# Fasting glycemia and glycated hemoglobin categories: Relationship to serum lipoprotein(a) level and disparity in 2 geographic regional groups of Turkey

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## Abstract

**Objective:** The goal of the present study was to determine covariates of serum lipoprotein (Lp) (a) within fasting glucose and glycated hemoglobin (HbA1c) categories, and to detect features that were different among covariates based on residence in Marmara and Central Anatolia (Marm-CA) regions or remaining 5 geographic regions of Turkey.
**Methods:** Data of randomly-selected group of 1167 men and women (mean age 61 years) who participated in biennial surveys of 2013 and 2015 were cross-sectionally analyzed in 6 categories.
**Results:** In multiple linear regression analysis of nondiabetic women, homeostatic model assessment (HOMA) index score was inversely associated with Lp(a) (β coefficient 0.49; p=0.001); this was not true for men. In the whole sample, Lp(a) was significantly positively associated with female sex and with serum creatinine, and inversely in each sex with HOMA index (β coefficient 0.63; p<0.001). Linear models within separate categories showed significant associations of Lp(a) only in individuals with no evidence of diabetes other than HbA1c >6.5%: in women, positive association with total cholesterol and inverse relationship with creatinine were found, and in men, positive association with apolipoprotein (apo) B was determined. Similar age, diastolic blood pressure, fasting glucose, triglyceride, uric acid, and C-reactive protein values were obtained from participants of 2 regional groups. Residents of the Marm-CA region who were nondiabetic exhibited significantly (by 23%) lower serum Lp(a) among individuals with HbA1c ≥5.7%, significantly higher HOMA index score, concentrations of apoB, and low-density lipoprotein cholesterol.
**Conclusion:** Hallmark of prediabetic and diabetic glycemia/HbA1c categories seems to be an independent inverse association between Lp(a) protein (yet not of apoB) and HOMA score, this being primarily so in residents of Marm-CA region. *(Anatol J Cardiol 2017; 17: 191-9)*
**Keywords:** apolipoprotein B; autoimmune activation; impaired fasting glucose; insulin resistance; lipoprotein(a); prediabetes

## Introduction

When compared to optimal oral glucose tolerance test (GTT) in diagnosis of diabetes and prediabetes, glycated hemoglobin (HbA1c)-defined prediabetes had low positive predictive value (1, 2). The reasons for this discrepancy remain unclear. Sex, age, and race seem to have an influence, since diabetes has been more likely to be identified in elderly American blacks and women using HbA1c than fasting glucose criteria (3). Conversely, among Hispanic and non-Hispanic patients assessed to have diabetes according to fasting glucose, HbA1c failed to identify it in approximately half of patients, especially in whites (4). Notably, lack of sensitivity and reliability of HbA1c in diagnosing prediabetes or impaired glucose tolerance (IGT) defined by glucose levels was demonstrated by Fajans et al. (5), who reported that 1 of every 3 such subjects had HbA1c value <5.7%. A similar conclusion was reached in a clinic-based study (6). Based on as yet unpublished experience of the present authors in both the Turkish Adult Risk Factor (TARF) study and a tertiary medical center study, we strongly suspect that autoimmune activation (7) comprising oxidatively-damaged HbA1c underlies paradoxical shifts in glycemia categories.

When examining prediabetic cohorts surveyed in 2013 and 2014, we noted 2 aspects in prediabetic individuals defined by

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**Accepted Date:** 08.09.2016 **Available Online Date:** 10.11.2016

*DOI:10.14744/AnatolJCardiol.2016.7190*

HbA1c value of 5.7% to 6.49% and normal fasting glucose: a) This subset had a high prevalence (two-fifths) among Turkish adults aged over 40 years; b) various anthropometric, lipid, and non-lipid characteristics were significantly different across these participant groups (8). Since oral GTT is not performed as part of TARF study, we postulated that these intriguing observations might be accounted for by substantial proportion of prediabetic individuals surveyed in 2013 representing either participants who were actually diabetic with "reduced" HbA1c or those with IGT.

The Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease (TURDEP-II) study, in contrast, has carried out oral GTT and determined blood HbA1c routinely (9). Thus, some aspects such as sex-specific regional prevalence of prediabetes and diabetes could be compared and reasonable deductions made.

We have recently documented prospectively that nondiabetic Turkish adults who subsequently developed new-onset diabetes (NOD) were distinguished, among other factors, primarily by reduced serum lipoprotein (Lp) (a), which was inversely associated with homeostasis model assessment (HOMA) index score, observations that were consistent with underlying autoimmune activation (10).

