.092	23(4.6)	15(4.8)	5(3.5)	0.824

Mean ± SD are shown for continuous variables and P value is calculated with ANOVA; % is shown for categorical variables with P value according to chi-square; NDM: new diagnosed diabetes mellitus, CVD: cardiovascular disease, FH: family history, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, HDL: high density lipoprotein, FPG: fasting plasma glucose, 2 h-PLG: 2 hour post load glucose, CHD: coronary heart disease, CAD: coronary artery disease, ECG: electrocardiogram.

Table 2
Sex stratified hazard ratios of CVD/CHD incidence and total mortality according to different glucose categories and silent CAD status.

	CVD		CHD		Total mortality	
	Incidence %	HR (95% CI)	Incidence %	HR (95% CI)	Incidence %	HR (95% CI)
Males						
Glycemic status						
NFG/NGT	25.6	Reference	21	Reference	14.1	Reference
Prediabetic	24.3	0.863(0.63–1.29) (p = 0.36)	19.4	0.83(0.58–1.18) (p = 0.30)	13.4	0.99(0.64–1.55) (p = 0.994)
NDM	35.6	1.49(1.05–2.13) (p = 0.026)	31	1.55(1.06–2.28) (p = 0.024)	27.9	2.39(1.56–3.67) (p = 0.00)
CAD status						
No silent CAD	24.7	Reference	20.5	Reference	13.8	Reference
With silent CAD	40.5	1.55(1.09–2.19) (p = 0.013)	33.3	1.54(1.05–2.25) (p = 0.027)	30.6	1.85(1.22–2.78) (p = 0.004)
Females						
Glycemic status						
NFG/NGT	11.3	Reference	9.4	Reference	6.4	Reference
Prediabetic	19.2	1.67(1.16–2.41) (p = 0.006)	17.2	1.80(1.21–2.68) (p = 0.004)	8	1.35(0.78–2.30) (p = 0.275)
NDM	26.1	2.32(1.52–3.56) (p = 0.00)	21.8	2.40(1.50–3.83) (p = 0.00)	10.6	1.80(0.95–3.39) (p = 0.07)
CAD status						
No silent CAD	14	Reference	12.1	Reference	7.1	Reference
With silent CAD	26.6	1.95(1.35–2.80) (p = 0.00)	22.1	1.94(1.31–2.90) (p = 0.001)	9.5	1.20(0.67–2.13) (p = 0.54)

Adjusted for: age, hypertension, hypercholesterolemia, BMI, and smoking.
NFG: normal fasting glucose, NGT: normal glucose tolerance, NDM: new diagnosed diabetes mellitus, CHD: coronary heart disease, CVD: coronary vascular disease, CAD: coronary artery disease, HR: hazard ratio, CI: confidence interval.

groups [25]. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, silent and clinical MI increased the risk of CVD events equally in patients with type 2 DM (both had a HR about 4.5) [26]. In the United Kingdom Prospective Diabetes Study (UKPDS) it was shown that silent MI in the NDM was significantly associated with 31 and 58% increased rates of all-cause mortality and the first fatal MI, respectively; however silent MI was not associated with the first non-fatal MI in this group. Furthermore, although female gender was protective for different events, they showed no significant interactions between sex and silent MI [8]. In the current study, the presence of silent CAD in NDM was significantly associated with 300% increased risk of CVD and more than 250% risk of all-cause mortality among the male population. In our previous study it was shown that silent CAD could be a prognostic value for incident CVD/CHD among a male diabetic population, including both new diagnosed and drug treated [27]. These discrepant results may reflect differences between the selected population in each cohort (i.e., NDM vs. NDM and known DM), differences in CVD risk factors and demographic baseline characteristics, length of follow-up and different approaches to analysis of data. As we showed, among a female Tehranian population with NDM, silent CAD did not provide any benefit in risk prediction of different outcomes, even in age adjusted analysis. However, similar to others, we previously showed that NDM among females had higher risk for incident CHD than among males (HR 3.1 vs. 1.7, respectively) [15,28]; the finding that might be attributable to more adverse lipid profile and systemic inflammatory markers among women than in men [29]. Therefore, since among female, NDM per se is a powerful predictor for incidence of CVD/CHD and mortality, compared to males, it was hypothesized that diagnosis of the silent CAD among NDM female population provides no additional information regarding different outcomes. Furthermore, the

Table 3
Sex stratified hazard ratios from age and multivariable adjusted proportional hazard models based on the presence or absence of silent CAD in different glucose tolerance statuses.

