ORIGINAL RESEARCH

Cross-sectional and longitudinal assessments of risk factors associated with hypertension and moderately increased albuminuria comorbidity in patients with type 2 diabetes: a 9-year open cohort study

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Background: Moderately increased albuminuria (MIA) is strongly associated with hypertension (HTN) in patients with type 2 diabetic mellitus (T2DM). However, the association between risk factors and coexisting HTN and MIA remains unassessed.

Objectives: This study aimed to determine both cross-sectional and longitudinal associations of risk factors with HTN and MIA comorbidity in patients with T2DM.

Methods: A total of 1,600 patients with T2DM were examined at baseline and longitudinal data were obtained from 1,337 T2DM patients with at least 2 follow-up visits to assess the presence of HTN alone (yes/no), MIA alone (yes/no) and the coexistence of both (yes/no) in a 9-year open cohort study between 2004 and 2013. Bivariate mixed-effects logistic regression with a Bayesian approach was employed to evaluate associations of risk factors with HTN and MIA comorbidity in the longitudinal assessment.

Results: After adjustment for age and BMI, patients with uncontrolled plasma glucose, as a combined index of the glucose profile, were more likely to have HTN [odds ratio (OR): 1.73 with 95% Bayesian credible intervals (BCI) 1.29–2.20] and MIA [OR: 1.34 (95% BCI 1.13–1.62)]. The risks of having HTN and MIA were increased by a one-year raise in diabetes duration [with 0.89 (95% BCI 0.84–0.96) and 0.81 (95% BCI 0.73–0.92) ORs, respectively] and a one-unit increase in non-high-density lipoprotein-cholesterol (Non-HDL-C) [with 1.30 (95% BCI 1.23–1.34) and 1.24 (95% BCI 1.14–1.33) ORs, respectively].

Conclusions: T2DM patients with HTN, MIA, and the coexistence of both had uncontrolled plasma glucose, significantly higher Non-HDL-C, and shorter diabetes duration than the other T2DM patients. Duration of diabetes and uncontrolled plasma glucose index showed the stronger effects on HTN and MIA comorbidity than on each condition separately.

Keywords: hypertension, moderately increased albuminuria, microalbuminuria, type 2 diabetes, comorbidity, risk factor

Introduction

Globally, the prevalence of type 2 diabetes mellitus (T2DM) continues to increase.[1,2] More than 50% of patients with diabetes mellitus have also hypertension (HTN)[3] with three times higher rate than the general population.[4] The risk of cardiovascular disease (CVD) in the T2DM patients with HTN is four-times higher than the

normotensive non-diabetic people.[5] Abnormal levels of urinary albumin, a marker of kidney disease, occur in 30–40% of patients with T2DM, and increase the mortality rate caused by CVD worldwide.[6] Furthermore, hypertensive patients with albuminuria have almost a four-fold increased risk of ischemic heart disease than hypertensive patients without albuminuria.[7] The association of HTN with moderately increased albuminuria (formerly called microalbuminuria) has been reported frequently.[8,9] However, there are limited numbers of cross-sectional studies, which evaluated the association of HTN with moderately increased albuminuria (MIA) in patients with T2DM.[10] Although the risk factors associated with only HTN or only MIA in patients with T2DM have been reported previously,[11,12] the association of risk factors with MIA and HTN comorbidity combined have yet to be determined.

The main objective of the present study was to identify and compare the risk factors associated with HTN, MIA, and the coexistence of both in patients with T2DM using the mixed-effects models. These approaches incorporate repeated HTN, MIA, and the coexistence of both prevalence data across visits which involve the same T2DM patients.

Methods
Setting and data collection
This study was focused on high-risk individuals with T2DM to identify the cross-sectional and longitudinal associations of risk factors with HTN and MIA comorbidity combined. Furthermore, within the longitudinal assessment, the repeated measurements of potential risk factors are considered as time-dependent covariates and repeated measurement of outcome variables took into account the participants' changes during the follow-up period.

The present study was conducted with data from the Isfahan Diabetes Open Cohort Study (IDOCS), an open cohort study in central Iran to determine various potential risk factors for CVD in the patients with T2DM. Details of the design and setting of the IDOCS have been described elsewhere.[11,12] In the IDOCS study, the participants were followed-up for detection of major CVD events, including myocardial infarction, unstable angina pectoris, stroke, and sudden cardiac death.

Study participants
The present study was performed as a sub-study of IDOCS. Therefore, we retrieved information of 1608

T2DM patients without any history of major CVD recorded in the database of the Isfahan Endocrine and Metabolism Research Center (IEMRC), between 2004 and 2013. Physical examination and laboratory measurements were conducted at baseline, and repeated for cases without any major CVD events. All participants received follow-up tests, according to the Standard of Medical Care in Diabetes, to update information on anthropometric and demographic characteristics, and to record diagnosed MIA and HTN.[12,13] Otherwise, the tests were repeated annually.

According to the inclusion criteria (Figure 1), T2DM patients with severely increased albuminuria (formerly called macroalbuminuria) or kidney transplantation[14] were excluded at baseline (8 out of 1,608 of patients). Albumin excertion (24 hrs urine albumin concentrations) above 300 mg was considered as severely increased albuminuria based on the guideline of the European Society of Cardiology.[15]

Definition and assessment of outcomes, determinants, and confounders
The blood pressure was taken twice on the right arm of patients in a seated position, after 15 and 20 mins of rest, using a standard mercury sphygmomanometer (ALPK2, Japan). The mean of two measurements was recorded as the blood pressure value. The hypertensive cases were identified according to the European Society of Cardiology and European Society of Hypertension criteria.[16] Patients were defined as hypertensive if they were already being treated with antihypertensive or had the systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg. The blood pressure values were coded as a binary variable by one in hypertensive patients and zero in normotensive patients.

In order to measure urinary albumin level accurately, patients were trained to collect urine samples. Urine samples with specific gravity of more than 1.015 were examined for MIA when there was no evidence of infection and/or hematuria in urinalysis. Urinary albumin and creatinine were measured by the kits, obtained from the Pars Azmoon Company, using BT3000, Zinsser Analytic, Germany. Urinary creatinine was measured by the Jaffe method to assure that 24 hrs urine was collected correctly.

The European Society of Cardiology criteria was used to diagnose MIA, and defined by a 24-hrs urine albumin concentration between 30 mg and 300 mg.[15] In cases that albumin concentration exceeded 30 mg, a second 24-hrs urine sample was collected and examined for MIA. Therefore, we