The aim of the current study was: a) to assess metabolic covariates of serum Lp(a) in (concordant and discordant) categories of HbA1c and fasting glucose, b) to determine whether 2 groups of middle-aged and elderly Turkish adults were distinguishable from each other and what any significantly different features were, and c) whether an underlying mechanism accounts for such differences. We first undertook the task of determining which of the 7 geographic regions in Turkey displayed the characteristics noted in the 2 surveys, in order to enable assessment of optimal distinction. Such an evaluation might reveal fundamental features of prediabetes and its progression to diabetes, including those related to autoimmune-induced low levels of Lp(a) and/or HbA1c. This study reports the findings based on records of 1167 patients.

## Methods

### Study sample

TARF study is a prospective cohort study of the prevalence of cardiac disease and risk factors in adults in Turkey carried out biennially since 1990 in 59 communities scattered throughout all geographical regions of the country (11). It comprises a random sample of the Turkish adult population, representatively stratified for sex, age, geographical region, and for rural-urban distribution. Present study sample is derived from 1167 unselected participants in whom HbA1c determinations were made in fasting state who responded in the 2013 and 2015 surveys by taking part in a physical examination and providing blood for biochemical analyses.

The current study was approved by the Ethics Committee of the İstanbul University Faculty of Medicine. Written informed consent was obtained from all participants. Data were obtained with history of past years provided via a questionnaire, physical examination of cardiovascular system, sampling of blood, and recording of resting 12-lead electrocardiogram (ECG).

### Measurement of risk factors

Blood pressure (BP) was measured with an aneroid sphygmomanometer (Erka Kallmeyer Medizintechnik GmbH & Co., Bad Tölz, Germany) on the right arm while in sitting position, and mean of 2 assessments taken 5 minutes apart was calculated. Waist circumference was measured at level midway between the lower rib margin and the iliac crest. Cigarette smoking status was categorized into never, former, and current smokers.

Blood samples were collected, spun at 1000g, shipped to İstanbul and stored in deep-freeze at -75°C, until analyzed within weeks. HbA1c measurements of whole blood samples were carried out with turbidimetric inhibition immunoassay using Hitachi Modular P800 chemistry analyzer (Roche Diagnostics GmbH, Basel, Switzerland). Serum concentrations of glucose, total cholesterol, fasting triglycerides, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and creatinine were determined using Hitachi Modular P800 chemistry analyzer (Roche Diagnostics GmbH, Basel, Switzerland). Serum concentrations of C-reactive protein (CRP), apolipoprotein (apo) B, apoA-I and Lp(a) were measured nephelometrically with BN ProSpec analyzer (Siemens Healthineers, Erlangen, Germany). Concentrations of insulin were determined by electrochemiluminescent immunoassay using COBAS e411 analyzer (Roche Diagnostics GmbH, Basel, Switzerland).

### Definitions

Diabetes was diagnosed based on criteria of the American Diabetes Association, that is, by self-report of antidiabetic medication use, plasma fasting glucose ≥126 mg/dL, or HbA1c value ≥6.5% (12). Prediabetes was identified by fasting glucose 100–125 mg/dL or HbA1c 5.7–6.4% (12). HOMA index of insulin resistance was calculated for participants who had concomitant fasting insulin and glucose measurements with formula of fasting insulin (μU/mL) x glucose (mmoL/L)/22.5.

Diagnosis of coronary heart disease was based on presence of angina pectoris, history of myocardial infarction with or without accompanying Minnesota ECG codes (13), or history of myocardial revascularization. Typical angina and, in women, age >45 years were prerequisites for diagnosis when angina was isolated. ECG changes of "ischemic type" of greater than minor degree were considered myocardial infarct sequelae or myocardial ischemia (codes: 1.1-2, 4.1-2, 5.1-2, 7.1).

