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ORIGINAL RESEARCH

Association of Lipid Profile with Type 2 Diabetes in First-Degree Relatives: A 14-Year Follow-Up Study in Iran

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Purpose: Dyslipidemia is claimed to be associated with an increased risk of type 2 diabetes mellitus (T2DM). However, first-degree relatives (FDRs) of patients with T2DM are reported to be at higher risk. The aim of this study was to evaluate the association between serum lipid profile and T2DM incidence in FDRs.

Patients and methods: Information on 1222 T2DM FDRs during 14 years of follow-up was retrieved. All individuals were examined for diabetes status and dyslipidemia once a year. We used a Bayesian joint longitudinal-survival model to assess the association.

Results: Our data showed that a 10 mg/dL increase in triglycerides (TG), very-low-density lipoprotein (VLDL), and non-high-density lipoprotein (non-HDL) cholesterol levels during the follow-up period was associated with an increased risk of diabetes by 5%, 29%, and 6.6%, respectively. Moreover, for every one-unit increase in the TG to HDL ratio, the T2DM incidence increased by 35%. Subgroup analysis also showed that the increased risk of diabetes was significant only in female FDRs, so that a 10 mg/dL increase in TG and VLDL cholesterol level and a one-unit increase in TG to HDL ratio in female FDRs resulted in an increased risk of diabetes by 7.8%, 46%, and 64%, respectively. However, analysis of HDL, low-density lipoprotein (LDL), total cholesterol (TC), TC to HDL, and LDL to HDL cholesterol levels/ratios did not find any statistically significant associations.

Conclusion: Increases in TG, VLDL, non-HDL cholesterol level, and TG to HDL ratio are associated with an increased risk of T2DM in FDRs, especially in female FDRs.

Keywords: diabetes mellitus, joint model, longitudinal studies, survival

Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder and is considered a major global health threat all over the world.[1] According to the report by the International Diabetes Federation in 2015, about one out of 11 adults had diabetes mellitus in the year 2017 and its prevalence is likely to increase to 642 million by 2040.[2] T2DM was estimated to account for about 6.8% of global mortality in adults aged 20–79 years in 2010.[3]

The mechanism of T2DM is largely understood. It is generally accepted that in normal circumstances, there is a feedback loop between insulin action and insulin secretion. When this feedback is disrupted, the sensitivity to insulin is impaired and insulin secretion is affected, resulting in abnormal blood levels of glucose.[4] Insulin resistance (IR) and β-cell dysfunction are the main hallmarks of T2DM.[5] A growing body of data has shown that an abnormal lipid profile has a close relationship with

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IR. IR also serves as the major component of other metabolic disorders, in addition to T2DM. For instance, IR has been indicated to be associated with a high level of very-low-density lipoprotein (VLDL), high concentrations of serum triglycerides (TG), and low serum high-density lipoprotein (HDL). Therefore, the lipid profile is emphasized in almost all follow-up programs of T2DM and serves as a serious risk factor.[6,7]

The etiology of T2DM is not completely clear, but decades of research have shown that T2DM involves complex genetic and environmental factors, including a family history of diabetes, advanced age, abdominal obesity, physical inactivity, and abnormal lipid metabolism. People with a positive family history of diabetes are subject to a 3–4 times higher risk of diabetes compared to those with a negative family history.[8–10] The risk of T2DM increases with the increasing number of affected relatives.[10,11] Further study on family history indicated that the risk of T2DM has a close correlation with the paternal or maternal relationship with the patients.[10] For instance, mothers with T2DM have more risk than fathers with diabetes. The first-degree relatives (FDRs) with diabetes are exposed to a higher risk than the second-degree relatives.[12] Amini and Janghorbani showed that the prevalence rates of T2DM in FDRs were significantly higher than those for a control population of the same age.[13] FDRs were also shown to have increased whole-body IR and reduced muscle glucose uptake.[14]

The longitudinal study is a research design that involves repeated observations or within-subject changes to follow particular individuals over a period of time. The covariates of analysis may be defined to assess their impact on the whole profile of the individual response. Therefore, this type of analysis can be useful particularly to evaluate a response that may occur during the follow-up period.

In this retrospective cohort study, data from a 14-year follow-up were analyzed using a Bayesian joint longitudinal-survival model aiming to evaluate the association between changes in lipid profile abnormalities in an Iranian population and the risk of developing diabetes in the FDRs of diabetic patients.

