# Patterns of changes in serum lipid profile in prediabetic patients: Results from a 16-year prospective cohort study

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**Research**

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## Abstract

# Background

Lipids abnormality pervasively is associated with the risk of Type 2 diabetes mellitus. To the best of our knowledge, there is no study that examined the longitudinal changes in wide range of serum lipid profile in prediabetic subjects in association with the risk of Type 2 diabetes mellitus in future. This study aimed to identify the patterns of changes in lipids profile over time in prediabetic patients and classify these subjects in order to highlight the high risk people for future diabetes risk.

# Methods

This prospective 16-year (2003–2019) cohort study was conducted among 1228 prediabetic subjects. The study subjects followed over time and changes in their lipid profile include Triglycerides, Cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol was evaluated. Latent Markov model was used for data analysis.

# Results

Mean (standard deviation) age of subjects was 44.00 (6.86) years and 73.6% were female. Latent Markov model identified two latent states of subjects in terms of change in lipid profile: low tendency to progress diabetes/ high tendency to progress diabetes (74%/ 26%). Latent Markov model showed that the transition probability from “low tendency to progress diabetic” state to “high tendency to progress diabetic” state was lower than the transition probability from “high tendency to progress diabetic” state to “low tendency to progress diabetic” state.

# Conclusion

In conclusion, abnormality of serum lipid profile remains a significant and growing problem in prediabetic subjects as high risk population. The reduction in the problem burden will require changes at the policy level as well as at the personal level.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease with major morbidities and mortality rates(1). The World Health Organization (WHO) estimated that the number of diabetic people in the world to reach 522 million by 2030, of whom 439 million will have T2DM (2, 3). The prevalence of diabetes between Iranians was 7.9% in 2010, but the distribution of this prevalence in Iran is also diverged widely between 1.3% and 14.5% in various provinces(4).

Prediabetes (PD) is the precursor stage to diabetes mellitus, in which the subject's plasma glucose is higher than normal level, but lower than diabetes mellitus thresholds(5). In recent years, PD prevalence has increased, especially in developing countries. PD prevalence is higher than T2DM (6). It is estimated that 5–10% of subjects with PD, will develop T2DM annually (7). About 30% of diabetic patients in Iran are not aware of their disease; therefore, more attention should be paid to diabetes in Iran(8).

The numerous comorbidities, including obesity and lipid abnormality problems are associated with the risk of developing diabetes (9). Previous evidences suggested that lipid abnormalities are common in people with T2DM and PD (10, 11). For instance, a meta-analytic review demonstrated that lipid profile disorders significantly associated with T2DM (12). A community based cross-sectional survey showed a strong association between serum lipid profile with T2DM and PD (13).

Prediabetic individuals often exhibit an atherogenic pattern of risk factors that includes higher levels of total cholesterol (CHOL), low-density lipoprotein cholesterol (LDL), Triglycerides (TG) and lower level of high-density lipoprotein cholesterol (HDL) than individuals who do not develop diabetes. Lipid abnormalities in diabetics patients, typically characterized by high CHOL, high TG, low HDL and high LDL levels(14).

Although the association between lipid abnormality and T2DM has been investigated in various populations, few studies have been conducted to evaluate such association in prediabetic patients as high risk population.

Due to the increased risk of diabetes progression over the following 5–10 years from the stage of PD (15–17), it is important to establish appropriate prevention strategies in PD. Lipid profile is not necessarily stable, especially in prediabetics; accordingly it is necessary to apply an appropriate analytical technique that can provide a comprehensive evaluation of subjects based on changes in lipid profile over time. Therefore, in current study, an advanced statistical method, i.e. latent Markov model (LMM) was used for addressing the above points.