### Data analysis

Data and analyses of study sample were categorized to 6 groups, depending on concordance or discordance of fasting glucose and HbA1c: normoglycemia; prediabetes, with concordant or discordant glucose; high HbA1c without diabetes; and diabetes, with concordant or discordant glucose. Descriptive

parameters were shown as mean±SD or percentages. For normally distributed parameters, analysis of variance and pairwise comparisons with post hoc Tukey HSD test were conducted to determine significance between groups. Two-sided t-tests and Pearson's chi-square tests were used to analyze differences between means and proportions of other groups. For parameters with skewed distribution, values derived from log-transformed (geometric) means were used. Significance testing between 2 groups was performed using Mann-Whitney U and asymptotic 2-tailed tests, and across multiple groups with Kruskal-Wallis test added to pairwise comparisons using Dunn's test. Multiple linear regression analyses for detection of independent variables of Lp(a) were performed with continuous parameters, indicating estimates of ß coefficients and SE in models adjusted for (sex and) age, expressed for each in terms of 1-SD increment. P value <0.05 on 2-tailed test was considered statistically significant. Statistical analyses were performed using SPSS version 10 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

### Prevalence of defined glucose/HbA1c categories in the study sample

In sample of 1167 participants, prevalence of the 6 categories was as follows: normoglycemia (324; 27.8%), prediabetes with normoglycemia (437; 37.4%), prediabetes (80; 5.9%), no diabetes with high HbA1c (63; 5.4%), diabetes with low HbA1c (81; 5.9%), diabetes (182; 15.6%). Range of HbA1c values varied non-significantly, by only 0.08% (1.4%), across regions. After examining certain sex-specific characteristics across the regions, it was decided to compare combined group of Marmara and Central Anatolia (Marm-CA) regions with group made up of the remaining 5 regions (5-R).

### Distinctive features across study categories

As can be noted from data in provided Table 1, the 6 HbA1c/glucose groups were composed of individuals with mean age

**Table 1. Characteristics of study sample by glycemia and glycated hemoglobin status, and presence of diabetes (n=1167)**

| | Normoglycemia | | Prediabetes | | | | Diabetes | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ng+A1c **5.7-6.49** | | IFG+A1c **5.7-6.49** | | IFG+A1c **>6.49** | | DM+**A1c <6.5** | | DM+ A1c>6.5 | | **ANOVA** |
| | **Mean±SD** | | **Mean±SD** | | **Mean±SD** | | **Mean±SD** | | **Mean±SD** | | **Mean±SD** | | ***P*** |
| | n=324 | | n=437 | | n=80 | | n=63 | | n=81 | | n=182 | | 0.094 |
| Sex, n, M/F | 170/154 | | 209/228 | | 35/45 | | 37/26 | | 32/49 | | 98/84 | | <0.001 |
| HbA1c, % | 5.38±.23 | | 5.94±.20 | | 5.88±.43 | | 6.83±.46 | | **5.93**±.36 | | **8.26**±1.55 | | <0.001 |
| Fasted glucose, mg/dL | 86.2±9.81 | | 88.7±10.6 | | 112±14.5 | | 103±25 | | 109±25 | | **173**±67 | | <0.001 |
| Age, years | 58.7±9.6 | | 60.5±9.5 | | 64.0±12 | | 61±8.7 | | 63.2±10 | | 63.4±12 | | 0.005 |
| Creatinine, mg/dL | 0.853±0.28 | | 0.835±0.24 | | 0.89±0.28 | | 0.87±0.20 | | .89±0.57 | | 0.94±0.83 | | 0.12 |
| Waist circumference, cm | 95.4±12.2 | | 99±12.2 | | 101.3±12.7 | | 102.6±11 | | 102.7±12 | | **107**±12 | | <0.001 |
| Systolic BP, mm Hg | 129±19 | | 133±20 | | 139±20 | | 135±22 | | 136.5±19 | | **145**±22 | | <0.001 |
| Diastolic BP, mm Hg | 78.4±12 | | 80.5±12.6 | | 81±12 | | 81±12.6 | | 81±13.7 | | **82**±12 | | 0.02 |
| Total cholesterol, mg/dL | 200±38 | | *210*±43 | | 207±39 | | 203±44 | | 196±42 | | 202±47 | | 0.006 |
| LDL cholesterol, mg/dL | 122±32 | | **133**±36.5 | | 132±32 | | 126±34.5 | | 121±36 | | 121±40 | | <0.001 |
| HDL cholesterol mg/dL | 50±14 | | 49±14 | | *47*±11 | | 45±12 | | 45.6±11 | | 44±12 | | <0.001 |
| Apolipoprotein A-I, g/L | 1.48±.26 | | 1.47±.26 | | 1.48±.23 | | 1.446±.22 | | 1.46±.21 | | 1.45±.28 | | 0.83 |
| Apolipoprotein B, g/L | 1.03±.26.5 | | 1.12±.27 | | 1.12±.30 | | 1.11±.27 | | 1.06±.29 | | 1.13±.31 | | <0.001 |
| Uric acid, mg/dL | 5.29±1.3 | | 5.31±1.26 | | 5.74±1.35 | | 5.02±1.20 | | 5.45±1.28 | | **5.61**±1.44 | | 0.001 |
| Current/former smoker % | 23.8; 23.2 | | 24.3; 21.5 | | **12.5**; 30 | | 34.9; 27 | | 19.8; 24.7 | | 13.3; **33.7** | | 0.002 |
| Prevalence CHD, n; % | 55; **19.1** | | *105; 27.7* | | 19; 25.7 | | 14; 26.9 | | 21; 28.0 | | 72; **43.6** | | <0.001 |
| F. triglycerides,¶ mg/dL | 121 | 88.0; 178.5 | 131 | 98; 179.5 | 138 | 102; 188.3 | **162** | 109; 203 | 145 | 97; 210.5 | **170** | 127; 239 | <0.001 |
| Lipoprotein(a),¶ mg/dL | 12.0 | 6.0; 28.0 | 13.0 | 5.0; 32.0 | 9.5 | 4.25; 26,0 | 9.0 | 4.0; 27.0 | 10.0 | 3.25; 26,0 | 11.0 | 5.0; 27.75 | 0.576 |
| C-reactive protein,¶ mg/L | 2.0 | 1.0; 4.0 | 2.0 | 1.0; 4.7 | 2.5 | 1.0; 5.0 | 3.0 | 1.0; 7.0 | 2.0 | 1.0; 4.0 | **2.0** | 1.0; 6.0 | 0.007 |
| Fasting insulin,¶ mIU/L | 8.7 | 5.3; 12.45 | **8.8** | 5.99; 12.84 | 10.97 | 7.7; 20,68 | **10.9** | 7.94; 17,2 | **9.93** | 7.13; 15,5 | 11.57 | 7.2;17.9 | |
| HOMA index¶ | 1.83 | 1.1; 2.69 | **1.89** | 1.30; 2,82 | 3.19 | 2.08; 5,44 | **2.81** | 1.97; 4,11 | **2.68** | 1.72; 4,20 | **4.50** | 2.56; 8.00 | <0.001 |

