Cardiovascular disease risk prediction among Iranian patients with diabetes mellitus in Isfahan Province, Iran, in 2014, by using Framingham risk score, atherosclerotic cardiovascular disease risk score, and high-sensitive C-reactive protein

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Abstract

BACKGROUND: Risk assessment in clinical practice plays an important role in classifying population for appropriate preventive medicine for each category. Several multivariable risk predictor algorithms and inflammatory biomarkers are developed for assessing risk for cardiovascular diseases (CVDs). We aimed to depict a picture of the cardiovascular risk profiles in the Iranian population with diabetes mellitus (DM) through three risk predictors for the first time, as the patients with DM have an increased risk for CVDs.

METHODS: In this cross-sectional study, the sample size consisted of 418 patients with DM from Diabetes Clinic of Shariati hospital, Isfahan, Iran, in February to July, 2014. We collected the latest information, and then calculated the 10-year CVD risk using Framingham risk score (FRS) and atherosclerotic cardiovascular disease (ASCVD) risk score; while high-sensitivity C-reactive protein (hs-CRP) was measured for them based on their physicians’ prescription. Finally, all data were analyzed using SPSS software.

RESULTS: The mean 10-year risk prediction of CVDs in the 30- to 74-year-old Iranian patients with DM was high in all three predictors based on their cut-off points, 16.31%, 12.39%, and 3.46 mg/l for FRS, ASCVD risk score, and hs-CRP level, respectively. Although the mean FRS and ASCVD risk scores were significantly higher among men than women (P < 0.0500), the mean hs-CRP level was slightly lower in men than women (P > 0.0500).

CONCLUSION: Mean FRS and ASCVD risk scores and hs-CRP in patients were high, and a considerable proportion of patients with DM in our study were at intermediate and high risk for CVDs in the next 10 years. Future cohort studies would investigate the accuracy of different predictors in upcoming years, and also help to derive a specific model or recalibrate existing predictors with characteristic of Iranian populations and specific target groups.

Keywords: Cardiovascular Diseases, Risk Assessments, Diabetes Mellitus, C-Reactive Protein, Risk Factor

Date of submission: 04 Oct. 2017, Date of acceptance: 18 May 2018

Introduction

Cardiovascular diseases (CVDs) are the single leading causes of death globally.¹ Data show that 17.3 million people died from CVDs in 2008, and almost 23.6 million people will die by the year 2030.² Multiple risk factors have been proved to play a role in the pathogenesis of CVDs in which diabetes mellitus (DM) is an important one. The total number of people with DM is going to be raised from 171 million in 2000 to 366 million in 2030.³ ⁴ Patients with DM have a 2-4 times greater chance of CVDs and death in comparison with those without DM.⁴ Therefore, multivariate cardiovascular risk scores have been used in many countries to identify individuals who are at high risk of getting CVDs.³ In addition, among inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) has been accepted as an independent
The aim of risk assessment is to categorize population into those at low, moderate, and high CVD risk for performing appropriate preventive approaches in each one.

Framingham Heart Study, which was conducted as a large project in 1948, could make algorithm to estimate CVD in general population, and widely was used for assessing major CVDs in future. Result of less than 10%, 10% to 20%, and more than 20% are defined as low, intermediate, and high risk, respectively. In 2013, National Heart, Lung and Blood Institute (NHLBI) in support of CVD prevention guidelines via Risk Assessment Work Group (RAWG) assessed CVDs risk factors and developed atherosclerotic cardiovascular disease (ASCVD) risk estimator for more practical risk assessment. In this measurement, result of less than 5%, 5% to 7.5%, and more than 7.5% were defined as low, intermediate, and high risk, respectively. Moreover, In the early 1990s, an inflammatory biomarker named hs-CRP had been shown to have relationship with CVDs. hs-CRP of less than 1, 1-3, and more than 3 mg/l are defined as low, intermediate, and high risk, respectively.

Some studies, done using different CVD risk calculators and biomarkers on different populations or certain target groups, showed controversial results. For instance, Framingham risk score (FRS) overestimates the risk of coronary heart disease in German, Chinese, and Mexican populations. While, Tehran Lipid and Glucose prospective study (TLGS) in Middle East showed the FRS function was good in normal population. Furthermore, ASCVD risk score is predicted to overestimate in some populations such as Chinese and Hispanic Americans. Moreover, there are few studies focus on suitable cut-off points of measuring hs-CRP in different groups or populations.

