

Cardiovascular Disease Risk Factors Profile in Individuals With Diabetes Compared With Non-Diabetic Subjects in North-East of Iran

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Abstract

Background: Diabetes mellitus is assumed to be a strong risk factor for cardiovascular diseases (CVD) and is frequently associated with other CVD risk factors.

Objectives: The aims of this study were to assess the prevalence of different patterns of dyslipidemia in individuals with diabetes compared with non-diabetic subjects and evaluate other accompanied CVD risk factors between the two groups.

Patients and Methods: This was an analytical cross-sectional study on 230 participants, aged 28 - 66 years old, who were referred to different urban health centers of Khorasan Razavi province (north-east of Iran). Data from the participants were collected during their first visit by primary care physicians. Statistical package for social science (version 11.5) was used to analyze the data. The chi-square or Fisher's exact, student's t or the Mann-Whitney U and correlation tests were used in the analysis.

Results: The age and gender of the participants were not different between the two groups ($P = 0.1$ and $P = 0.4$, respectively). The most common patterns of dyslipidemia in both groups were isolated dyslipidemia followed by combined dyslipidemia. Prevalence of dyslipidemia as a whole (one, two or three lipid profile abnormalities) in patients with diabetes and non-diabetic participants was 89.3% and 82.6%, respectively and the difference between the two groups was not statistically significant ($P = 0.1$). Subjects with diabetes had higher systolic blood pressure ($P < 0.001$), higher diastolic blood pressure ($P = 0.002$) and higher body mass index ($P = 0.09$) compared to non-diabetics. Moreover, they were more likely to have higher levels of total cholesterol ($P = 0.01$), triglycerides ($P = 0.001$) and low density lipoprotein cholesterol ($P = 0.009$) and lower levels of high density lipoprotein cholesterol ($P = 0.2$).

Conclusions: Cardiovascular diseases risk factors are more common in patients with diabetes; however, non-diabetic individuals also had a high prevalence of risk factors in our region, predisposing them to diabetes. Therefore, further attention by the medical community is necessary to choose effective strategies for a more aggressive approach to prevent and manage these risk factors.

Keywords: Cardiovascular Diseases, Risk Factors, Diabetes Mellitus, Dyslipidemias

1. Background

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in individuals with diabetes, so that they have a two fold increase in all-cause mortality and three-fold increase in cardiovascular mortality (1). Nowadays, diabetes mellitus (DM) incidence is rising due to population growth and urbanization, aging and increasing prevalence of obesity and physical inactivity (2, 3). Seventy percent of diabetic patients were living in low and middle income countries in 2010. In Iran, the prevalence of DM was estimated around 8% during the same year (4-6).

Diabetes mellitus is assumed as a major risk factor for CVD and it is frequently associated with other CVD risk factors as well. Over the last two decades, evidence support

that glycemic control as well as management of other major risk factors, including high blood pressure and dyslipidemia (DLP) are tremendously helpful in prevention and retardation of the onset and severity of DM complications (7, 8).

It has been confirmed that DLP is an important risk factor for macro-vascular complications in diabetic patients and its prevalence is 10% - 37% in these patients (9, 10). Furthermore, DM by itself is a secondary cause of DLP, especially if glycemic control is poor (11).

Despite eminent progress in the management of cardiovascular risk factors, diabetic patients still have significantly increased mortality rates compared with the general population (1). Therefore, it is important to assess the existing situation of cardiovascular risk factors in associ-

ation with DM and understand the etiology of the excess CVD risk in patients with diabetes. Considering that DM and DLP generally coexist, it is important to deduce the different patterns of DLP in this population, in order to attain a better understanding of its role. In our experience we found that very few patients with diabetes had normal lipid profile, provoking us to assess lipid profile pattern among our patients. We did not find any study from our region looking at the pattern of dyslipidemia in patients with diabetes.

2. Objectives

The primary purpose of our study was to assess the prevalence of different patterns of DLP in individuals with diabetes and compare this with non-diabetic subjects. The secondary purpose was to evaluate other cardiovascular risk factors including systolic and diastolic blood pressure, body mass index (BMI) and waist circumference (WC) between the two study groups and to determine the association between fasting plasma glucose (FPG) and these different risk factors.