The previous studies have described the association between lipid profiles with diabetes, without exploring the patterns of changes in lipid profile over time. LMM, a latent state-switching approach, offer a straightforward approach to classify subjects (latent state) according to the patterns of changes in lipid profile over time. The application of this method results in the identification of subjects within each latent state who are highly similar to each other and uniquely different from those in other states. The model allows us to estimate the probability to move between the states or to retain the same state. The LMM estimates the probability to move between the states or to remain in the same state. Subjects were assigned to the latent states which they had the highest probability for membership. This study aimed to identify the patterns of changes in lipid profile over time in prediabetic patients and classify these subjects in order to highlight the high risk people for future diabetes risk.

# 2. Material And Methods

# 2.1. Study design and participants

The current study was conducted under the framework of the Isfahan Diabetes Prevention Study (IDPS), which was initiated in 2003 among 3,483 subjects. The IDPS is an ongoing longitudinal study carried out in a cohort of the first-degree relatives (FDR) of patients with T2DM in Isfahan the largest city in center of Iran to assess the various potential risk factors for diabetes in subjects with a family history of T2DM. Recruitment methods and examination procedures have been described previously(18). They completed laboratory tests, including a standard 75 g 2-h oral glucose tolerance test (OGTT), and a questionnaire on their health status and on various potential risk factors of diabetes. The subjects were followed up according to standard medical care in diabetes (19). Of the 3,483 subjects who participated at baseline, 1228 had been diagnosed with PD. We used data from 1228 prediabetics. Data include, the baseline, the last measurements and the mean of measurements was recorded among baseline and last, as the second of measurement. Written informed consent was obtained from all subjects in IDPS. The current secondary study has been approved by Bioethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.532).

# 2.2. Laboratory parameters

Biochemical tests including lipid profile, fasting plasma glucose (FPG) and OGTT were carried out for all subjects. To determine lipid profile and FPG, a blood sample was drawn from all subjects after 10–12 h overnight fasting. Postprandial plasma glucose was measured using venous blood sample at 30, 60, and 120 min after oral glucose administration. Plasma glucose and lipid profile concentrations were determined using enzymatic colorimetric method (ParsAzmoon, Tehran, Iran) adapted to a Selectra-2 auto-analyzer (Vital Scientific, Spankeren, Netherlands). Serum concentration of LDL was calculated by Friedwald equation in subjects with serum TG levels < 400 mg/dL(20). Serum concentration of HDL, CHOL and TG measured using standardized procedures (20).

Definitions and diagnostic criteria were based on the American Diabetes Association (ADA) guidelines. Symptomatic subjects with FPG ≥ 11.1 mmol/L were considered diabetic. If FPG was ≥ 7 and < 11.1 mmol/L, a second FPG was measured on another day. If the second FPG was also ≥ 7 mmol/L, subjects were classified as diabetic. FPG ≥ 7 mmol/L or 2-hour PG ≥ 11.1 mmol/L also defined diabetes mellitus. Impaired glucose tolerance (IGT) was interpreted as 7.8 ≤ 2hpost glucose load (75 g glucose) ≤ 11.0 mmol/L(5). If FPG was in the range 5.6 ≤ FPG ≤ 6.9 mmol/L, it was considered as impaired fasting glucose (IFG) (5). In addition, all subjects developing IFG and IGT were pooled in a unique" impaired glucose metabolism "(IGM) group in the analyses.

In the analyses, we considered following categories as abnormal: TG level of more than 150 mg/dL; LDL level of more than 100 mg/dL and CHOL level more than 200 mg/dL; in both men and women(21), HDL level of less than 40 mg/dL in men; less than 50 mg/dL in women(21) and HDL level > 60 mg/dL, optimal condition, considered protective against heart disease (21).

# 2.3. Other variables

The subjects completed a demographic questionnaire including age and gender. Physical activity recorded in an International Physical Activity Questionnaire) IPAQ) (22). Anthropometric and clinical measurements, including body mass index (BMI) (by dividing weight [kg] to the square of height [$m^2$]), FPG and lipid profile include TG, CHOL, HDL and LDL was recorded. The process of administering and collecting the questionnaires was conducted at the Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences.