Numbers in boldface denote significant difference and italics indicate borderline significant difference compared to normoglycemia group. In parameters with skewed distribution (¶), median and interquartile ranges are given; Kruskal-Wallis and subsequent Dunn's tests were used to determine significance

ANOVA - analysis of variance; BP - blood pressure; CHD - coronary heart disease; F - female; HbA1c - glycated hemoglobin; HDL - high-density lipoprotein; HOMA - homeostatic model assessment; IFG - impaired fasting glucose; LDL - low-density lipoprotein; M - male; Ng - normoglycemia

**Table 2. Multiple linear regression to detect independent variables of Lp(a)¶ by sex (n=988)**

| | Total n=988 | | | Men n=485 | | | Women n=503 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Whole sample** | **β coeff.** | **SE** | ***P*** | **β coeff.** | **SE** | ***P*** | **β coeff.** | **SE** | ***P*** |
| Sex, female | **1.24** | 1.08 | 0.005 | | | | | | |
| Age, 10 years | 1.02 | 1.05 | 0.66 | 1.02 | 1.05 | 0.52 | 0.999 | 1.05 | 0.98 |
| Total cholesterol, 40 mg/dL | 1.096 | 1.096 | 0.18 | 1.096 | 1.096 | 0.20 | 1.00 | 1.096 | 0.52 |
| Apolipoprotein B, 35 mg/dL | 1.08 | 1.08 | 0.26 | 1.08 | 1.08 | 0.49 | 1.08 | 1.08 | 0.22 |
| Apolipoprotein A-I, 30 mg/dL | 0.93 | 1.07 | 0.44 | 0.93 | 1.07 | 0.23 | 1.0004 | 1.07 | 0.95 |
| Waist circumference, 12 cm | 1.00 | 1.03 | 0.82 | 0.973 | 1.06 | 0.50 | 1.00 | 1.06 | 0.82 |
| HOMA index ¶ | **0.63** | 1.12 | <0.001 | **0.71** | 1.17 | 0.026 | **0.55** | 1.18 | <0.001 |
| Creatinine, 0.22 mg/dL | **1.045** | 1.21 | 0.018 | 1.032 | 1.24 | 0.14 | *1.075* | 1.04 | 0.051 |
| Variance explained, $r^2$ | Const. **5.9**¸ 0.036, ***P***<0.001 | | | Const. **9.9**¸ 0.024, ***P*** 0.03 | | | Const. **6.95**¸ 0.036, ***P*** 0.002 | | |
| **Nondiabetic sample** | n=774 | | | n=379 | | | n=395 | | |
| Total cholesterol, 40 mg/dL | 1.00 | 1.096 | 0.48 | 1.00 | 1.096 | 0.73 | 1.096 | 1.096 | 0.49 |
| Apolipoprotein B, 35 mg/dL | 1.08 | 1.08 | 0.34 | 1.08 | 1.08 | 0.71 | 1.08 | 1.08 | 0.27 |
| HOMA index ¶ | **0.665** | 1.16 | 0.005 | 0.84 | 1.22 | 0.40 | **0.49** | 1.25 | 0.001 |
| Creatinine, 0.22 mg/dL | 1.02 | 1.16 | 0.64 | 0.99 | 1.06 | 0.86 | 1.04 | 1.07 | 0.52 |
| Variance explained, $r^2$ | Const. **5.7**¸ 0.02, ***P***=0.004 | | | Const. **11.5**¸ 0.00, ***P*** 0.88 | | | Const. **6.2**¸ 0.03, ***P***=0.024 | | |
| **N'glyc** with HbA1c <5.7% | n=268 | | | n=137 | | | n=131 | | |
| Total cholesterol, 40 mg/dL | 1.086 | 1.096 | 0.46 | 0.90 | 1.20 | 0.52 | 1.15 | 1.20 | 0.36 |
| Apolipoprotein B, 35 mg/dL | 1.16 | 1.17 | 0.26 | *1.37* | 1.17 | 0.099 | 1.10 | 1.17 | 0.58 |
| HOMA index ¶ | 0.67 | 1.31 | 0.14 | 0.64 | 1.52 | 0.29 | **0.62** | 1.11 | 0.05 |
| Creatinine, 0.22 mg/dL | 1.005 | 1.07 | 0.95 | 1.014 | 1.12 | 0.21 | 1.001 | 1.12 | 0.99 |
| Variance explained, $r^2$ | Const. 3.6¸ 0.02, ***P*** 0.25 | | | Const. 11.0¸ 0.05, ***P*** 0.27 | | | Const. 1.5¸ 0.06, ***P*** 0.14 | | |