Patients and Methods

Participants

In this study, information on 3492 FDRs of diabetic patients, including siblings and children, between 2003 and 2017, were extracted from the Database of the Endocrinology and Metabolism Research Center of Isfahan University of Medical Sciences, known as the Isfahan Diabetes Prevention Study. Diabetes was defined as fasting plasma glucose (FPG) ≥126 mg/dL or 2-h plasma glucose ≥200 mg/dL or HbA_{1c} ≥6.5%. Prediabetes was defined as impaired fasting glucose (IFG) (FPG: 100–125 mg/dL and 2-h plasma glucose <140 mg/dL) or impaired fasting glucose (IGT) (FPG <126 mg/dL, but with 2-h plasma glucose concentration ≥140 and <200 mg/dL) or HbA_{1c} 6.0–6.49%.[15] Finally, normal glucose tolerance was defined as FPG below 100 mg/dL and 2-h plasma glucose smaller than 140 mg/dL and HbA_{1c} <6.0%.[16,17] Additional information about this cohort study has been published elsewhere.[18,19] Among all the participants, the last status of 1488 FDRs was missed. Since our goal was to assess the risk of diabetes in FDRs, those individuals whose status on the last visit was prediabetes (792 FDRs with either IFG or IGT) were excluded. The information on the remaining subjects (1222 FDRs) was included in the analysis to examine the trends in the lipid profiles and their impact on the risk of diabetes. All individuals signed informed written consent for their participation. The present study was performed according to the principles of the Declaration of Helsinki and the ethical committee of Isfahan University of Medical Sciences (approval ID: IR.MUI.RESEARCH.REC.1398.102).

Statistical Analysis

We applied a joint longitudinal-survival model with a linear mixed-effects model for the longitudinal measurements and a Cox proportional hazards model for the time to diabetes, both adjusted for age, sex, HbA_{1c} and weight to height ratio (WHR) as confounders. We used a logarithmic transformation of the longitudinal responses to respect the normal distribution assumption. The following formulation was specifically used for the longitudinal response:

$$\begin{aligned} log(y_i(t)) &= \eta_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 Time + \beta_2 Sex + \beta_3 Time \times Sex \\ &\quad + \beta_4 WHR + \beta_5 HbA1C + b_{0i} + b_{1i} Time + \varepsilon_i(t) \end{aligned}$$

$$b_{ri} \sim N\left(0, {\sigma_r}^2\right)$$

$$and\ \varepsilon_i(t) \sim N\left(0, {\sigma_\varepsilon}^2\right)$$

and the following hazard function for the event process:

$$h_i(t) = h_0(t) exp(\alpha\ \eta_i(t))$$

In this formulation, $y_i(t)$ is the observed longitudinal lipid values from the ith individual, $\beta_r (r = 0, 1, 2, 3, 4, 5)$ are fixed-effect terms; $b_{ri} (r = 0, 1)$ represent subject-specific

random intercept and random-slope effect terms; $\varepsilon_i(t)$ is the normal error term; and $h_0(t)$ is the baseline hazard.

In this model, the longitudinal and survival processes are linked through a shared parameter α, known as the association parameter, where for C unit increase in lipid value within a period, the hazard ratio of developing diabetes is calculated as $HR = \exp(\alpha \times C)$. We applied separate joint models for each lipid factor under a Bayesian approach using JMBayes package in R, which is available at https://cran.r-project.org/web/packages/JMbayes/index.html. The level of significance was set at 0.05.

Results

There were 327 (26.8%) male FDRs with a total mean age of 42.90±6.47 years. The median follow-up time was 11 years (mean ± SD 10.69±3.23 years) and the median number of visits was 8 (7.01±4.65). During the follow-up period of this study, 391 individuals (32%) were diagnosed with T2DM, 107 (27.4%) of whom were male. Table 1 presents further information regarding socio-demographic, clinical, and anthropometric characteristics of the participants.

Figure 1 shows the trajectory plot of the lipid factors over the follow-up period, reflecting the time-varying property of the responses. Table 2 presents the estimations of the shared parameter joint model for each longitudinal lipid profile and time to diabetes.