## 2.4. Statistical analysis

Continuous and categorical basic characteristics of study subjects were presented as mean (standard deviation (SD)) and frequency (percentage), and compared between study groups using analysis of variance (ANOVA) or independent samples T-Test and Chi-square tests, respectively.

To analysis the patterns of changes in serum lipid profile over time in prediabetic patients, LMM was applied (23). We used three measures of lipid indices obtained from subjects including first measure at baseline, mean values during follow up period and last measure. LMM identified number of latent states in studied subjects based on patterns of changes in study lipid measures, also provided the probability moving between various states. The process of LMM fitting was as follows: the following LMM were estimated, 2-State 1-Class, 2-State 2-Class, 2-State 3-Class, 3-State 1-Class, 3-State 2-Class and 3-State 3-Class sequentially, and the model with 2-State 1-Class was selected based on goodness of fit criteria.

The balance between fit and parsimony (number of parameters) of different models was estimated using Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The optimum number of states was determined through comparing the AIC, BIC, classification error and entropy indices across models. Lower AIC, BIC and classification error and higher entropy, indicate the better model fitting and the better states separation (24, 25). We extracted two latent states from TG, CHOL, LDL and HDL in order to evaluate their association with progress diabetes over time, and were labelled as “State1” and “State2”.

After selecting the number of proper latent states, the LMM without/with covariates including age, gender, physical activity, BMI, and FPG were fitted and the patterns of changes in serum lipid profile over time in prediabetic patients was evaluated. The fitted model was adopted separately in gender subgroups. The interpretation of extracted latent states was done based the mean values of lipid profiles calculated by LMM.

Our model also allows estimate the longitudinal change in the metabolic condition of prediabetic subjects. The LMM estimates the initial and transition probabilities according to the mean values of TG, CHOL, LDL and HDL. The initial probability define as, probability of current state is that is needed to predict the future. The transition probability is defined as, probability to move of subjects between different latent states. The subjects in the PD state can remain and/or move to other latent states. The proposed model was fitted using the LMest package (26) developed within the R free statistical Software (version 3.6.3) (27).

# 3. Results

General characteristics of subjects at baseline are presented in Table 1. Of 1228 study subjects with mean (SD) 44.007 (6.86) years, 73.6% were females. The baseline demographic, age was not different between the males and females. General characteristics of subjects at the end of follow up are presented in Table 2. Over the 16-year follow-up, 339(27.6%) became diabetic, 204(16.6%) was normal, 403 (32.8%) remained PD (IFG and IGT) and the data about final status of 282 (23%) of subjects was not available.

Table 1
Basic demographic and clinical characteristics of prediabetic subjects at the baseline (Mean ± SD)

| Variables | Number | Male(n = 324) | Female(n = 904) | Total(n = 1228) | P-value |
|---|---|---|---|---|---|
| Age(years) | 1215 | 44.19 ± 7.02 | 43.94 ± 6.80 | 44.00 ± 6.86 | 0.577 <0.001 <0.001 |
| BMI(kg/$m^2$) | 702 | 28.21 ± 3.10 | 29.54 ± 4.30 | 29.20 ± 4.07 | 0.016 |
| FPG (mmol/l) | 1227 | 106.20 ± 9.25 | 103.72 ± 10.16 | 104.37 ± 9.99 | |
| Physical activity(min/week) | 1228 | 36.52 ± 67.94 | 48.52 ± 79.92 | 45.35 ± 77.10 | |

BMI (Body mass index), FPG (Fasting blood glucose in the baseline), T- Test, P-value < 0.05 is considered as significant