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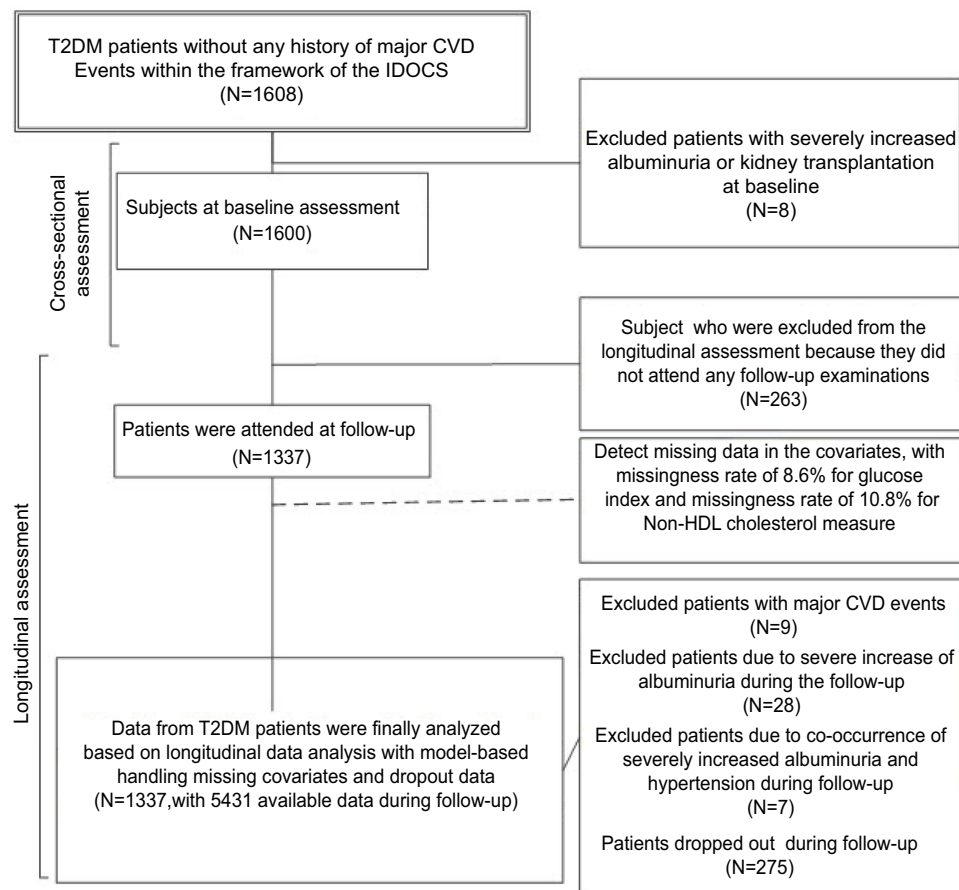
Figure 1 Flow diagram of inclusion data in the presented study.
Abbreviations: T2DM patients, type 2 diabetic mellitus patients; CVD, cardiovascular disease; IDOCS, Isfahan Diabetes Open Cohort Study; HDL, high-density lipoprotein.

coded urinary albumin level as a binary response variable by one, in patients with MIA, and zero in patients with normoalbuminuria (24 hrs urine albumin concentrations of <30 mg).

Information on anthropometric indices, duration of diabetes, blood pressure, lipid profile, and plasma glucose were collected at baseline and through follow-up intervals. All clinical examination and laboratory measurements at baseline and at follow-up visits were performed, using the same standardized protocol. Anthropometric assessment, including weight and height, were conducted while participants were barefoot and lightly clothed. Patients' weight was measured to the nearest 0.1 kg, using the Seca scale (Hamburg, Germany). Height was measured while patients were in a standing position with their shoulders in the normal position, using the Seca stadiometer. The BMI (kg/m^2) was calculated as the weight (kg) divided by height (m) squared. Duration of diabetes was obtained by the interval between the age of the patient and their age in which the diabetes was diagnosed.

Blood samples were taken after 12 hrs overnight fasting to measure biochemical characteristics. FPG was analyzed by the glucose oxidase method (Clinical Chemistry Analyzer Liasys, Roma, Italy). HbA1c was measured, using a DSS machine and the ion-exchange chromatography method. Total cholesterol and HDL-C were measured. LDL-C and Non-HDL-C were calculated by the Friedewald's equation[17] and subtracting HDL-C from the total-cholesterol, respectively. All biochemical characteristics were measured in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using the enzyme-linked method.

Statistical analysis

Results were reported as mean (SE) for the quantitative continuous variables and percentages for the categorical variables. At baseline, the mean age and BMI of four groups were compared, including patients with neither HTN nor MIA as control group, with only MIA, with

only HTN, and with the coexistence of both, using one-way analysis of variance (ANOVA) and Tukey's post-hoc test. The age- and BMI-adjusted means of the selected baseline characteristics including diabetes duration, glucose, and lipid profile were calculated and compared between four groups, based on one-way ANCOVA and Bonferroni correction post-hoc test. The numbers of patients with HTN, MIA, and the coexistence of both were changing during 9 years of follow-up; therefore, we presented the prevalence of these conditions, annually in Table 1, and used the mean of prevalence (overall prevalence) over the duration of the study.

In the longitudinal assessment, double univariate binary logit components were obtained from separate logistic regressions for blood pressure variable alone (dichotomized into "HTN" versus "normotension") and urinary albumin level variable alone (dichotomized into "MIA" versus "normoalbumin"). We used the bivariate longitudinal logistic model to consider the inherent association between two above-mentioned binary outcomes. The dropouts (unbalanced longitudinal data) are shown in Figure 2. In order to determine the longitudinal associations between predictors and outcomes, considering the dropout data, mixed-effects logistic regression was performed as an appropriate method with enough precision.[18] In addition to dropouts, there was missing data in the covariates (described in Figure 1). We use all the available follow-up data (Figure 2) in the open cohort database to maximize the power and generalizability of the longitudinal results. We adopted the Bayesian approach, as an advanced statistical approach to estimate parameters while of the missing covariates handled in the above-mentioned models. The Bayesian data analysis was conducted, using Open BUGS version 3.2.3.[19] The results of the applied models were demonstrated as odds ratios (ORs) and related 95% Bayesian credible intervals (BCI). Deviance information criterion (DIC) was used to select the best model; a lower value of DIC, indicating better model fitness. Based on all available data and the literature, the potential confounders were also identified; the confounders were then selected based on the significant correlation (or association) of the potential confounding variables with both the outcomes and the risk factors of interest.

We realized that there is a statistically significant correlation between lipid and glucose profile using Pearson's coefficient with $P<0.01$ (Table S1). Therefore, to deal with the multicollinearity and to include somehow all lipid and glucose profiles in the fitted longitudinal models, Non-HDL-C was

Table 1 Number (percent) and status of type 2 diabetic patients that newly entered into the present open cohort in each year

Status	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	2010–2011	2011–2012	2012–2013	Overall
Neither MIA nor HTN[a]	3 (2.9)	28 (7.9)	34 (12.5)	42 (25.4)	78 (58.7)	94 (55.0)	125 (73.5)	118 (57.3)	15 (53.6)	537 (33.6)
Only MIA	60 (58.8)	158 (44.8)	139 (51.1)	65 (39.4)	26 (19.5)	35 (20.5)	18 (10.6)	42 (20.4)	8 (28.6)	551 (34.4)
Only HTN	5 (4.9)	20 (5.7)	17 (6.3)	19 (11.5)	20 (15.0)	29 (17.0)	21 (12.4)	31 (15.0)	3 (10.7)	165 (10.3)
Coexisting HTN and MIA	34 (33.3)	147 (41.6)	82 (30.1)	39 (23.6)	9 (6.8)	13 (7.6)	6 (3.5)	15 (7.3)	2 (7.1)	347 (21.7)
Total number of subjects at baseline	102 (100)	353 (100)	272 (100)	165 (100)	133 (100)	171 (100)	170 (100)	206 (100)	28 (100)	1600 (100)