Based on these estimations, changing longitudinal trends in TG, TG to HDL, VLDL, and non-HDL cholesterol levels were associated with increased risk of diabetes in the total population. We showed that a 10 mg/dL increase in TG, VLDL, and non-HDL cholesterol levels, as well as a one-unit increase in the TG to HDL ratio during the follow-up period, increased the risk of diabetes by 5%, 29%, 6.6%, and 35%, respectively. Subgroup analysis by gender showed that the increased risk of diabetes was significant only in females, except for non-HDL cholesterol, which did not show any significant increase in either gender. Specifically, in female FDRs, for every 10 mg/dL increase in TG and VLDL cholesterol level, as well as one-unit increase in TG to HDL ratio during the follow-up period, the risk of diabetes increased significantly, by 7.8%, 46%, and 64%, respectively. In male FDRs, although our findings revealed an increased risk of diabetes for all the lipid factors, none of them was statistically significant. Further analysis of other factors, including HDL, low-density lipoprotein (LDL), total cholesterol (TC), and TC to HDL and LDL to HDL ratios, found no statistically significant associations, either in the total population or within the sex groups.

Table 1 Socio-Demographic and Lipid Characteristics of Participants

Sex (Male)	**327 (26.8)**
Age (years)	42.90±6.47
BMI (kg/m^2)	28.84±4.33
WHR	0.83±0.07
HbA_{1c} (%)	5.05±0.81
Triglycerides (mg/dL)	159.01±93.74
Total cholesterol (mg/dL)	195.17±39.45
HDL cholesterol (mg/dL)	45.35±11.58
LDL cholesterol (mg/dL)	123.78±29.20
Triglycerides to HDL cholesterol ratio	3.90±2.98
Total cholesterol to HDL cholesterol ratio	4.53±1.31
LDL cholesterol to HDL cholesterol ratio	2.88±0.95
VLDL cholesterol (mg/dL)	42.89±6.23
Non-HDL cholesterol (mg/dL)	28.84±4.33

Note: Values are mean ± standard deviation or number (percent).

Discussion

Today, it is generally accepted that dyslipidemia is associated with T2DM. Patients with combined high TG and low HDL-C levels had 12.75 and 4.89 times higher odds of developing diabetes and prediabetes, respectively.[20] Diabetic dyslipidemia is often characterized by high TC, high TG, low HDL cholesterol, and increased level of LDL.[21,22] A lipid profile assessment in T2DM FDRs may be useful to reduce the risk of disease progression and also for early intervention. The exact mechanism of this risk is not fully understood, but at first, this may be due to genetic factors. For instance, a study of Japanese-American males reported an increased risk of diabetes incidence among those with a parental history of diabetes (odds ratio 1.73).[23] Bjørnholt et al analyzed healthy Caucasian male FDRs with normal fasting blood glucose. They found that maternal diabetes is associated with an increased risk of diabetes.[24]

T2DM has a high prevalence in the Iranian population. It has been determined that 3.6% (4.3% women and 2.6% men) in the general population of Iran aged more than 30 years are suffering from diabetes.[25] Rashedi et al reported that the prevalence of T2DM was 14.4% among Iranian older adults.[26]

Our data indicated that lipid panel changes were related to changes in diabetes onset in the Iranian population. We specifically showed that for every 10 mg/dL increase in TG, VLDL, and non-HDL cholesterol level during the follow-up, the risk of developing diabetes in FDRs increased by 5%, 29%, and 6.6%, respectively. Similarly, for every one-unit increase in the TG to HDL ratio in