| N'glyc with HbA1c 5.7–6.5% | n=379 | | | n=178 | | | n=201 | | |
| Total cholesterol, 40 mg/dL | 1.002 | 1.10 | 0.97 | 1.007 | 1.10 | 0.64 | 1.07 | 1.10 | 0.56 |
| Apolipoprotein B, 35 mg/dL | 1.12 | 1.08 | 0.27 | 1.09 | 1.17 | 0.96 | 1.26 | 1.17 | 0.10 |
| HOMA index ¶ | 0.69 | 1.25 | 0.10 | 0.83 | 1.35 | 0.52 | 0.57 | 1.42 | 0.10 |
| Creatinine, 0.22 mg/dL | 0.92 | 1.78 | 0.14 | 0.91 | 1.08 | 0.24 | 1.005 | 1.10 | 0.97 |
| Variance explained, $r^2$ | Const. **11.9**¸ 0.03, ***P*** 0.026 | | | Const. **11.6**¸ 0.03, ***P*** 0.25 | | | Const. **16.0**¸ 0.01, ***P***=0.52 | | |
| **PreDM** with HbA1c <6.5% | n=72 | | | n=33 | | | n=39 | | |
| Total cholesterol, 40 mg/dL | 1.24 | 1.20 | 0.29 | 1.29 | 1.45 | 0.51 | 1.17 | 1.32 | 0.57 |
| Apolipoprotein B, 35 mg/dL | 0.76 | 1.27 | 0.23 | 1.95 | 1.48 | 0.28 | 0.84 | 1.38 | 0.53 |
| HOMA index ¶ | 0.66 | 1.47 | 0.28 | 1.15 | 1.56 | 0.75 | 0.31 | 1.70 | 0.15 |
| Creatinine, 0.22 mg/dL | 1.12 | 1.12 | 0.28 | 0.95 | 1.20 | 0.76 | 1.24 | 1.17 | 0.20 |
| Variance explained, $r^2$ | Const. *23* 0.01, ***P*** 0.43 | | | Const. 11.5¸ 0.09, ***P*** 0.36 | | | Const. 145¸ 0.06, ***P***=0.41 | | |
| NonDM with HbA1c >6.5% | n=49 | | | n=28 | | | n=21 | | |
| Total cholesterol, 40 mg/dL | 1.38 | 1.20 | 0.074 | 0.99 | 1.32 | 0.96 | **1.99** | 1.32 | 0.018 |
| Apolipoprotein B, 35 mg/dL | 1.06 | 1.32 | 0.81 | **2.24** | 1.38 | 0.037 | 1.12 | 1.38 | 0.72 |
| HOMA index ¶ | 0.99 | 1.80 | 0.99 | 0.66 | 1.94 | 0.54 | 6.75 | 3.12 | 0.096 |
| Creatinine, 0.22 mg/dL | 0.81 | 1.26 | 0.37 | 0.59 | 1.58 | 0.25 | **0.40** | 1.51 | 0.044 |
| Variance explained, $r^2$ | Const. **0.76** 0.045, ***P*** 0.13 | | | Const. 2.34¸ **0.43**, ***P*** 0.018 | | | Const. **0.0001**¸ 0.50, ***P***=0.04 | | |
| DM with HbA1c <6.5% | n=71 | | | n=27 | | | n=44 | | |
| Total cholesterol, 40 mg/dL | 1.01 | 1.20 | 0.95 | 0.993 | 1.32 | 0.82 | 1.096 | 1.20 | 0.67 |
| Apolipoprotein B, 35 mg/dL | 1.11 | 1.17 | 0.57 | 1.74 | 1.38 | 0.13 | 0.90 | 1.27 | 0.72 |
| HOMA index ¶ | 0.59 | 1.49 | 0.18 | 1.23 | 2.42 | 0.82 | 0.67 | 1.63 | 0.42 |
| Creatinine, 0.22 mg/dL | *0.90* | 1.05 | 0.056 | 0.63 | 1.35 | 0.13 | *1.12* | 0.076 | 0.056 |
| Variance explained, $r^2$ | Const. **88**¸ 0.08, ***P*** 0.21 | | | Const. 1.27¸ 0.12, ***P***=0.36 | | | Const. **128**¸ 0.08, ***P***=0.36 | | |
| **DM** with HbA1c >6.5% | n=149 | | | n=82 | | | n=67 | | |
| Total cholesterol, 40 mg/dL | 1.096 | 1.096 | 0.22 | **1.27** | 1.096 | 0.04 | 1.05 | 1.096 | 0.69 |
| Apolipoprotein B, 35 mg/dL | 1.09 | 1.08 | 0.44 | 1.02 | 1.17 | 0.92 | 1.11 | 1.17 | 0.53 |
| HOMA index ¶ | **0.49** | 1.25 | 0.002 | **0.44** | 1.33 | 0.005 | 0.59 | 1.46 | 0.16 |
| Creatinine, 0.22 mg/dL | *1.04* | 1.02 | 0.065 | 1.04 | 1.02 | 0.092 | 1.12 | 1.15 | 0.37 |
| Variance explained, $r^2$ | Const. 2.45 **0.11**, ***P*** 0.005 | | | Const. 1.94¸ **0.18**, ***P*** 0.007 | | | Const. 2.72¸ 0.02, ***P***=0.65 | | |