Table 2
Basic demographic and clinical characteristics of different categories of subjects at the end of follow-up (Mean ± SD)

| Variables | Pre diabetic | | | | | P-value |
|---|---|---|---|---|---|---|
| | IFG (n = 303) | IGT (n = 100) | IGM (n = 403) | NGT(n = 204) | DM (n = 339) | |
| Age(years) | 43.89 ± 7.12 | 42.19 ± 5.20 | 43.48 ± 6.74 | 42.96 ± 6.35 | 44.51 ± 6.80 | 0.021* |
| (Male/Female)(%) | (7.0/ 25.1) | (2.4/ 8.1) | (9.4/ 33.2) | (7.2/ 14.4) | (9.5/ 26.3) | 0.011** |
| BMI(kg/$m^2$) | 29.13 ± 3.74 | 28.96 ± 3.64 | 29.08 ± 3.71 | 28.84 ± 4.26 | 29.60 ± 4.35 | 0.150* |
| FPG (mmol/l) | 105.18 ± 8.56 | 97.92 ± 9.67 | 103.37 ± 9.37 | 101.12 ± 8.63 | 106.20 ± 11.16 | <0.001* |
| Physical activity(min/week) | 49.16 ± 81.29 | 63.36 ± 98.79 | 52.68 ± 86.05 | 46.02 ± 79.08 | 54.08 ± 72.11 | 0.498* |

IFG (impaired fasting glucose), IGT (impaired glucose tolerance), IGM (impaired glucose metabolism, including subjects with IGT and/or IFG), NGT (normal glucose tolerance), DM (diabetes group), BMI (Body mass index), FPG (Fasting blood glucose in the baseline), ANOVA test *, Chi-Square test**, P-value < 0.05 is considered as significant

We estimated a series of LMM to determine the number of latent states (2-3State 1-3Class). All models' fit criteria as well as interpretability of extracted states strongly suggested a LMM with two latent states based on the patterns of changes in lipid profile. According to fit criteria, 2-State 1-Class model selected, with lower AIC, BIC, parameter number and classification error and as well as higher entropy (Table 3).

Table 3
Model fitting criteria for prediabetic subjects by latent Markov analysis

| Fitted models | Log Likelihood | BIC | AIC | Number of parameters | Classification. Error | Entropy R-squared |
|---|---|---|---|---|---|---|
| 2-State 1-Class | -54789.4762 | 109714.1020 | 109616.9523 | 19 | 0.0920 | 0.6052 |
| 2-State 2-Class | -54782.2414 | 109728.0850 | 109610.4828 | 23 | 0.0944 | 0.5924 |
| 2-State 3-Class | -54782.1874 | 109756.4296 | 109618.3748 | 27 | 0.0944 | 0.5925 |
| 3-State 1-Class | -53737.2923 | 107702.2051 | 107538.5846 | 32 | 0.1421 | 0.6681 |
| 3-State 2-Class | -53722.8693 | 107737.3773 | 107527.7385 | 41 | 0.1412 | 0.6695 |
| 3-State 3-Class | -53717.2883 | 107790.2337 | 107534.5766 | 50 | 0.1427 | 0.6656 |

Table 4 presents the identified latent states of subjects based on lipid profile resulted from LMM, in total, males and females sample. For total/ males/ and females sample, two latent states were identified. Interpretation of states is based on the mean of lipid profile. The state1 consists of subjects who had lower problem in lipid profile levels; the subjects in this state had relatively low values of lipid profile. This state is interpreted as low tendency to progress diabetes in future and consists 74%/ 74%/ 69% of the sample. The state2 consists of subjects who had higher problem in lipid profile levels; the subjects in this state had relatively high values of lipid profile. This state is interpreted as high tendency to progress diabetes in future and consist 26%/ 26% / 31% of the sample. Similar findings were observed when LMM was fitted separately in male and female genders (Table 4).