3. Materials and Methods

The sample for this cross sectional study was from the national non-communicable risk factors surveillance system data repository. This system has been established since 2004 in our country, under the supervision of diseases control and prevention units of the health ministry. National and provincial large-scale surveys have been conducted by the state health centers in every province of Iran to find out the existing situation of non-communicable disease risk factors in the Iranian population and to monitor the trends. We used part of the information of this national survey, which had been gathered in the first two years of the survey (2007) in Mashhad (the second most populated city of Iran and capital of Razavi Khorasan province, located in the north east of Iran. In the 2011 census, its population was recorded as 3131586).

The sample size for this study was estimated at the provincial level by considering the prevalence of risk factors, with $\alpha = 0.05$ and $\beta = 0.2$; finally 1000 participants were selected for the Razavi Khorasan province. According to our inclusion and exclusion criteria (Box 1) 225 out of 1000 participants (75 in the diabetic and 150 in the control group) were included in the study. Inclusion and exclusion criteria of the study are provided in Box 1. Data from participants were collected during their first visit by primary care physicians, according to the instructions recommended by the health ministry. These physicians were

trained through several sessions and all of the instruments were calibrated daily.

From the ethical point of view, we obtained permission from the Mashhad University of Medical Science in order to use part of their data, and we were then provided a written letter by the University to the state health center to obtain the agreement of the authorities. Also, the required information for the study from the subject's files was obtained from their physicians and not by the researchers. All of the participants signed an informed consent and the study was approved by the national ethics committee (12).

Weight and height and waist circumference (WC) were measured by trained technicians with standardized equipment. Body weight and height were measured using a digital column scale (Seca 703) and the participants only had one uniform layer of clothing and were not wearing shoes or headgear. All scales were calibrated every day. Body mass index (BMI) was calculated through dividing the weight (kg) by the square of height (13).

Waist circumference was measured using a flexible tape in the standing position, and measuring midway between the lowest rib and the superior border of the iliac crest. Waist circumference of ≥ 102 cm in males and ≥ 88 cm in females was defined as central obesity, according to the world health organization (WHO) criteria (14).

Blood Pressure was calculated based on the mean of the two measurements taken five and ten minutes after resting with a digital automatic blood pressure monitors (Omron M7, Omron healthcare). All monitors were adjusted every day. According to the 2013 American diabetes clinical practice guidelines, hypertension (HTN) was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg (15).

Blood samples were taken from all participants after 8 - 12 hours of fasting to determine lipid profile and fasting plasma sugar (FPG). These tests were performed using standardized automatic devices in the laboratory of Razavi Khorasan province health centre, under the supervision of the central national laboratory. Pars Azmoon kits and BT1500 machinery were used for fraction of plasma lipids and FPG. Patients with one or more abnormal lipid parameters, as recommended by the American diabetes association, were considered as having DLP. These parameters include triglycerides (TGs) ≥ 150 mg/dL, low density lipid cholesterol (LDL-C) ≥ 100 mg/dL, high density lipid cholesterol (HDL-C) ≤ 40 mg/dL in males and ≤ 50 mg/dL in females (16). Patients with DLP were further subdivided to those with mixed DLP (all of the parameters outside the target), combined DLP (two of the parameters outside the target) and isolated single parameter DLP.

All qualitative variables were presented as exact amounts and percentages. If the quantitative variables

Box 1. Inclusion and Exclusion Criteria

Criteria
Inclusion Criteria
Males and Females aged > 18 years old with established diabetes mellitus who were taking anti-diabetic medications
Males and Females aged > 18 years old with abnormal plasma glucose (≥ 126 mg/dL) in laboratory examination following at least 8 hours of fasting
Exclusion Criteria
History of malignancy
History of liver disease
History of chronic kidney disease
History of drug abuse during at least the previous two years
Hormone replacement therapy or consumption of oral contraceptives during the last 3 months
Pregnant or breast feeding women
Refusal to give informed consent