Note: [a]Control group.
Abbreviations: HTN, hypertension; MIA, moderately increased albuminuria.
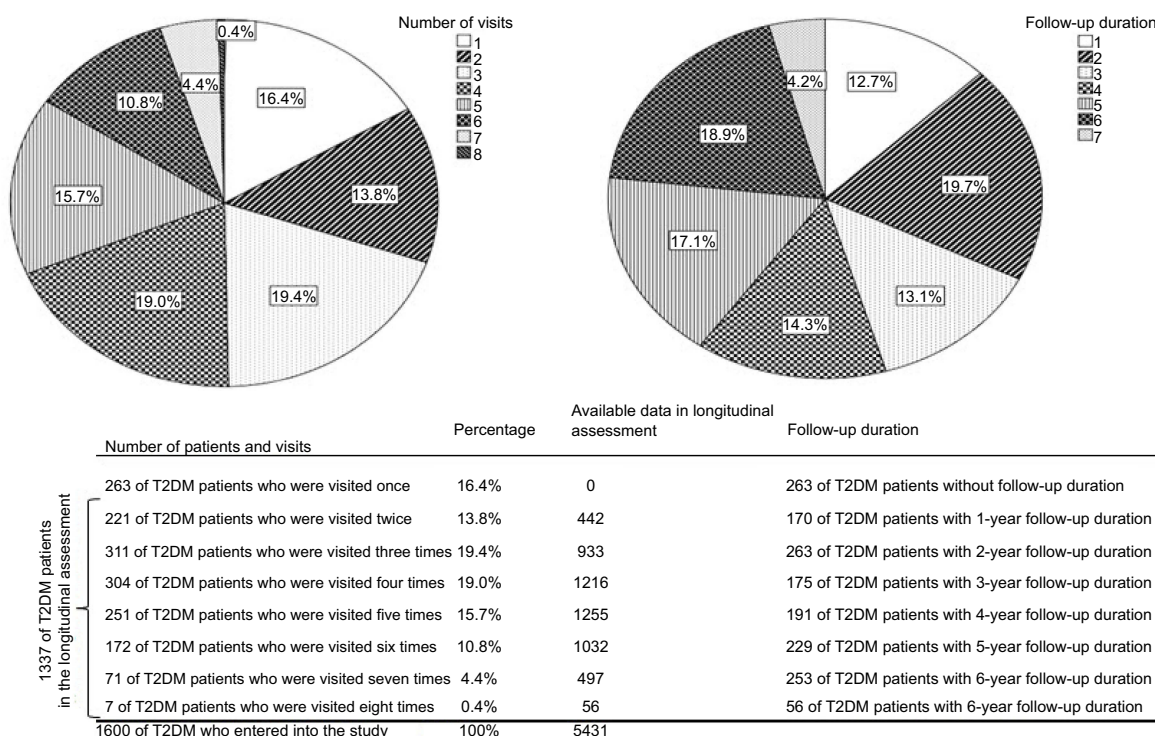
Figure 2 Description of participants' number of visits and follow-up durations of type 2 diabetic patients during the follow-up period in the open cohort study.
Abbreviations: T2DM patients, type 2 diabetic mellitus patients.

presented as lipid profile. Non-HDL-C includes various fractions of lipoproteins: low-density lipoprotein, intermediate-density lipoprotein, and very low-density lipoprotein. We also proposed the uncontrolled plasma glucose index as a combined index of the glucose profile that was coded as a binary variable. According to the glycemic control recommendation in non-pregnant diabetic patients,[20] we created a local definition for the uncontrolled plasma glucose index; the FPG of ≥7.2 mmol/L (130 mg/dL) and/or 2 hrs PPG of ≥10 mmol/L (180 mg/dL) and/or HbA1$_C$ of ≥7% were coded 1 and 0 otherwise. On the other hand, age and BMI were significantly correlated with gender, uncontrolled plasma glucose, diabetes duration, Non-HDL-C, and the outcomes with (P<0.001). Therefore, in our implemented longitudinal models, gender and time-dependent variables including diabetes duration, uncontrolled plasma glucose index, and non-HDL-C were considered as the determinants, and age and BMI were counted as the confounders. Age and BMI adjusted-odds ratios were presented to determine the association of the gender, diabetes duration, uncontrolled plasma glucose index, and increasing Non-HDL-C with the adjusted-odds of having HTN and MIA, during follow-up visits.

The bivariate logistic regression with random subject-effects of longitudinal binary responses as blood pressure

and urinary albumin level variables is provided (Equation (1) and Equation (2)). Where i =1, 2, …, 1,337 is the number of subject, t=1,2,3, …, 9 is the time point of subject i and β_{k1}, β_{k2}, k = 0, …, 6 are fixed-effect terms; u_{i1}, u_{i2} present subject-specific random intercepts for i-th subject.

$$\begin{cases} (\text{Blood pressure})_{it} | x_{it}, u_{i1} \sim \text{bern}(\pi_{1it}) \\ (\text{Albumin})_{it} | x_{it}, u_{i2} \sim \text{bern}(\pi_{2it}) \end{cases} \qquad 1$$

$$(u_{i1}, \ u_{i2}) \sim BN(0, \Sigma)$$

where

$$\begin{cases} \text{logit}(\pi_{1it}) = \beta_{10} + \text{Gender}_{it}\beta_{11} + \text{Age}_{it}\beta_{12} + \text{BMI}_{it}\beta_{13} \\ \qquad + \text{Diabetes duration}_{it}\beta_{14} + \text{Glucose\_index}_{it}\beta_{15} \\ \qquad + \text{NonHDLChol}_{it}\beta_{16} + u_{1i} \\ \text{logit}(\pi_{2it}) = \beta_{20} + \text{Gender}_{it}\beta_{21} + \text{Age}_{it}\beta_{22} + \text{BMI}_{it}\beta_{23} \\ \qquad + \text{Diabetes duration}_{it}\beta_{24} + \text{Glucose\_index}_{it}\beta_{25} \\ \qquad + \text{NonHDLChol}_{it}\beta_{26} + u_{2i} \end{cases} \qquad 2$$

A model which uses HbA1$_C$ instead of the uncontrolled plasma glucose index was further examined to assess whether the association of glucose profile (based on the HbA1$_C$ as the gold standard of glycemic control), lipid profile, and diabetes duration with having HTN and MIA was appropriate. Finally, the above-mentioned model that

included uncontrolled plasma glucose index was selected based on the model's selection criteria.

A *p*-value of <0.05 was considered statistically significant for all tests, which were two-tailed. The 95% Bayesian credible intervals do not include the one value for considering significant effects of risk factors in the univariate and bivariate Bayesian models.

Results
Results of the descriptive analysis
The mean of prevalence over subsequent years of the open cohort study (overall baseline prevalence) for HTN, MIA, and the coexistence of both in patients with T2DM is 10.3% (95% confidence interval [CI] 8.8–11.8), 34.4% (95% CI 32.7–36.7), and 21.7% (95% CI 19.6–23.7), respectively (Table 1). Overall, the prevalence of HTN alone is lower than the prevalence of MIA and the prevalence of MIA and HTN combined. Moreover, Table 1 indicates that the prevalence of MIA and HTN decreases over time.

Results of the cross-sectional assessment
No statistically significant difference is observed in most baseline characteristics between attendees at the follow-up visits and non-attendees including systolic blood pressure, diastolic blood pressure, 24 hrs urine albumin concentrations, age, diabetes duration, height, weight, body mass index (BMI), glycosylated hemoglobin (HbA1c) level, fasting plasma glucose (FPG), 2 hrs postprandial plasma glucose (PPG) levels, triglyceride, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and non-high-density lipoprotein-cholesterol (Non-HDL-C) concentrations (Table S2).