Table 4
Latent states of prediabetic in terms of mean values of lipid profile identified by latent Markov analysis

| Group | Lipid profile | Levels of diabetes tendency(without covariates) | | Levels of diabetes tendency(with covariates) | |
|---|---|---|---|---|---|
| | | Low( State1 ) | High( State2) | Low( State1 ) | High( State2 ) |
| Total($n$=1228) | State size | 0.7430 | 0.2570 | 0.7345 | 0.2655 |
| | TG | 142.9682 | 265.1101 | 142.5925 | 262.1813 |
| | CHOL | 192.1266 | 227.3209 | 191.6593 | 227.4827 |
| | HDL | 44.9375 | 44.7703 | 44.9247 | 44.8123 |
| | LDL | 117.2795 | 133.8731 | 116.8747 | 134.5226 |
| Males($n$=324) | State size | 0.7355 | 0.2645 | 0.7404 | 0.2596 |
| | TG | 159.8346 | 307.1037 | 160.0979 | 296.2107 |
| | CHOL | 191.4662 | 216.0068 | 191.2984 | 216.4241 |
| | HDL | 39.7675 | 41.1365 | 39.7413 | 41.2079 |
| | LDL | 117.7630 | 121.8403 | 117.5796 | 122.4382 |
| Females($n$=904) | State size | 0.6916 | 0.3084 | 0.6833 | 0.3167 |
| | TG | 133.7960 | 240.4687 | 133.5538 | 238.1966 |
| | CHOL | 190.4004 | 229.3418 | 189.8000 | 229.6404 |
| | HDL | 46.3990 | 47.1298 | 46.3120 | 47.3042 |
| | LDL | 116.1769 | 136.4491 | 115.6906 | 137.0170 |
| The covariates include: age, gender, BMI, FPG and Physical activity | | | | | |

Table 5 presents the initial and transition probabilities observed during the study from one particular state to other states. On the basis of the estimates, at the beginning of the period of investigation, in all groups include total, males, and females more than of half (initial probability was 73%/ 74% / 68%) of subjects were in the latent states1. The probability of being in the state1 (without/with covariates) is higher than the state2.

Table 5
Initial and transition's probabilities (%) of prediabetic identified by latent Markov analysis

| Group | Status | Levels of diabetes tendency(without covariates) | | Levels of diabetes tendency(with covariates) | |
|---|---|---|---|---|---|
| | | Low( State1 ) | High( State2) | Low( State1 ) | High( State2 ) |
| Total ($n$ = 1228) | State0 | 0.7260 | 0.2740 | 0.7260 | 0.2740 |
| | State1 | 0.9414 | 0.0586 | 0.9385 0.2320 | 0.0615 0.7680 |
| | State2 | 0.2236 | 0.7764 | | |
| Males($n$ = 324) | State0 | 0.7433 | 0.2567 | 0.7433 | 0.2567 |
| | State1 | 0.9585 | 0.0415 | 0.9655 | 0.0345 |
| | State2 | 0.1040 | 0.8960 | 0.1078 | 0.8922 |
| Females($n$=904) | State0 | 0.6776 | 0.3224 | 0.6776 | 0.3224 |
| | State1 | 0.9198 | 0.0802 | 0.9151 | 0.0849 |
| | State2 | 0.2170 | 0.7830 | 0.2289 | 0.7711 |

The state0 is initial state. Probabilities represent the probability of transition from a particular state to other states from row to column

According to these results, a subject in the state1 or in the state2 will remain at the same condition (without/with covariates) with the probability of ranging from 77%to 97%. In all groups include total, males and females the transition probability from the state1 to the state2 is lower than the transition probability from the state2 to the state1.

# 4. Discussion And Conclusions

In this prospective longitudinal study, we followed 1228 prediabetic patients from 2003 to 2019 and evaluated the changes in serum lipid profile over time using LMM. Two latent states were identified based on the patterns of changes in lipid profiles mean and the states characterized by levels of tendency to progress diabetes (low/ high) with prevalence rates of (74%/ 26%), respectively. We observed that the lipid profile mean; in subjects assigned to “high tendency to progress diabetes” state was more than “low tendency to progress diabetes” state. The transition probability from the low to high tendency state was lower than the transition probability from high to low tendency state.

We did not find any study such as current one, which classified prediabetic patients into homogeneous states based on lipid profile mean over time using LMM. However, there are many studies in this regard among general population, and some specific population with applying simple statistical methods(9, 10, 28, 29).