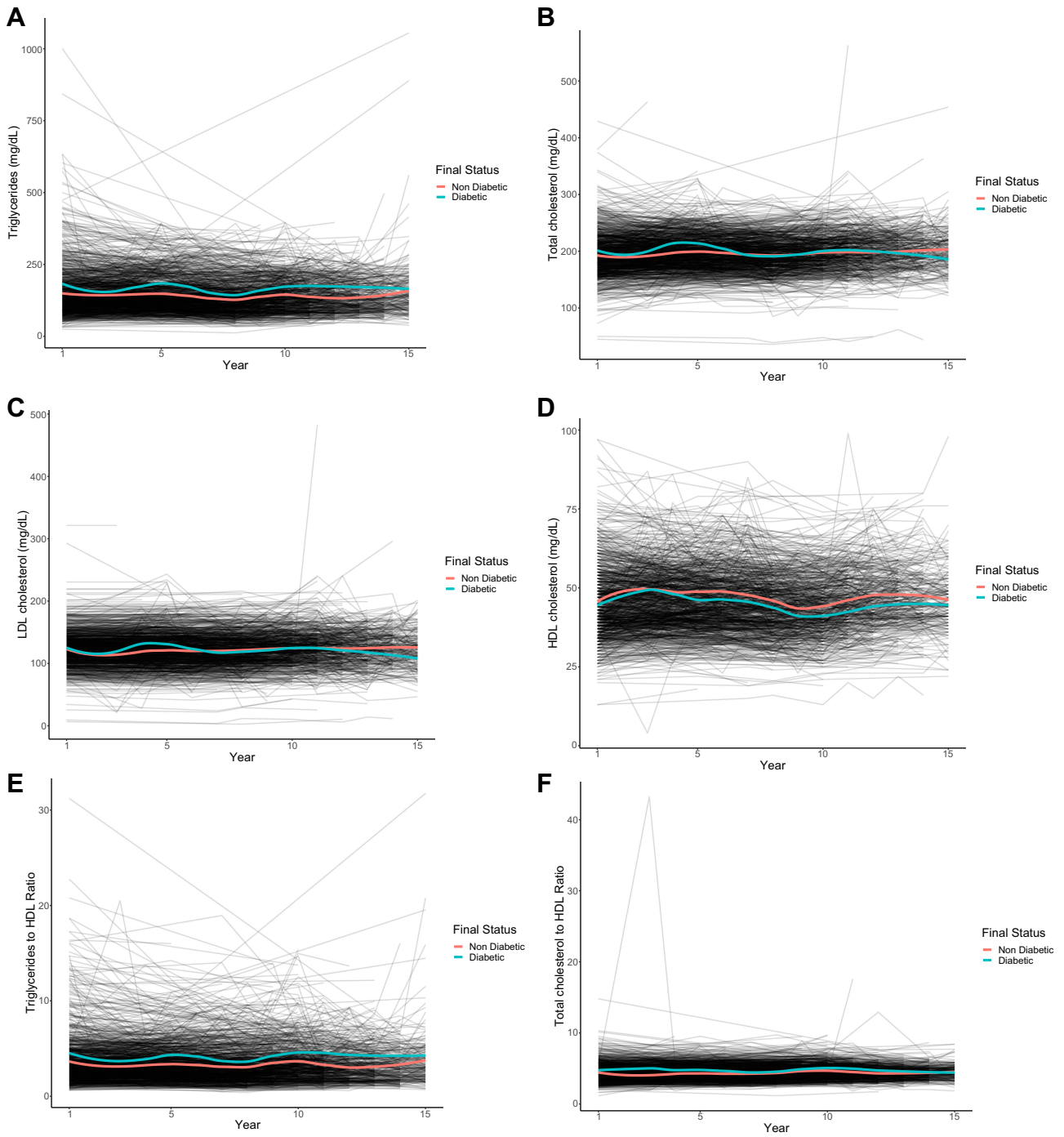

Figure 1 Continued.

FDRs, we found a 35% increase in the risk of developing diabetes.

To determine the exact mechanism of the effects of TG, VLDL, and non-HDL cholesterol in T2DM, decades of research have been performed. Diabetic dyslipidemia is not yet fully understood; however, IR and relative insulin deficiency are commonly observed in patients with T2DM. Moreover, some adipocytokines, such as adiponectin, may contribute to the development of diabetic dyslipidemia.[27]

The effect of high levels of lipid factors on increasing the risk of diabetes was also confirmed by previous studies. For instance, Azmatulla et al examined the body fat distribution, cardiorespiratory fitness, and lipid profile of T2DM FDRs. They showed that an abnormal lipid profile in FDRs was associated with the development of other