The baseline characteristics of the normotensive normoalbuminuric T2DM patients and T2DM patients with HTN, MIA, and the coexistence of both are shown in Table 2. The gender was balanced between the groups. However, significant differences were observed in mean age, age-adjusted means of BMI, age- and BMI-adjusted means of FPG, HbA1$_C$, 2 hrs PPG, total-cholesterol, LDL-C, Non-HDL-C, across different study groups. According to the post-hoc comparisons of Bonferroni-corrected test, adjusted by the baseline age and BMI, the age- and BMI-adjusted mean differences of glucose and lipid profile are statistically significant between the group of patients with the MIA and HTN comorbidity, and the group with neither MIA nor HTN (*P*<0.001, Table S3 and Figure S1).

Among 1,600 participants at the baseline (1,071 men and 529 women), 263 subjects were also excluded from longitudinal assessment because they did not attend the follow-up examination. Therefore, 1,337 patients (912 men and 425 women) with a mean (standard error [SE]) baseline age of 45.0 (0.24) years old (range 30–81 years old) who participated in repeated measurements with available information on outcomes and covariates were included in the longitudinal assessments. Patients were followed up until detecting major CVD events (n=9), severely increased albuminuria (n=35), dropping out (n=275), or reaching the end of the study (see Figure 1), all of whom had at least one subsequent review, during the follow-up duration (median of 4 years and a range of 1–7 years). The detailed description of the participants' numbers of visits and follow-up duration of visits are presented in Figure 2 for T2DM patients.

Results of the longitudinal analysis
The results of the selected univariate and bivariate longitudinal models (Figure 3 and Table S4) determine the association of the risk factors with MIA and HTN comorbidity (for bivariate strategy), in comparison with the longitudinal association of the risk factors with MIA, and HTN disorders separately (for univariate strategies) during follow-ups. In the bivariate model, a joint significant positive association between HTN and MIA was estimated to be 0.47 (95% CI: 0.36–0.57) during the follow-up period. The bivariate model fits better to the collected data than the separate analysis of each outcome variable, resulted in a smaller DIC (Table S4). The associations of potential risk factors with HTN and MIA in the T2DM patients were determined after measurement and adjustment for age and BMI. The results of the un-selected univariate and bivariate longitudinal models, which include Hba1c instead of glucose index, are also presented in Table S5.

The results of the selected models indicated that the odds of HTN, MIA, and the coexistence of both were significantly higher in the patients with uncontrolled plasma glucose, higher Non-HDL-C, and shorter diabetes duration than the normotensive and normoalbuminuric T2DM patients, after age- and BMI-adjustment. Furthermore, female patients are more likely to have MIA alone and MIA with HTN comorbidity than male patients (Table S4 and Figure 3).

During follow-up, diabetes duration (age- and BMI-adjusted ORs [95% BCIs] of HTN: 0.95 [0.91, 0.98] and MIA: 0.87 [0.80, 0.96] in univariate model versus age- and BMI-adjusted ORs [95% BCIs] of HTN: 0.89 [0.84–0.96]

Table 2 Baseline characteristics in the different groups of type 2 diabetic patients

Characteristic	T2DM patients with neither MIA nor HTN (n=537)	T2DM patients with only MIA (n=551)	T2DM patients with only HTN (n=165)	T2DM patients with coexistence of HTN and MIA (n=347)
	Mean (SE)			
Age (year)	45.40 (0.35)	45.24 (0.36)	47.14 (0.72)	47.58 (0.49)[a]
Height (cm)	158.96 (0.37)	158.72 (0.37)	158.77 (0.66)	158.53 (0.46)
Weight (kg)	73.23 (0.23)	72.96 (0.36)	73.16 (0.64)	72.82 (0.65)
Body mass index (kg/m^2)	28.66 (0.21)	28.69 (0.20)	29.32 (0.36)	29.89 (0.25)[a]
Fasting plasma glucose (mmol/L)	8.22 (0.11)	8.31 (0.11)	8.54 (0.20)	8.88 (0.14)[a]
2-h post prandial plasma glucose (mmol/L)	11.35 (0.17)	11.56 (0.17)	12.06 (0.31)	12.43 (0.21)[a]
Glycosylated hemoglobin (%)	7.26 (0.08)	7.57 (0.08)	7.55 (0.14)	7.73 (0.10)[a]
Triglyceride (mmol/L)	1.96 (0.06)	2.07 (0.06)	2.01 (0.10)	2.17 (0.07)
Total-cholesterol (mmol/L)	4.87 (0.05)	4.97 (0.05)	5.02 (0.08)	5.16 (0.06)[a]
LDL-cholesterol (mmol/L)	2.83 (0.04)	2.91 (0.04)	2.88 (0.07)	3.09 (0.05)[a]
HDL-cholesterol (mmol/L)	1.16 (0.01)	1.17 (0.01)	1.19 (0.02)	1.18 (0.02)
Non HDL-cholesterol (mmol/L)	3.71 (0.04)	3.79 (0.05)	3.79 (0.08)	4.05 (0.06)[a]
	Median (IQR)			
Diabetes duration (year)	3 (5)	4 (5)	3 (5)	3 (6)
	No. (%)			
Sex				
Male	363 (22.7)	350 (21.9)	117 (7.3)	241 (15.0)
Female	174 (10.9)	201 (12.6)	48 (3.0)	106 (6.6)
Plasma glucose index				
Uncontrolled level of glucose	458 (28.7)	479 (30.6)	148 (9.5)	308 (19.7)[b]
Normal level of glucose	76 (4.9)	55 (3.5)	16 (1.0)	34 (2.2)