As there was no study evaluate these three risk predictors in patients suffering DM in Iranian population before this study, we aimed to assess the 10-year ASCVD risk, FRS, and hs-CRP levels in 30- to 74-year-old Iranian patients with DM through a cross-sectional study for the first time. Knowing 10-year risk of CVD is helpful in strengthen preventive medicine.

Materials and Methods

This cross-sectional study that was conducted from February 2014 to July 2014, and in patients with DM aged between 30-74 years that were visited two days per week during that period in Diabetes Clinic of Shariati hospital, Isfahan, Iran. Based on 2 different calculators, we collected required parameters to calculate 10-year CVD risk for patients with DM. Anyone who had one or more than one DM criteria was included in the study (glucose tolerance test ≥ 200 mg/dl, or random glucose ≥ 200 mg/dl, or hemoglobin A1c (HbA1c) ≥ 6.5%, or fasting blood sugar ≥ 126 mg/dl).

In 2153 patients, the demographic information such as sex, age, race, and smoking status, as well as presence/absence of hypertension treatment and blood pressure level that was taken with a standard method by their physicians, and other routine check-up measurements such as total cholesterol, high-density lipoprotein (HDL) cholesterol, and hs-CRP level that were recorded in patients’ files, were gathered through a checklist. If patient showed any manifestation of atherosclerotic disease such as cerebrovascular accident (CVA) or transient ischemic attack (TIA), coronary artery disease, carotid artery disease, peripheral vascular disease, positive exercise tolerance test, typical angina history, congestive heart failure (CHF), or electrocardiography (ECG) with evidence of myocardial infarction (MI) or ischemic heart disease (IHD), he/she was excluded from study.

After applying these criteria, 418 patients were eligible for entering to our study. Research protocol was approved by the Research Review Board of School of Medicine, Najafabad Branch, Islamic Azad University, Najafabad, Iran. Patients’ names were not used in the study for confidentiality reasons, and instead of their names, codes were used. In addition, for all participants, written informed consent was provided. This research was conducted by personal funds.

In our study, age, sex, and race were demographic variables. DM, hypertension, smoking, total cholesterol, HDL cholesterol, and hs-CRP were independent variables. CVDs were dependent variables.

After excluding duplicate or missing data, CVD risk assessment was performed all 418 patients using FRS and ASCVD risk calculators for. Finally, for quantitative variables, results were presented as mean ± standard deviation (SD); and categorical variables were demonstrated as frequencies and percent. Analysis was applied based on gender and age categories (less than 56, 56-65, and more than 65 years). For categorical variables, chi-square test was used. 95% of confidence interval (CI) was considered, too. For FRS, we used 10-year CVD risk calculator that required sex, age, systolic blood pressure, existence of hypertension treatment, DM, smoking status, HDL level, and total cholesterol level.
In FRS, result of less than 10%, 10% to 20%, and more than 20% were defined as low, intermediate, and high risk, respectively. ASCVD risk calculator required gender, age, race, HDL cholesterol, total cholesterol, systolic blood pressure, existence of hypertension treatment, DM, and smoking status. In ASCVD risk score, result of less than 5%, 5% to 7.5%, and more than 7.5% were defined as low, intermediate, and high risk, respectively. In addition, hs-CRP of less than 1 mg/l, 1-3 mg/l, and more than 3 mg/l were defined as low, intermediate, and high risk, respectively. P-values of less than 0.05 were considered statistically significant. T test was used for quantitative variables. All statistical analysis was performed using SPSS software (version 20, IBM corporation, Armonk, NY, USA).

### Results

From the total of 418 participants, 166 (39.7%) were men and 252 (60.3%) were women. The mean age was 59.84 years with the SD of 8.77. Sex-specific age distribution showed the mean age of 60.5 ± 9.5 and 59.5 ± 8.3 years for men and women, respectively, but the difference was not statistically significant (P = 0.21). Of the patients, 132 had 55 years or less, 161 were between 56 and 65 years, and 125 patients had 66 years or more.