	CVD			CHD			Total mortality		
	Without silent CAD	With silent CAD		Without silent CAD	With silent CAD		Without silent CAD	With silent CAD	
		Male	Female		Male	Female		Male	Female
NFG/NGT									
Model 1	1	1.63(0.99–2.68) (p = 0.055)	2.34(1.32–4.17) (p = 0.004)	1	1.68(0.97–2.89) (p = 0.062)	2.23(1.17–4.25) (p = 0.015)	1	1.71(0.94–3.10) (p = 0.08)	1.06(0.43–2.60) (p = 0.90)
Model 2	1	1.49(0.88–2.51) (p = 0.134)	2.40(1.33–4.35) (p = 0.004)	1	1.50(0.85–2.65) (p = 0.16)	2.34(1.20–4.56) (p = 0.013)	1	1.84(0.97–3.48) (p = 0.06)	1.06(0.43–2.60) (p = 0.90)
PreDM									
Model 1	1	1.29(0.69–2.42) (p = 0.42)	2.04(1.15–3.62) (p = 0.015)	1	1.11(0.53–2.33) (p = 0.77)	2.16(1.19–3.93) (p = 0.012)	1	1.59(0.73–3.45) (p = 0.24)	1.45(0.57–3.70) (p = 0.43)
Model 2	1	1.11(0.57–2.14) (p = 0.76)	2.04(1.14–3.63) (p = 0.016)	1	0.91(0.41–1.99) (p = 0.81)	2.20(1.21–4.01) (p = 0.01)	1	1.41(0.61–3.23) (p = 0.42)	1.48(0.58–3.77) (p = 0.41)
NDM									
Model 1	1	2.91(1.52–5.59) (p = 0.001)	1.27(0.59–2.71) (p = 0.54)	1	3.28(1.65–6.53) (p = 0.001)	1.15(0.49–2.70) (p = 0.75)	1	2.71(1.32–5.57) (p = 0.006)	0.91(0.26–3.22) (p = 0.88)
Model 2	1	3.04(1.53–6.05) (p = 0.002)	1.29(0.58–2.85) (p = 0.53)	1	3.64(1.73–7.64) (p = 0.001)	1.09(0.45–2.62) (p = 0.85)	1	2.60(1.22–5.56) (p = 0.013)	0.92(0.25–3.37) (p = 0.90)

Model 1: adjusted for age.
Model 2: adjusted for age, hypertension, hypercholesterolemia, BMI, and smoking.
NFG: normal fasting glucose, NGT: normal glucose tolerance, DM: diabetes mellitus, NDM: new diagnosed diabetes mellitus, CHD: coronary heart disease, CVD: cardiovascular disease, CAD: coronary artery disease.

Table 4
Hazard ratios from adjusted proportional hazard models based on the presence or absence of minor ischemic changes in ECG, in different glucose tolerance statuses.

	CVD		CHD		Total mortality	
	Without minor ischemic changes	With minor ischemic changes	Without minor ischemic changes	With minor ischemic changes	Without minor ischemic changes	With minor ischemic changes
NFG/NGT						
Model 1	1.06(0.61–2.79) (p = 0.48)	1	0.89(0.33–2.40) (p = 0.82)	1	1.89(0.77–4.65) (p = 0.17)	1
Model 2	1.35(0.64–2.89) (p = 0.43)	1	0.90(0.33–2.45) (p = 0.84)	1	1.99(0.81–4.95) (p = 0.13)	1
PreDM						
Model 1	1.11(0.45–2.71) (p = 0.82)	1	0.76(0.24–2.41) (p = 0.65)	1	0.95(0.23–3.89) (p = 0.94)	1
Model 2	0.94(0.38–2.33) (p = 0.90)	1	0.67(0.21–2.14) (p = 0.50)	1	0.94(0.22–3.91) (p = 0.93)	1
NDM						
Model 1	3.50(1.61–7.62) (p = 0.002)	1	4.15(1.89–9.10) (p = 0.000)	1	3.28(1.17–9.19) (p = 0.02)	1
Model 2	3.43(1.55–7.56) (p = 0.002)	1	4.13(1.85–9.23) (p = 0.001)	1	3.44(1.19–9.94) (p = 0.023)	1

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, hypertension, hypercholesterolemia, BMI, and smoking.
NFG: normal fasting glucose, NGT: normal glucose tolerance, DM: diabetes mellitus, NDM: new diagnosed diabetes mellitus, CHD: coronary heart disease, CVD: cardiovascular disease.

lack of association between silent CAD among the NDM female population with different outcomes might be attributable to lower rates of events, leading to wide confidence intervals for non-significant HRs. Importantly, for the first time we demonstrated the importance of minor ischemic changes in ECG among NDM by showing significant increased risk of CVD/CHD in gender and other risk factor adjusted analysis.