Note: Type 2 diabetic patients with neither microalbuminuria nor hypertension are considered as control group. [a]Significant results from one-way ANOVA for age and BMI, and ANCOVA for other variables, *p*-value<0.01. Age and body mass index-adjusted group means were calculated using general linear models. [b]Significant results from Chi-square test, *p*-value <0.05.
Abbreviations: n, number of participants; MIA, moderately increased albuminuria; HTN, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range.
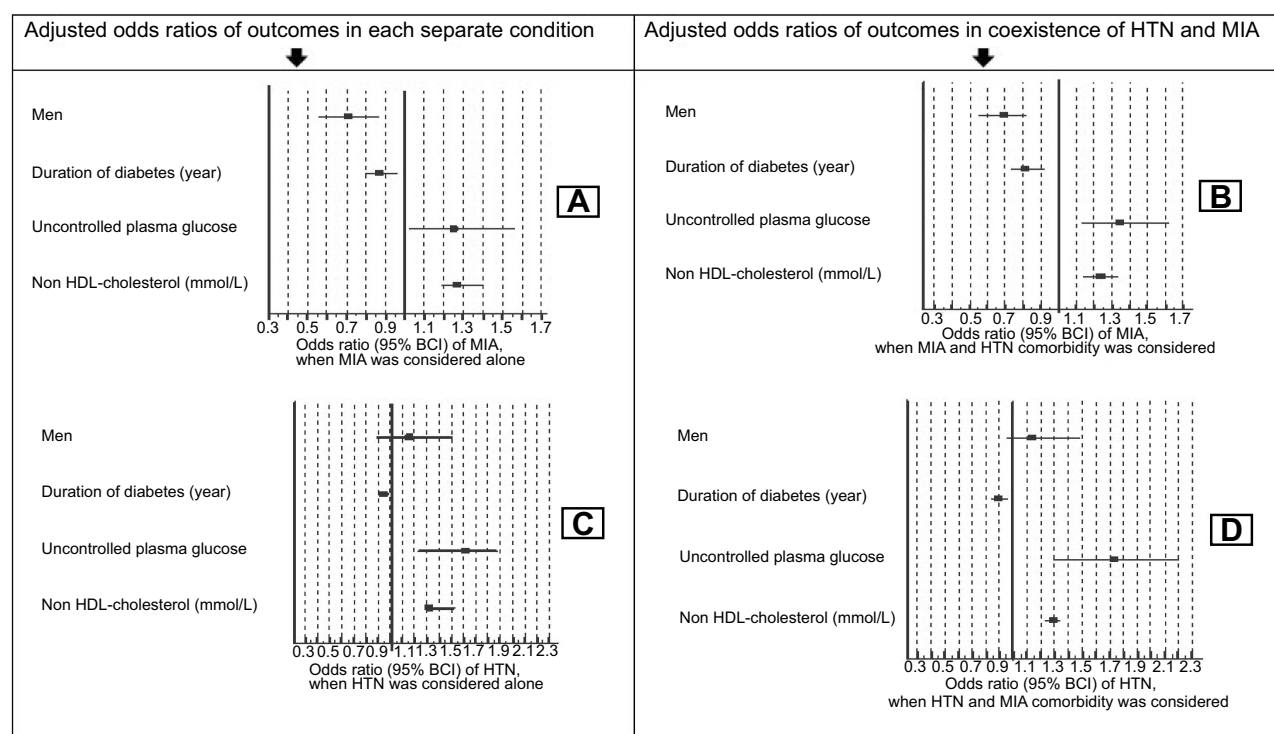
Figure 3 Effects of risk factors on moderately increased albuminuria and hypertension, when occurred alone or co-occurred with each other in longitudinal assessment. **(A)** Effects of risk factors on moderately increased albuminuria, when occurred alone in longitudinal assessment. **(B)** Effects of risk factors on moderately increased albuminuria, when co-occurred with hypertension in longitudinal assessment. **(C)** Effects of risk factors on hypertension, when occurred alone in longitudinal assessment. **(D)** Effects of risk factors on hypertension, when co-occurred with moderately increased albuminuria in longitudinal assessment.
Abbreviations: MIA, moderately increased albuminuria; HTN, hypertension.

and MIA: 0.81 [0.73–0.92] in bivariate model) showed considerably stronger effects on HTN and MIA in bivariate model than in univariate model ($P<0.05$). Uncontrolled plasma glucose index (age- and BMI-adjusted ORs [95% BCIs] of HTN: 1.62 [1.23, 1.86] and MIA:1.25 [1.02, 1.56]: in univariate model versus age- and BMI-adjusted ORs [95% BCIs] of HTN: 1.73 [1.29–2.20] and MIA: 1.34 [1.13–1.62] in bivariate model) shows significant stronger effects on coexisting hypertension and moderately increased albuminuria than on each condition separately in Table S4 and Figure 3 ($P<0.05$).

Discussion

The current study demonstrated a high baseline prevalence of MIA and its coexistence with HTN, among Iranian patients with T2DM; the prevalence of HTN and MIA comorbidity was much higher than the prevalence of HTN alone in the baseline assessment. A large number of T2DM patients are at high risk for ischemic heart disease due to HTN and MIA comorbidity.[7] Moreover, decreasing trend of the prevalence of MIA and/or HTN indicates that diabetes care in Iran has improved since the beginning of our study.[21] In parallel, the Tehran Lipid and Glucose Study cohort reported that the use

of antihypertensive, antihyperglycemic, and antihyperlipidemic medications was increased substantially over a follow-up period of more than a decade (1999–2011) among Iranian patients with type 2 diabetes.[21] Hence, in the current follow-up study of 1,337 T2DM patients, after age- and BMI-adjustment during follow-up, the effects of glucose, lipid profile, and diabetes duration on having HTN and MIA separately and the coexistence of both were also estimated using relevant statistical methods.

After adjustment for age and BMI, the risk of having MIA in women was significantly higher than men, similar to the previous study, disregarding the MIA and HTN comorbidity in T2DM patients after adjusting for age.[22] Although estrogen has protective effects on CVD, our data might be influenced by the use of oral contraceptive in the pre-menopausal women or post-menopausal setting and hormone replacement therapy after menopause, which were shown to be associated with an increased prevalence of MIA.[23] However, our findings indicated that male patients show a slightly higher risk of having HTN, when HTN occurred separately or simultaneously with MIA in age- and BMI-adjusted analysis; the association of the gender with HTN became insignificant. This finding

is consistent with previous report where the age was adjusted.[11] The higher risk of HTN in male patients with type 2 diabetes might originate from poor blood pressure control in this group of patients.[3]

At the follow-up, T2DM patients with shorter diabetes duration were at higher risk of having MIA and/or HTN, where HTN and MIA occurred separately or simultaneously after age- and BMI-adjustment. This is in agreement with the previous cross-sectional (without adjustment for confounders) and longitudinal studies (after base adjustment for randomized treatments) conducted on the T2DM patients;[24,25] however, the association of the diabetes duration with the HTN and MIA comorbidity was not considered. The longer duration of diabetes was reported as a strong risk factor for MIA and HTN disorders separately,[12] without considering diabetes duration as a time-dependent variable and the longitudinal analysis. Although we anticipated higher accuracy in our findings, this discrepancy might also originate from divergent distribution of participants' diabetes duration or difficulties in recording the duration of diabetes for T2DM patients in different studies; hyperglycemia usually starts 4–7 years before the clinical diagnosis of diabetes.[26] Moreover, in our study, the effect of diabetes duration on the risk of HTN and MIA comorbidity is noticeably stronger than that of HTN or MIA disorders separately. The results obtained from the effects of shorter diabetes duration on HTN and/or MIA suggest that genetic factors might play a role in the pathogenesis of diabetes complications, including hypertension, moderately increased albuminuria, and the coexistence of both conditions at an early stage of the disease.

At baseline, the age- and BMI-adjusted means of FPG, 2h-PP, and HbA1c were significantly higher for T2DM groups with high blood pressure, MIA, and combined conditions than the normotensive normoalbuminuric T2DM patients. This was in agreement with parallel results for glucose profile of T2DM patients with only MIA or with only HTN in the previous studies.[11,12] A systematic review and a meta-analysis study[27] showed that 2 h-PPG and FPG with HbA1c contributes significantly to overall glycemic control. Furthermore, monitoring of 2 h-PPG will be more helpful to prevent long-term diabetes complications and achieve optimal glycemic control than FPG alone in the absence of HbA1c, especially in developing countries.[27] On the other hand, FPG and 2 h-PPG were recommended as short-term indicators, in addition to the long-term measure of HbA1c, to improve the quality of glycemic control.[28]

Therefore, it was suggested that these three indices should be considered simultaneously as a useful glycemic control index for predicting different diabetes complications. According to this recommendation and to deal with the observed multicollinearity in glucose profile, we combined the cut-off points for 2 h-PPG, FPG, and HbA1c variables to generate a new uncontrolled plasma glucose index, based on the glycemic control recommendation in non-pregnant diabetic patients.[20]