FRS percentages were between 1.30% and 57.90%, and the mean 10-year risk of CVD based on FRS was 16.31% (95% CI: 15.31-17.30). The frequency of low-, intermediate-, and high risk patients based on FRS was 30.40%, 40.90%, and 28.70%, respectively. The mean FRS were significantly higher in men than women (P < 0.0001). The mean FRS increased significantly by increasing age to reach 23.90% in age group over 66 years, compared with 9.30% in age group of below 55 years (P < 0.0001). Moreover, the frequency of high-risk patients was significantly higher in higher groups in FRS (P < 0.0001); and the frequency of high-risk patients in men was significantly higher than women (P < 0.0001) (Table 1).

ASCVD risk scores were between 0.50% to 54.30%, and the mean 10-year risk of ASCVD risk score on target group was 12.39% (95% CI: 11.32-13.47). The frequency of low-, intermediate- and high-risk patients based on ASCVD risk was 28.90%, 12.10%, and 59.00% respectively. The mean ASCVD risk were significantly higher in men than women (P < 0.0001). The mean ASCVD risk increased significantly by increasing age to reach 23.83% in age group of over 66 years, compared with 3.82% in age group of below 55 years (P < 0.0001). In addition, the frequency of high-risk patients in ASCVD risk score was significantly higher in age group over 66 years than lower age groups (P < 0.0001). The frequency of high-risk patients in men was significantly higher than women (P < 0.0001) (Table 2).

### Table 1. The mean and intensity of Framingham risk score (FRS) in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

| Characteristics       | Mean (95% CI) | Low (< 10%) | Intermediate (10%-20%) | High (> 20%) |
|-----------------------|--------------|-------------|------------------------|--------------|
| Total (n = 418)       |              | 127 (30.40) | 111 (44.00)            | 120 (28.70)  |
| Gender                |              | 111 (44.00) | 111 (44.00)            | 111 (44.00)  |
| P                     |              | < 0.0001    | < 0.0001               | < 0.0001     |
| Age group (year)      |              | 84 (63.60)  | 90 (55.90)             | 90 (55.90)   |
|                       | ≤ 55 (n = 132)|            |                        |              |
|                       | > 56-65 (n = 161)|          |                        |              |
|                       | ≥ 66 (n = 125)|            |                        |              |
| P                     |              | < 0.0001    |                        | < 0.0001     |

### Table 2. The mean and intensity of atherosclerotic cardiovascular disease (ASCVD) risk score in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

| Characteristics       | Mean (95% CI) | Low (< 5%) | Intermediate (5%-15%) | High (> 25%) |
|-----------------------|--------------|------------|-----------------------|-------------|
| Total (n = 339)       |              | 98 (28.90) | 98 (28.90)            | 100 (30.40) |
| Gender                |              | 15 (11.90) | 15 (11.90)            | 20 (24.20)  |
| P                     |              | 102 (81.00)| 102 (81.00)           | 102 (81.00) |
| Age group (year)      |              | 11 (10.50) | 11 (10.50)            | 11 (10.50)  |
|                       | ≤ 55 (n = 106)|            |                        |              |
|                       | > 56-65 (n = 136)|          |                        |              |
|                       | ≥ 66 (n = 98)|            |                        |              |
| P                     |              | 97 (99.00) | 97 (99.00)            | 97 (99.00)  |

P: Confidence interval
CVD risk prediction by FRS, ASCVD, & hs-CRP

Table 3. The mean and intensity of high-sensitivity C-reactive protein (hs-CRP) level in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

| Characteristics | Mean (95% CI) | Intensity [n (%)] | Low (< 1 mg/l) | Intermediate (1-3 mg/l) | High (> 3 mg/l) |
|-----------------|--------------|-------------------|----------------|------------------------|----------------|
| Total (n = 418) |              |                   |                |                        |                |
| Gender          |              |                   |                |                        |                |
| Men (n = 166)   | 3.46 (3.08-3.84) | 65 (15.60) | 192 (45.90) | 161 (38.50) |
| Women (n = 252) | 3.60 (3.10-4.10) | 33 (19.90) | 72 (43.40) | 61 (36.70) |
| P               | 0.3600       | 32 (12.70) | 120 (47.60) | 100 (39.70) |
| Age group (year) |              |                   |                |                        |                |
| ≤ 55 (n = 132)  | 3.53 (2.88-4.18) | 22 (16.70) | 54 (40.90) | 56 (42.40) |
| 56-65 (n = 161) | 3.19 (2.61-3.78) | 21 (13.00) | 87 (54.00) | 53 (32.90) |
| ≥ 66 (n = 125)  | 3.73 (2.96-4.50) | 22 (17.60) | 51 (40.80) | 52 (41.60) |
| P               | 0.5100       |                   |                |                        |                |