had a normal distribution, mean \pm standard deviation (SD) was used and if not, median and interquartile range was reported. The association between qualitative variables was assessed by the chi-square test or Fisher's exact test. Comparison between means was done with the student's t test or the Mann-Whitney U test after assessing the condition of normality by using Kolmogorov-Smirnoff test. The association between FPG and other variables was determined using the correlation test. Univariate linear regression models were run to assess the unadjusted relationship between FPG and specified covariates of interest. A multivariate regression model was used in which the dependent variable was FPG and the independent variables included total cholesterol, TG, LDL, HDL, age, BMI and waist circumference, in order to assess the adjusted relationship between FPG and these independent variables. Covariates with a p-value of 0.10 from the univariate analysis were entered in the multivariate regression model and step-wise selection was used to include significant covariates. In all calculations, P values of < 0.05 were considered statistically significant.

Statistical package for social science (version 11.5) was used to analyze the data.

4. Results

The distributions of age, gender, place of residence, smoking, occupation, and family history of DM in the two study groups are shown in [Table 1](#).

The main features of DLP of the two study groups are shown in [Table 2](#). The most common pattern of DLP in both groups was isolated DLP with high LDL-C, followed by combined DLP with high LDL-C and low HDL-C. Altogether, DLP

patterns of the two groups were similar. Prevalence of DLP as a whole (one, two or three lipid parameter abnormality) in patients with diabetes and control participants was 89.3% and 82.6%, respectively, which was not statistically significant ($P = 0.1$).

The main clinical traits of participants with respect to their diabetic status are listed in [Table 3](#). Compared with non-diabetic individuals, subjects with diabetes had higher systolic blood pressure ($P < 0.001$), higher diastolic blood pressure ($P = 0.02$) and higher BMI ($P = 0.09$). Furthermore, patients with diabetes were more likely to have higher levels of total cholesterol ($P = 0.01$), TGs ($P = 0.001$) and LDL-C ($P = 0.009$) and lower levels of HDL-C ($P = 0.2$). Sub-analysis of females with isolated HDL-C revealed statistically significant differences between the two study groups ($P = 0.005$). Females with isolated low HDL-C were more common in the diabetic than the non-diabetic group ($P = 0.005$).

There was no significant difference in the incidence of HTN between the two groups (34.7% of participants with diabetes compared with 23.9% of the non-diabetic individuals, $P = 0.08$).

Patients with diabetes also had higher WC than non-diabetic individuals ($P = 0.01$). When subgroup analysis was performed, all the males had normal WC while females had higher than normal WC. However, the difference in WC between the two study groups, with respect to gender, was not significant ($P = 0.07$ in males and $P = 0.09$ in females).

In multivariate analysis, using multiple linear regression, the results showed that TG and age had independent effects on FPG ([Table 4](#)). Spearman correlation test showed that FPG levels were significantly correlated with TGs ($r = 0.37$, $P < 0.001$), LDL-C ($r = 0.23$, $P < 0.001$) and HDL-C ($r = -$

Table 1. Baseline Characteristics^a

Demographic Information	Diabetics (75)	Non-Diabetics (150)	P Value
place of residence			0.04
Urban	42 (56)	108 (69.7)	
Rural	33 (44)	47 (30.3)	
Gender			0.4
Male	34 (45.3)	78 (50.3)	
Female	41 (54.7)	77 (49.7)	
Family history of diabetes mellitus	32 (42.7)	35 (22.6)	0.002
Smoking	11 (14.7)	31 (20)	0.3
occupation			0.11
Un-employed	2 (2.7)	6 (4.1)	
Employed	37 (50.7)	91 (61.5)	
House wife	34 (46.6)	51 (34.5)	
Age	50.6 ± 10.6	48.4 ± 10.8	0.1

^aValues are expressed as mean ± SD or No. (%).