We assessed and compared the glycemic status with uncontrolled plasma glucose index as a combined index of the glucose profile and HbA1c among patients with T2DM. The results obtained from the use of HbA1c instead of uncontrolled plasma glucose index indicated that the associations of the indicator of glycemic control based on Hba1c with the risk of having HTN and/or MIA weakened and are insignificant; however, the associations of other determinants and confounders with the HTN and MIA remained significant. In parallel, partial raw data of the current study were used to estimate the incidence and risk factors of HTN in T2DM patients[11] similar to the current study where the continuous form of HbA1c was included, no significant effect of HbA1c was detected as an indicator of glycemic control, even after the data were adjusted for other variables such as cigarette smoking and therapeutic regimen besides to age and BMI. In the present study, univariate and bivariate models included uncontrolled plasma glucose index as a combined index of the glucose profile, instead of using HbA1c. This model was selected based on the selection criteria described in methods. In fact, the uncontrolled plasma glucose index as a combined index of the glucose profile provided us with a more reliable risk assessment for HTN, MIA, and the coexistence of both conditions. Hence, we showed the longitudinal association of uncontrolled plasma glucose level with HTN, MIA, and the coexistence of both, based on uncontrolled plasma glucose index as a combined index of the glucose profile, after age- and BMI-adjustment. This supported the results of a recent study, showing an increased prevalence of HTN in T2DM patients with poor glycemic control (HbA1$_C$ of $\geq6.5\%$), without adjustment for confounder effects.[29] Moreover, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease (ADVANCE) study, and the Veterans Affairs Diabetes Trial (VADT) showed the importance of glycemic control (HbA1$_C$ of $<6.5\%$) on MIA, after therapy adjustments.[30] However, discordance existed between the research evidence and clinical policy statements about the

intensity of glycemic control required to reduce micro- and macro-vascular complications; because population studies were different in terms of glycemic targets, used anti-hyper-glycemic agents, comorbidities, and duration of diabetes mellitus.[31,32] T2DM patients with uncontrolled plasma glucose have a different phenotype (who predominately have a loss of beta cells) to those who have controlled plasma, such that microvascular damage is experienced.[33] Moreover, reduced arterial elasticity, due to long-term exposure of the vascular wall to elevated glucose level, leads to HTN by increasing peripheral vascular resistance.[34]

In the current study, uncontrolled plasma glucose further showed the stronger effect on MIA and HTN comorbidity than on each disorder separately. The relationship between uncontrolled plasma glucose and the HTN and MIA comorbidity was not investigated previously.

The Non-HDL-C was used as representative of lipid profile in the longitudinal assessment. Non HDL cholesterol provides a single index of apolipoprotein B-containing lipoproteins.[35] This parameter includes very low-density lipoproteins remnants and potentially atherogenic particles which are important participants in the development of CVD disease.[36] Our results showed higher age and BMI-adjusted odds for HTN and MIA in patients with higher Non-HDL-C, in agreement with the results of previous studies without considering the coexistence of both and without adjustment for confounder effects;[36,37] however, the longitudinal association of non-HDL-C with HTN and MIA comorbidity were not considered in those reports.

It should be noted that the comparison of our findings with the previous literature is difficult, especially when it comes to comparing the effect of risk factors on MIA and HTN comorbidity with the effect of risk factors on MIA, and HTN disorders separately, because previous cross-sectional or longitudinal studies on the associations of risk factors with HTN and MIA in patients with T2DM have not tended to focus on HTN and MIA comorbidity.

Study strengths

The strengths of the current study include the use of samples, consisting of both men and women, using standard criteria for information on potential determinants of HTN and MIA. All measurements performed by trained staff; and the same methods were used to obtain both the baseline and the follow-up laboratory data. There was no difference between the potential risk factors of HTN and/ or MIA in participants who were examined once, non-attendees and those with the follow-up.

Furthermore, we used univariate/bivariate mixed-effects (with random subject effects) logistic regression. This statistical model is an appropriate and efficient method for the analysis of natural history longitudinal data with dropout. Although it has been common to use traditional univariate/bivariate fixed-effect logistic regression for the cross-sectional analysis, and standard univariate/bivariate Cox models for time to incident detection of the outcomes, these common approaches do not make use of all the available repeated measures data.[18] Bayesian inference was practically feasible for univariate/bivariate mixed-effects logistic regression, as well as for model-based handling missing covariates at random with higher statistical power than complete case (eliminate cases with missingness) method.[38]

Study limitations

Several limitations need to be considered in interpreting our results. First, we were unable to include several possible confounding variables that were known as risk factors for HTN and MIA, such as the type of treatment (diet, pills, and insulin), smoking behavior, alcohol and salt consumption (sodium-intake), sleeping disorder, socioeconomic status, and genetic factors. Previous studies[11,12] on Iranian population showed no statistically significant association between smoking, the type of treatment and HTN and MIA, considering other covariates and disregarding the coexistence of both disorders. The second limitation is the observational design of our cohort study, which makes it impossible to assess the exposure that is not made by the researcher (there is no intervention); it is difficult to assess the causal-effects of risk factors. Furthermore, the probability of exposure can be influenced by extraneous factors, or confounders, which can also affect the outcome of the study. Therefore, the causal-effects of the risk factors are also influenced by unmeasured confounding factors. However, our modifications of the statistical models (specifically the random-subject effects in the univariate/ bivariate mixed-effects logistic regressions) allowed us to somehow overcome this issue in the statistical analysis. Hence, the random subject effects often interpreted as latent characteristics that are specific to the subject represent the collective impact of factors relevant to the outcome variables but not included in the model.[39] Nonetheless, we do not claim the inclusion of the random subject effects as 'adjustment' for unmeasured confounding variables.

Conclusion

The high prevalence rates of moderately increased albuminuria and its coexistence with hypertension at baseline have been shown in T2DM patients. The age- and BMI-adjusted odds of having hypertension, moderately increased albuminuria, and the coexistence of both conditions were significantly increased by increasing non-high-density lipoprotein cholesterol, shorter diabetes duration, and uncontrolled plasma glucose. Furthermore, after adjustment for age and BMI during follow-up visits, diabetes duration and uncontrolled plasma glucose showed significant stronger effects on coexisting hypertension and moderately increased albuminuria than on each separate condition. Our findings encourage comprehensive and motivated bad lipid and glucose profile-loss programmers at an early stage of the diagnosis of the type 2 diabetes to prevent hypertension, moderately increased albuminuria, and particularly the coexistence of both.

Ethics approval and informed consent

The present study conforms to the principles outlined in the Declaration of Helsinki. The protocol of the IDOPS was also approved by the Ethics Committee of the Isfahan University of Medical Sciences (IUMS) and Research Ethics Committee of Isfahan Endocrine and Metabolism Research Center (IEMRC) (No. 394909). Informed consent was obtained from all individual participants included in the study.

Data availability

The data used to support the findings of the present study are available from the corresponding authors upon request.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in regard to this work.

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Supplementary materials

Table S1 Correlation between fasting plasma glucose, 2 hrs postprandial plasma glucose, and glycosylated hemoglobin at baseline

	FPG (mmol/l)	2-HPPG (mmol/L)	HbA1C (%)	T-Chol (mmol/L)	LDL-Chol (mmol/L)
2-HPPG (mmol/L)	r=0.698[a]				
HbA1C (%)	r=0.532[a]	r=0.537[a]			
T-Chol (mmol/L)	r=0.185[a]	r=0.140[a]	r=0.119[a]		
LDL-Chol(mmol/L)	r=0.120[a]	r=0.101[a]	r=0.189[a]	r=0.844[a]	
HDL-Chol (mmol/L)	r=- 0.020	r=- 0.011	r=- 0.043	r=- 0.217[a]	r=- 0.130[a]

Note: [a]Correlation is significant at the 0.01 level.
Abbreviations: r, pearson correlation coefficients; FPG, fasting plasma glucose; 2-HPPG, 2 hr postprandial plasma glucose; HbA1$_C$, glycosylated hemoglobin; T-Chol, total cholesterol; HDL-Chol, high-density lipoprotein cholesterol; LDL-Chol, low-density lipoprotein cholesterol.