Previous studies have focused on investigating the association of each lipid profile; TG, CHOL, HDL and LDL with the risk of diabetes in future or concurrently, separately. For instance, in Framingham Heart (30) study, T2DM subjects compared to those without T2DM, had higher plasma TG levels and lower HDL levels. Vineetha et al. in a case control study, was documented statistically significant higher values for TG and lower values for HDL in subjects with PD (31).

It is believed that lipid profile abnormality is a strong risk factor for T2DM in prediabetic patients (17, 32). In the present study, the subjects in high tendency to progress diabetes state had lipid profile abnormality. We observed that the mean of lipid profile abnormality associated with “high/low tendency to progress diabetes” states. This finding is in line with the results of previous studies have emphasized on the association of lipid profile disorders with the risk of diabetes (11, 12, 23, 33–36).

The Bhowmik et al. study obtained similar results with our study in terms of levels of dyslipidemia. Results showed a strong association between serum lipid profile and T2DM and PD. In addition, high levels of TG in combination with low levels of HDL showed the highest association with T2DM and PD. The levels of high CHOL, high TG, and low HDL were more elevated among subjects with T2DM and PD (13).

In the present study, in an irregular pattern, low HDL level was not associated with increased T2DM. In line our study, Hasse et al. reported that genetically reduced HDL was not associated with increased T2DM, suggesting that the corresponding observational association is due to confounding and/or reverse causation(9). In contrast, Hirano in the Hawaii- Los Angeles- Hiroshima study found that HDL is a predictor of T2DM, independent of age and gender in both Japanese-American and native Japanese(37). Janghorbani et al. in a population based longitudinal survey showed that low HDL level was a weak predictor of T2DM independent of age and gender in a cohort of high-risk individuals in Iran(38).

Although numerous researches exist about the risk factors of diabetes, but most research has ignored the complexity of diabetes disease and the reversible of diabetic states. In the current study, the probability for a subject in low tendency to progress diabetic state and to remain in the same condition was more than the probability for a subject in a high tendency to progress diabetic state which to remain in the same condition. Further, the transition probability from the low tendency to progress diabetic state to high tendency to progress diabetic state was lower than the transition probability from the high tendency to progress diabetic state to low tendency to progress diabetic state.

It is important to recognize some strengths and limitations of the present study. A major strength of our study is the applications of latent Markov model for classifying subjects according to the patterns of changes in lipid profile over time, instead of considering them as a single index. Other strengths of this study are population consisting of a large cohort of prediabetic patients, and the long-lasting followed-up of these subjects (16-year) and adjustment for some potential confounders in the analyses. The current findings were drawn from a study population of prediabetic patients; therefore, the results may not be applicable to all populations. We found that states identified based on lipid profile by LMM, in particular

“low tendency to progress diabetes” and “high tendency to progress diabetes” are associated with the risk of diabetes in future in prediabetic patients.

In conclusion, abnormality of serum lipid profiles remains a significant and growing problem in prediabetic subjects as high risk population. The reduction in the problem burden will require changes at the policy level as well as at the personal level. Finally, should draw attention to abnormalities of lipid profiles is as an important step in preventing and managing diabetes.

## Declarations

# • Ethics approval and consent to participate

The current secondary study has been approved by Bioethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.532). Written informed consent was obtained from all subjects in IDPS.

**• Consent for publication**

Not applicable

**• Availability of data and materials**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**• Competing interests**

No potential conflict of interest was reported by the authors.

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# • Authors' contributions

AF, MA and AA contributed to the conception and design of the main study, collection and assembly of the data. AF supervised the current secondary study in the framework of a PhD thesis. SS contributed to the statistical analysis, AF and SS contributed to the interpretation of the results. AF and SS contributed to drafting the manuscript. AF, MA and AA revised it critically for important intellectual content in order for

the final approval of the version to be published. All authors read the final version of manuscript and approved it.

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