Table 2. Patterns of Dyslipidemia in Patients With Diabetes Compared With Non-diabetic Individuals^a

Kind of Dyslipidemia	Diabetic (75)	Non-Diabetic (150)	P Value
Mixed dyslipidemia			
High TGs, high LDL-C and low HDL-C	17 (22.7)	15 (9.7)	0.008
Combined dyslipidemia			
High TGs and low HDL-C	1 (1.3)	2 (1.3)	0.9
High TGs and high LDL-C	6 (8)	3 (1.9)	0.02
High LDL-C and low HDL-C	18 (24)	36 (23.2)	0.8
Isolated single parameter dyslipidemia			
High TGs	0	0	NA
High LDL-C	21 (28)	60 (38.7)	0.1
Low HDL-C	4 (5.3)	12 (7.7)	0.5

Abbreviations: HDL-C, high density lipid cholesterol; LDL-C, low density lipid cholesterol; NA, not available; TGs, triglycerides.

^aValues are expressed as No. (%).

0.17, $P = 0.009$). Furthermore, FPG was also significantly correlated with age ($r = 0.2$, $P < 0.001$), BMI ($r = 0.2$, $P < 0.001$) and WC ($r = 0.2$, $P < 0.002$) (Figure 1).

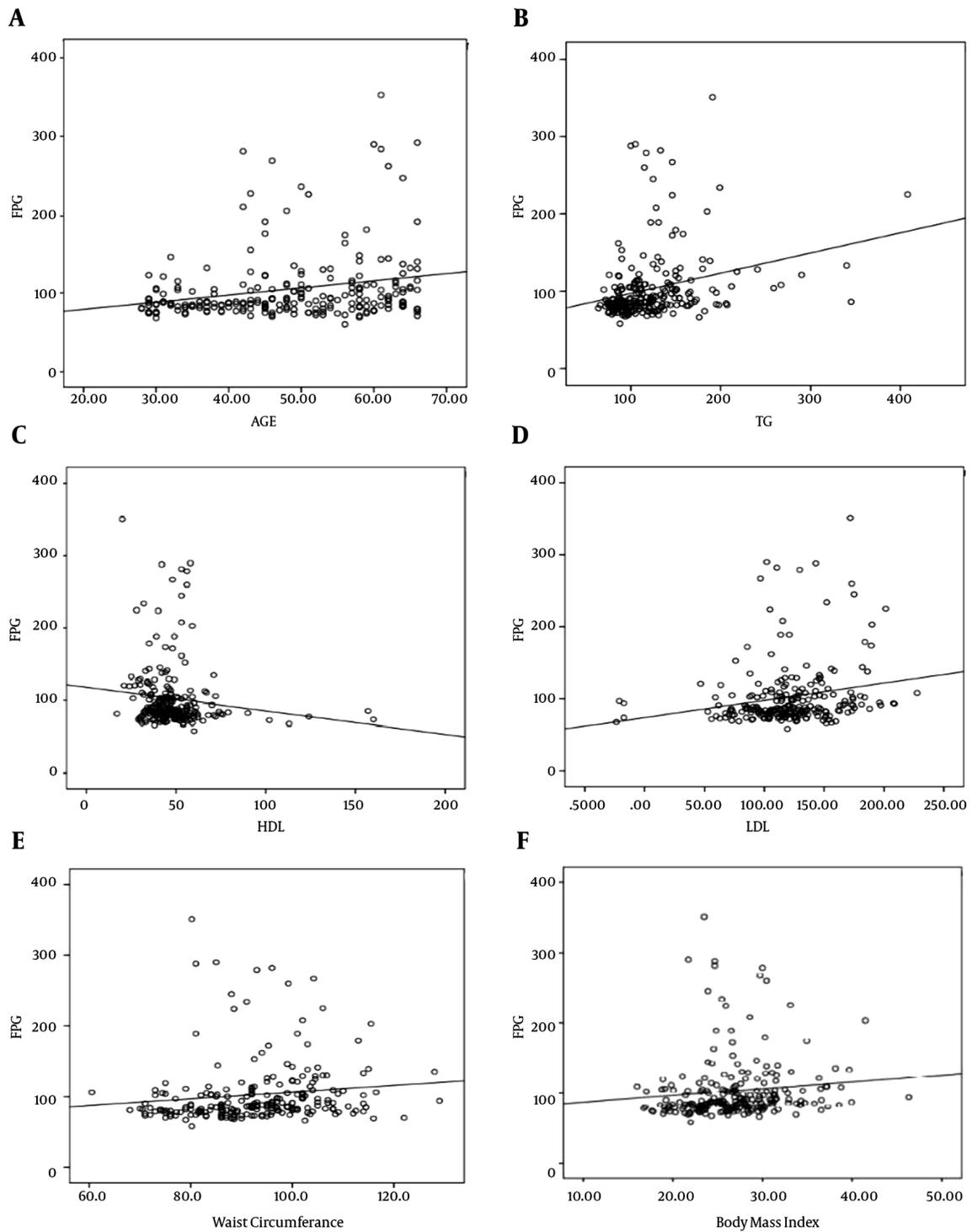
5. Discussion

In our study, the mean of systolic and diastolic blood pressure, total cholesterol, LDL-C, HDL-C, TGs, BMI and WC in individuals with diabetes were higher compared to non-diabetic participants, and these differences were statistically significant except for BMI and HDL-C amongst males.

In this study the most common pattern of DLP among patients with diabetes as well as those without diabetes was isolated high LDL-C. In a study done by Rakesh et al. the most common pattern was combined DLP with high LDL-C and low HDL-C (17). However, this pattern was the second most common pattern among patients with and those without diabetes in our study. In another study, the most common pattern was combined DLP with high TGs and low HDL-C among males and combined DLP with high LDL-C and low HDL-C among females (18).

In the Framingham Heart Study and also UK Prospec-

Figure 1. Scatter Plots of Fasting Plasma Sugar (FPG)



A, Age; B, triglyceride; C, high density lipoprotein; D, low density lipoprotein; E, waist circumference; F, body mass index with the corresponding fitted regression lines.

Table 3. The Main Study Findings^a

	Diabetic (75)	Non-Diabetic (150)	P Value