Table S2 Baseline characteristics in T2DM patients with or without follow-up

	Attendees	Non-attendees	P-value
Characteristic	**Mean (SD)**		
Age (year)	46.34 (8.65)	46.7 (8.66)	0.54
Height (cm)	158.7 (8.54)	159.8 (8.69)	0.08
Weight (kg)	73.04 (11.79)	74.22 (12.56)	0.14
Body mass index (kg/m^2)	29.14 (4.61)	29.66 (4.49)	0.09
Fasting plasma glucose (mmol/L)	8.49 (2.45)	8.47 (2.89)	0.93
2-hrs post prandial plasma glucose (mmol/L)	11.85 (3.82)	11.88 (4.14)	0.91
Glycosylated hemoglobin (%)	7.53 (1.76)	7.57 (1.67)	0.71
Triglyceride (mmol/L)	2.05 (1.31)	2.07 (1.15)	0.86
Total-cholesterol (mmol/L)	5.01 (1.01)	4.89 (1.05)	0.09
LDL-cholesterol (mmol/L)	2.93 (0.82)	2.84 (0.86)	0.08
HDL-cholesterol (mmol/L)	1.18 (0.30)	1.15 (0.28)	0.14
Non HDL-cholesterol (mmol/L)	3.84 (0.95)	3.77 (0.99)	0.25
Systolic blood pressure (mmHg)	125 (8.62)	124 (4.92)	0.07
Diastolic blood pressure (mmHg)	79.11 (9.30)	77.98 (8.97)	0.07
24 hrs urine albumin concentrations (mg)	45.74 (10.32)	44.62 (9.23)	0.10
Diabetes duration (Year)	4.55 (4.40)	4.93 (4.59)	0.20
	N (%)		
Sex			
Male	906 (56.6)	166 (10.4)	0.14
Female	431 (26.9)	97 (9.1)	

Abbreviations: T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table S3 Results of multiple pairwise comparisons between the groups at baseline

Variable	Group (A)	Group (B)	Mean Difference (A-B)[b]	Std. Error	P-value[c]
Fasting plasma glucose (mmol/L)	Neither MIA nor HTN[a]	Only MIA	-0.10	0.16	0.99
		Only HTN	-0.33	0.23	0.90
		Coexisting MIA and HTN	-0.67	0.17	0.001
	Only MIA	Only HTN	-0.23	0.23	0.99
		Coexisting MIA and HTN	-0.57	0.18	0.007
	Only HTN	Coexisting MIA and HTN	-0.34	0.24	0.91
2-hrs postprandial plasma glucose (mmol/L)	Neither MIA nor HTN	Only MIA	-0.20	0.24	0.99
		Only HTN	-0.70	0.35	0.28
		Coexisting MIA and HTN	-1.07	0.28	<0.001
	Only MIA	Only HTN	-0.50	0.35	0.94
		Coexisting MIA and HTN	-0.87	0.27	0.01
	Only HTN	Coexisting MIA and HTN	-0.37	0.37	0.99
Glycosylated hemoglobin (%)	Neither MIA nor HTN	Only MIA	-0.31	0.11	0.04
		Only HTN	-0.29	0.16	0.41
		Coexisting MIA and HTN	-0.48	0.13	<0.001
	Only MIA	Only HTN	-0.02	0.16	0.99
		Coexisting MIA and HTN	-0.17	0.13	0.89
	Only HTN	Coexisting MIA and HTN	-0.18	0.17	0.99
Total-cholesterol (mmol/L)	Neither MIA nor HTN	Only MIA	-0.10	0.06	0.68
		Only HTN	-0.16	0.09	0.54
		Coexisting MIA and HTN	-0.30	0.07	<0.001
	Only MIA	Only HTN	-0.06	0.09	0.99
		Coexisting MIA and HTN	-0.20	0.07	0.04
	Only HTN	Coexisting MIA and HTN	-0.14	0.10	0.93
LDL-cholesterol (mmol/L)	Neither MIA nor HTN[a]	Only MIA	-0.09	0.06	0.82
		Only HTN	-0.05	0.08	0.99
		Coexisting MIA and HTN	-0.26	0.07	<0.001
	Only MIA	Only HTN	0.04	0.08	0.99
		Coexisting MIA and HTN	-0.18	0.07	0.06
	Only HTN	Coexisting MIA and HTN	-0.21	0.09	0.09
Non HDL-cholesterol (mmol/L)	Neither MIA nor HTN	Only MIA	-0.08	0.06	0.99
		Only HTN	-0.08	0.09	0.99
		Coexisting MIA and HTN	-0.34	0.07	<0.001
	Only MIA	Only HTN	-0.01	0.09	0.99
		Coexisting MIA and HTN	-0.26	0.08	0.004
	Only HTN	Coexisting MIA and HTN	-0.26	0.1	0.06

Note: [a]Control group. [b]Based on estimated marginal means. [c]Adjustment for age and BMI, multiple comparisons based on Bonferroni correction.
Abbreviations: HTN, hypertension; MIA, moderately increased albuminuria; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table S4 Result of Bayesian univariate and bivariate logistic regression with random subject effect, with and without considering moderately increased albuminuria and hypertension comorbidity

Response variable	Covariate	Category	Having only MIA versus not having MIA (univariate logistic regression) Odds ratio (95% BCI)	Having only HTN versus not having HTN (univariate logistic regression) Odds ratio (95% BCI)	Having MIA and HTN comorbidity versus not having MIA and not having HTN (bivariate logistic regression) Odds ratio (95% BCI)
MIA					
	Sex	Male	0.71 (0.56, 0.86)[a]		0.69 (0.55,0.82)[a]
		Female	–		–
	Diabetes duration (year)		0.87 (0.80, 0.96)[a,b]		0.81 (0.73, 0.92)[a,b]
	Age (year)		0.95 (0.93, 0.96)[a]		0.94 (0.92, 0.97)[a]
	Body mass index (kg/m²)		1.019 (1.007, 1.037)[a]		1.023 (1.014, 1.044)[a]
	Glucose index	Uncontrolled plasma glucose	1.25 (1.02, 1.56)[a,b]		1.34 (1.13, 1.62)[a,b]
		Controlled plasma glucose	–		–
	Non HDL-cholesterol (mmol/l)		1.27 (1.19, 1.40)[a]		1.24 (1.14, 1.33)[a]
HTN					
	Sex	Male		1.16 (0.89, 1.50)	1.14 (0.95, 1.48)
		Female		–	–
	Diabetes duration (year)			0.95 (0.91, 0.98)[a,b]	0.89 (0.84, 0.96)[a,b]
	Age (year)			1.008 (0.994, 1.022)	1.004 (0.973, 1.012)
	Body mass index (kg/m²)			1.070 (1.041, 1.100)[a]	1.071 (1.042, 1.093)[a]
	Glucose index	Uncontrolled plasma glucose		1.62 (1.23, 1.86)[a,b]	1.73 (1.29, 2.20)[a,b]
		Controlled plasma glucose		–	–
	Non HDL-cholesterol (mmol/L)			1.32 (1.29, 1.52)[a]	1.30 (1.23, 1.34)[a]
DICs			Both separate univariate mixed-effect logistic models: 8702+ 8478=17,180	Bivariate mixed-effect logistic model: 8940.0	

Notes: The patients with uncontrolled plasma and diabetes duration, and females are the references group. Adjusted odds ratio are reported after measurement and adjustment for age and BMI during follow-up. [a]Significant results based on 95% Bayesian credible intervals. [b]Significant difference between univariate and bivariate logistic regressions (P-value <0.05).
**Abbreviations:** MIA, moderately increased albuminuria; HTN, hypertension; HDL, high-density lipoprotein; BCI, Bayesian Credible interval; DIC, deviance information criterion.