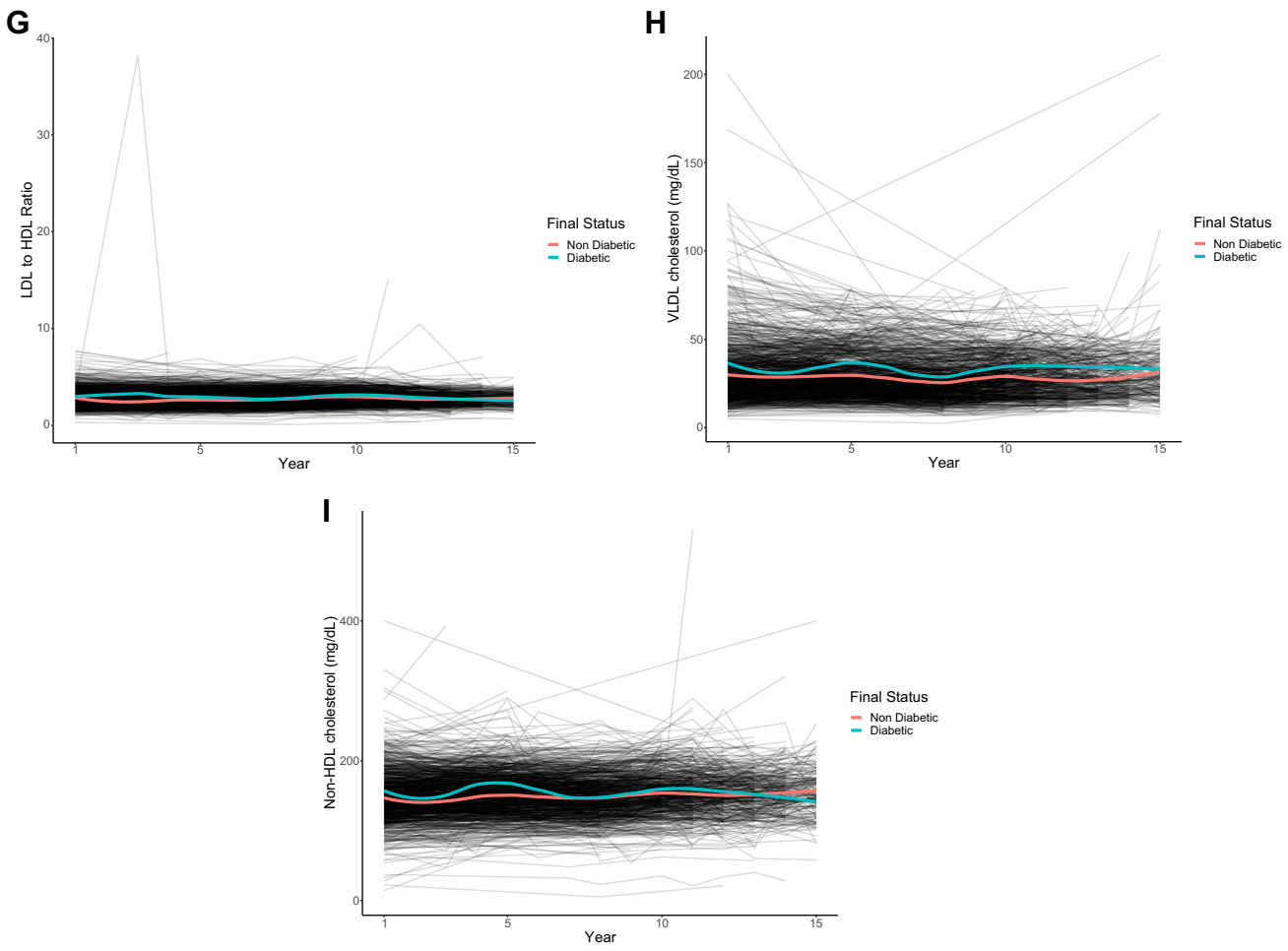

Figure 1 Trajectory plots of lipid factors over the follow-up time in first-degree relatives of diabetic patients. (**A**) Triglycerides level; (**B**) total cholesterol level; (**C**) low-density lipoprotein (LDL) cholesterol level; (**D**) high-density lipoprotein (HDL) cholesterol level; (**E**) triglycerides to HDL ratio; (**F**) total cholesterol to HDL ratio; (**G**) LDL to HDL ratio; (**H**) very-low-density lipoprotein (VLDL) cholesterol level; (**I**) non-HDL cholesterol level.