CI: Confidence interval

hs-CRP values were between 0.00 to 33.01 mg/l, with a mean level of 3.46 (95% CI: 3.08-3.84). The frequency of low-, intermediate- and high-risk patients based on hs-CRP level was 15.60%, 45.90%, and 33.00%, respectively. The mean level of hs-CRP was slightly lower in men than women (P > 0.0500). The mean hs-CRP level increased insignificantly by increasing age (P > 0.0500). The frequency of high-risk patients in men was slightly lower than women (P > 0.0500) (Table 3).

Discussion

The aim of this research was assessment of cardiovascular risk prediction in the Iranian population with DM through FRS and ASCVD risk scores, and hs-CRP predictors in the 30-74-year-old patients. According to our findings, the mean FRS was considerably high (16.31%) in Iranian population with DM, and FRS was higher in men compared with women. While some studies suggested the FRS varies between populations,19 FRS have been shown good efficacy in Iranian normal population in TLGS, previously.20-21 The difference between this study and TLGS is that while both focused on same age range and same race, but they targeted different groups, those with DM vs. normal population. Moreover, we found out that the mean ASCVD risk score is significantly high (12.39%) in Iranian population with DM. Similar to FRS, the mean ASCVD was higher in men compared with women. In one retrospective cohort study done by Chia et al., 922 individuals were selected, and FRS and ASCVD risk scores were calculated for each one. The result showed that ASCVD overestimated CVD risks rather than FRS. Due to their research design, recall bias would be a great limitation in that article. In addition, they focused on different age group (40-79 years) and normal population.22

The mean hs-CRP level was considerably high (3.46 mg/l) in this study, same as for FRS and ASCVD risk scores; but hs-CRP level was very slightly lower in men compared with women. Seo et al. showed that hs-CRP had significant correlation with CVD risk in 1561 patients with established DM or CHD over 18 years of age in Korean population.23 Besides, Ballantyne et al. showed that hs-CRP in middle-aged men and women was related to CHD risk.24

In this study, FRS and ASCVD risk scores were higher in men, and in older age groups; while hs-CRP was not age-related. Ford et al.25 and Motamed et al.26 studies declared the same concept for FRS and ASCVD risk scores. Moreover, Khra et al. found out that race and gender could affect the distribution of CRP in different populations.27

One possible theory about the difference between the results of FRS and ASCVD calculators with hs-CRP level could be due to the role of hs-CRP as an acute phase reactant, that is increased in presence of insulin-resistance situation as well as other chronic conditions; and the other one is the fact for calibration of different risk calculators based on certain parameters, such as race and baseline diseases, in target groups.

Like other researches, our study was not free of limitations. Participants for contributing in this study were chosen from one DM clinic and with small sample size. In addition, as this study was cross-sectional, we cannot comment about correlation of future CVD events based on risk predictors. So, other studies should be done on larger DM population, and in different cities, with cohort design.

Conclusion

In conclusion, this study showed that mean FRS and ASCVD risk scores in the 30- to 74-year-old Iranian
patients with DM are significantly high. These results demonstrated that in the upcoming years, the Iranian population is going to be in great risk for cardiovascular events, and as this study was the first done in literature evaluating the cardiovascular risk through three CVD risk estimators in Iranian patients with DM, it would be useful for initiating cohort researches to find out which one can predict CVD most accurate in 10 years. Moreover, those studies will help to derive a model with characteristic of Iranian populations and specific target groups, or recalibration of existing predictors.

Acknowledgments

We would like to thank Pishtaz Teh Zaman Diagnostics for cooperating in this study. In addition, we have to thank all our colleagues in Diabetes Clinic of Shariati hospital and laboratory, for their help and support in advancement of this research.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Alaei Faradonbeh N, Nikaeen F, Akbari M, Almasi N, Vakhshoori M. Cardiovascular disease risk prediction among Iranian patients with diabetes mellitus in Isfahan Province, Iran, in 2014, by using Framingham risk score, atherosclerotic cardiovascular disease risk score, and high-sensitive C-reactive protein. ARYA Atheroscler 2018; 14(4): 163-8.