Total cholesterol	202 ± 40.3	188.9 ± 38.3	0.01
LDL-C	130.41 ± 35.4	116.48 ± 38.2	0.009
HDL-C	43.4 ± 11.2	49.9 ± 18.9	0.2
Male	44 (35 - 48)	43 (37 - 52)	0.8
Female	45 (35 - 52)	49 (43 - 56)	0.005
Triglycerides	129 (105 - 153)	103 (88 - 129)	0.001
Waist Circumference			
Male	94.3 ± 11.19	90.1 ± 11.1	0.07
Female	6.8 ± 13	92.8 ± 11.8	0.09
Body Mass Index	27.7 ± 5.4	26.5 ± 4.8	0.09
Systolic blood pressure	133.8 ± 23.1	123.8 ± 18.8	< 0.001
Diastolic blood pressure	83 (77 - 90)	78.5 (70.5 - 88)	0.02
Hypertension	26 (34.7)	37 (23.9)	0.08

Abbreviations: HDL-C, high density lipid cholesterol; LDL-C, low density lipid cholesterol.

^aValues are expressed as mean ± SD or No. (%) or median (IQR).

Table 4. Factors Significantly Associated With Fasting Plasma Sugar Based on Multiple Stepwise Linear Regression Analysis

Dependent Variables	Coefficients	SE	t	P Value
FPG				
TG	0.24	0.06	4.122	< 0.001
Age	0.84	0.25	3.365	0.001

tive Diabetes Study, patients with diabetes had an increased prevalence of high TGs and low HDL-C levels, yet their LDL-C levels were not different from non-diabetic participants (19, 20).

A very important finding of our study was the higher prevalence of some risk factors in non-diabetic participants. In our study most of the non-diabetic participants (82.6%) had at least one abnormality in their lipid profile. Furthermore, non-diabetic individuals had a higher prevalence of isolated high LDL-C and isolated low HDL-C compared to patients with diabetes. Moreover, some other risk factors including BMI and WC were outside the target in this study group. It has been well established that WC, being overweight and DLP increase the incidence of type II DM in the general population (21, 22). The presented results are consistent with the study of Wild et al. who described that the Middle East is estimated to bear one of the world's greatest increases in the burden of DM in the subsequent decades where the increase in patients with diabetes will occur in the economically productive 45 - 64 year-old population compared with developed countries where individ-

uals ≥ 65 year-old are more affected (4).