disorders, such as severe cardiovascular impairments.[28] Iraj et al analyzed 793 individuals with prediabetes in T2DM FDRs. They reported that the mean level of LDL was significantly higher in the isolated impaired fasting glucose group than in the isolated impaired glucose tolerance group.[29] In addition, our subgroup analysis showed that dyslipidemia increased the risk of diabetes mostly in female FDRs. Similarly, Jafari-Koshki et al reported that although there was a significant association between risk of diabetes in FDRs and waist circumference and waist/hip ratio, these findings were present only in females, and not in males.[30]

The use of joint models has received a lot of attention in the literature on longitudinal studies. However, there are many challenges involved in adopting these models, including multivariate integration of distributions of random effects, more complex situations where there is more than one longitudinal response, the existence of competing risks and recurrent events, and issues regarding different types of censoring. Nonetheless, Bayesian methods have provided a path to overcome most of these challenges. Comprehensive reviews in this context have been presented by various authors.[31,32]

The present study is subject to some limitations. For instance, although joint models respond relatively well to unbalanced designs with missing data and do not impose strict assumptions on data design, the lower the rate of missing data, the more accurate the estimates would be. In addition, by applying multivariate joint models, the existing correlations among responses could be taken into account, which may prevent increases in type I errors. However, these models require some additional assumptions, including the multivariate normal distribution. Moreover, recording and

Table 2 Association of Time-Dependent Lipid Factors and Risk of Diabetes in the First-Degree Relatives of Diabetic Patients in the Joint Longitudinal-Survival Model

Factor	Population	α	SE	P	HR
TG	Total	0.0049	0.0015	0.0015*	1.0049
	Male	0.0046	0.0038	0.2265	1.0046
	Female	0.0076	0.0014	<0.0001*	1.0076
TC	Total	0.0044	0.0032	0.1629	1.0044
	Male	0.0052	0.0067	0.4424	1.0052
	Female	0.0067	0.0043	0.1213	1.0067
LDL	Total	0.0015	0.0030	0.6135	1.0015
	Male	0.0005	0.0064	0.9414	1.0005
	Female	−0.0006	0.0041	0.8891	0.9994
HDL	Total	0.0152	0.0129	0.2366	1.0153
	Male	−0.0175	0.0304	0.5638	0.9827
	Female	0.0012	0.0145	0.9354	1.0012
TG:HDL	Total	0.3013	0.1491	0.0433*	1.3516
	Male	0.5264	0.3268	0.1072	1.6928
	Female	0.4952	0.1717	0.0039*	1.6408
TC:HDL	Total	0.4264	0.3867	0.2702	1.5317
	Male	0.2178	0.2311	0.3459	1.2433
	Female	0.2740	0.4367	0.5303	1.3152
LDL:HDL	Total	0.0418	0.2246	0.8524	1.0427
	Male	0.7677	0.5804	0.1859	2.1548
	Female	−0.2194	0.2531	0.3860	0.8030
VLDL	Total	0.0255	0.0077	0.0009*	1.0258
	Male	0.0255	0.0190	0.1791	1.0258
	Female	0.0379	0.0068	<0.0001*	1.0386
Non-HDL	Total	0.0064	0.0031	0.0432*	1.0064
	Male	0.0082	0.0073	0.2629	1.0082
	Female	0.0073	0.0042	0.0864	1.0073

Notes: *Statistically significant associations ($P<0.05$). Adjusted for confounders: age, sex, HbA_{1c}, and WHR.

Abbreviations: α, association parameter; SE, standard error; *P*, *P*-value; HR, hazard ratio; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG:HDL, triglycerides to HDL ratio; TC:HDL, total cholesterol to HDL ratio; LDL:HDL, LDL to HDL ratio; VLDL, very-low-density lipoprotein; Non-HDL, non-HDL cholesterol.

measuring the genetic information of individuals along with lipid factors could also be of great help in demonstrating the genetic role in the prognosis of the disease. The findings of this study are specifically related to the Iranian population and further research in other populations is recommended.

Conclusion

In the present study, the trend in the lipid profile was assessed during 14 years of follow-up in FDRs of patients with T2DM. Our findings showed that TG, TG to HDL ratio, VLDL, non-HDL cholesterol levels, and TG to HDL ratio were associated with T2DM onset. This study thus found that lipid profile was associated with T2DM, although the relationships were significant only in females. However, other parameters of dyslipidemia were not able to predict the risk of T2DM.

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Disclosure

The authors report no conflicts of interest in this work.

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