In the current study we observed no significant difference in prevalence of silent CAD among females with different categories of glucose regulation. Lundblad et al., however, showed that previously unknown Q wave MI was considerably higher among women with IGT than in those with NGT [30]. Among non-diabetic women, we observed that silent CAD had more than 2 fold increased risk for CVD/CHD, independent of traditional risk factors. In a cross-sectional study of non-diabetic and diabetic men and women, it was shown that, non-diabetic women tended to have more favorable risk factors and were less insulin resistant than non-diabetic men, but this was diminished in the diabetic state. Hence as acknowledged by Wannamethee S.G. et al. [31], "as women go from non-diabetes to diabetes, they need to 'travel' to a more adverse risk profile, i.e., they need to put on more weight, and deteriorate their insulin sensitivity and related risk factors to a more extent than do men". These findings could highlight the presence of silent CAD as a stronger predictor of CVD/CHD in non-diabetic women compared to male population in which higher risk profile might hide the presence of silent CAD as a significant risk factor. Recently we also demonstrated that in a general population, in females with intermediate Framingham risk, ECG abnormalities were associated with increased risk of developing CHD and addition of the ECG abnormalities to the Framingham risk assessment improved the classification of CHD risk [32]. Hence, regarding high prevalence and importance of silent CAD among a non-diabetic female population we suggest that screening of ECG abnormalities among non-diabetic female might be more important than among diabetic ones. Regarding male population, the prevalence of silent CAD among non-diabetic men was lower than NDM; however the presence of silent CAD among this group increased the risk of all-cause mortality events about 63% which was marginally significant. Intzilakis et al. emphasized that the presence of IFG and silent myocardial ischemia indicates an increased risk of death or myocardial infarction (HR: 2.5), compared with NFG subjects with no silent myocardial ischemia; however since they did not apply OGTT to exclude the diabetic population, the probability of misclassification among the study population should be considered [10].

5. Study strengths and limitations

Some limitations of this study need to be mentioned. First, data regarding use of medication and serum electrolytes which might affect ECG abnormalities were not available. Second, our study was conducted in a population aged ≥50 years, residents of Tehran; thus we cannot generalize the findings to other age groups or to the whole country. Third, we defined glucose categories using OGTT once as applied in other epidemiological studies, and this might lead to misclassification among glucose categories. Among the 978 NFG/NGT population, 363 had incident pre-diabetes and 37 of NFG/NGT population developed DM during the follow-up and among the 560 pre-diabetes population 172 cases developed DM and vice versa we found that among the 560 pre-diabetes population, 144 cases regressed to NFG/NGT. However, most other studies [33–35] also used only baseline glucose values, except for one study [36] that excluded incident diabetes. Fourth, regarding TLGS protocol, HbA1c measurement is not performed for participants; hence it was not possible to control the level of HbA1C in our data analysis. Last, but not the least, in different categories of glucose regulation we did not examine the added value of ECG abnormalities to traditional risk factors in risk prediction of incident CVD. The strengths of our study include its large sample size, and using both FPG and 2 h-PLG for determining categories of glucose regulation and assessing better discrimination of CVD outcomes in different categories. Furthermore, regarding the importance of gender in the association of different glucose regulations with incident CVD, our data was separately analyzed for both genders.

6. Conclusion

To conclude, we showed similar prevalence of silent CAD among normoglycemic, pre-diabetic and NDM females; however only non-diabetic women had significant increased risk of CVD/CHD in the presence of silent CAD. Additionally, NDM males with silent CAD showed significant risk for CVD/CHD and mortality events. Thus different strategies might be appropriate regarding the presence of silent CAD in males and females with different categories of glucose regulation. It seems that screening ECG for prevention of CVD events might be considered mainly among non-diabetic female and NDM male populations. However more studies should be performed to confirm the screening strategy.

7. Conflict of interest

None to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.017.

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