When all the three lipid parameters were perceived together, it was illustrated that 22.7% of the diabetic participants and 9.7% of non-diabetic individuals had abnormality in all the three components (mixed DLP). According to some other studies, all types of DLP identified in the general population could occur in diabetic patients because of insulin resistance and insulin deficiency (23), however, mixed DLP is particularly common in individuals with diabetes (24-27).

Increased levels of blood pressure were more common in patients with diabetes in our study. Nevertheless, this was remarkably common in non-diabetic participants as well. Furthermore, HTN increases long term vascular complications of DM including stroke, chronic kidney disease, CVD and death. The prevalence of HTN among patients with diabetes in Iran was estimated below 50% in a previous study (28). Similarly, HTN rate among patients with diabetes was higher compared with the rate reported for the general population (29).

In the present study we found a significant associa-

tion between FPG and serum lipid parameters including LDL-C, HDL-C, TG and also age, BMI and waist circumference. Considering all of these factors, TG and age were influential factors on FPG, according to the multiple linear regression. The results of the other studies were inconsistent. Some studies demonstrated a positive correlation between HbA1C and serum lipid profile (30, 31). However, a study by Jayarama et al. did not show a significant relationship between HbA1C and serum lipid parameters (18). Another study did not report a correlation between HbA1C and serum cholesterol levels (32).

The participants with diabetes had a higher WC and BMI compared with non-diabetic individuals. In this study we found a positive association between overall and central obesity and FPG. In agreement with the results of our study, several studies demonstrated a relationship between obesity, CVD and DM. These associations are mediated through the release of adipokines from visceral fat (33-36). Some other studies concluded a correlation between WC and BMI, and DM prevalence (37-40). It has been well established that abdominal obesity is significantly related to insulin resistance (41) and increases the risk of developing type II DM (42). On the other hand, insulin resistance is associated with a higher TGs and lower HDL-C level (43).

In our study the mean WC was higher in females compared with males. This was consistent with other studies implemented in Iran (44, 45) yet not with the world health organization (WHO) criteria for determining central obesity. This difference has been reported by other studies conducted in Iran, which believed that WHO cut off point for WC is not suitable for the Iranian population (46, 47).

The main limitation of our study was that the study concentrated on CVD risk factors and DM status at the same time; however, it is likely that CVD risk factors have been developed decades before the time of DM diagnosis so that this cross sectional study cannot remark any temporal trend or causality. Therefore, a large cohort study that examines lifelong CVD risk factors before the clinical onset of DM is recommended. Also lack of appropriate medical screening and availability of laboratory reports were another limitation of this study. Regarding the increasing prevalence and changing epidemiology of DM and CVD risk factors and the high probability of their coexistence in our region, this study provides important information required for the control of risk factors in this vulnerable population. This study is probably the first report, which provides such data on the Iranian people and might work as a base line of comparison with other parts of the country.

5.1. Conclusions

Our study showed that CVD risk factors were more common in patients with diabetes; however, non-diabetic

individuals also had high prevalence of risk factors predisposing them to DM. Therefore, further attention by the medical community is necessary to choose effective strategies for a more aggressive approach to prevent and manage these risk factors, especially in patients with diabetes. It is recommended for Iranian health policy-makers to establish more health promotional agendas. We hope our study could facilitate the way for future research in this area. The results of this study contribute to the evolution of knowledge about CVD risk factors in Iranian patients with diabetes. These findings may be useful in clinical practice and policy making to identify patients with diabetes prone to CVD development.

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Footnotes

Authors' Contribution: Shabnam Niroumand was involved in the concept, design, definition of intellectual content, literature search, and analysis, manuscript preparation, editing and review. Maliheh Dadgarmoghaddam was involved in the concept, design, definition of intellectual content, manuscript preparation, editing and review. Babak Eghbali, Maryam Abrishami and Arash Gholoobi were involved in concept, design and data acquisition. Hamid Reza Bahrami Taghanaki was involved in the Study concept and design and editing. Mohammad khajedaluee was involved in the concept, design, analysis, editing and review. All authors read and approved the final manuscript.

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