Table S5 Result of Bayesian univariate and bivariate logistic regression with random subject effect, with and without considering moderately increased albuminuria and hypertension comorbidity

Response variable	Covariate	Category	Having only MIA versus not having MIA (univariate logistic regression)	Having only HTN versus not having HTN (univariate logistic regression)	Having MIA and HTN comorbidity versus not having MIA and not having HTN (bivariate logistic regression)
			Odds ratio (95% BCI)	Odds ratio (95% BCI)	Odds ratio (95% BCI)
MIA					
	Sex	Male	0.69 (0.55, 0.85)[a]		0.68 (0.54, 0.85)[a]
		Female	–		–
	Diabetes duration		0.85 (0.82, 0.87)[a]		0.83 (0.81, 0.86)[a]
	Age (year)		0.944(0.933, 0.955)[a]		0.998 (0.983, 1.01)
	Body mass index (kg/m²)		1.024 (1.003, 1.051)[a]		1.019 (1.007, 1.037)[a]
	Glycosylated hemoglobin (%)		1.05 (1.01, 1.09)[a]		1.06 (1.01, 1.11)[a]
	Non HDL-cholesterol (mmol/l)		1.04 (1.01, 1.04)[a]		1.03 (1.03, 1.07)[a]
HTN					
	Sex	Male		1.16 (0.89, 1.52)	1.11 (0.84, 1.45)
		Female		–	–
	Diabetes duration			0.94 (0.92, 0.97)[a]	0.91 (0.89, 0.94)[a]
	Age (year)			1.009 (0.995, 1.022)	0.998 (0.983, 1.011)
	Body mass index (kg/m²)			1.078 (1.046, 1.122)[a]	1.079 (1.033, 1.108)[a]
	Glycosylated hemoglobin (%)			1.03 (0.95, 1.09)	1.04 (0.97, 1.10)
	Non HDL-cholesterol (mmol/l)			1.016 (1.013, 1.019)[a]	1.015 (1.012, 1.018)[a]
DICs			Both separate univariate mixed-effect logistic models: 8722+ 8794=17,516		Bivariate mixed-effect logistic model: 10,880

Notes: The patients with uncontrolled plasma glucose and females are the references group. Adjusted odds ratio are reported after measurement and adjustment for age and BMI during follow-up. [a]Significant results based on 95% Bayesian credible intervals. Significant difference between univariate and bivariate logistic regressions (P-value <0.05).
Abbreviations: MIA, moderately increased albuminuria; HTN, hypertension; HDL, high-density lipoprotein; BCI, Bayesian credible interval; DIC, deviance information criterion.

A

B
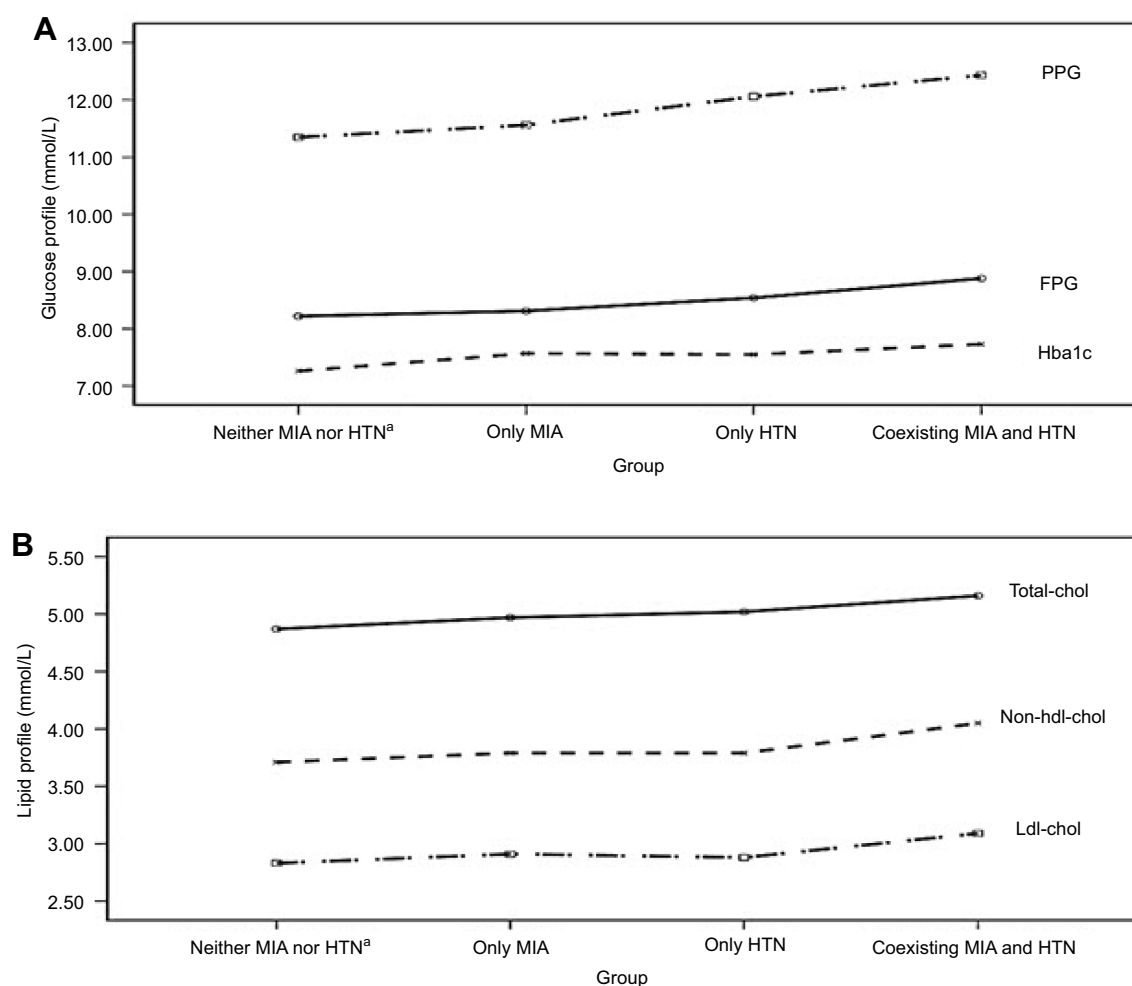
Figure S1 Age and body mass index-adjusted means of lipid and glucose profiles in different groups of type 2 diabetic patients. (**A**) Age and body mass index-adjusted means of glucose profile in different groups of type 2 diabetic patients. (**B**) Age and body mass index-adjusted means of lipid profile in different groups of type 2 diabetic patients.
Note: [a]control group.
Abbreviations: MIA, moderately increased albuminuria; HTN, hypertension; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1C, glycosylated hemoglobin; Total-Chol, total cholesterol; Non-HDL-Chol, non-high-density lipoprotein cholesterol; LDL-Chol, low density lipoprotein cholesterol.