All models were additionally adjusted for age, WC, and apolipoprotein A-I. Values were missing in 14% of participants. Numbers in boldface highlight significant difference; italics indicate borderline significant difference. ¶ log-transformed values. DM - diabetes mellitus; HbA1c - glycated hemoglobin; HOMA - homeostatic model assessment; N'glyc - normoglycemic

of 61 years and there were significant differences in anthropometric and metabolic parameters, except for serum creatinine, apoA-I, and Lp(a) concentrations.

**Sex-modulated association of relevant parameters with Lp(a)**

1. Multiple linear regression models consisting of age, total cholesterol, apoB, apoA-I, waist girth, HOMA index, and creatinine level were analyzed for association with log-transformed Lp(a) stratified to gender (Table 2). In the whole sample, serum Lp(a) was significantly positively associated with female sex, serum creatinine, and inversely with HOMA index (ß coefficient 0.63x1.12; p<0.001). HOMA was inversely associated in each sex as well, whereas creatinine was associated only in women (at borderline significance). In nondiabetic women, but not men, HOMA index was inversely associated with Lp(a). Across individual groups, except for individuals with no history of diabetes yet with HbA1c >6.5%, HOMA was uniformly associated inversely with Lp(a) in each sex, whereas association reached significance in normoglycemic women and diabetic men.
2. ApoB or total cholesterol figure was generally positively associated with Lp(a), significantly so in men and women with or without diabetes but with HbA1c >6.5%.
3. In women with HbA1c in the range of diabetes but in whom no diabetes was identified, WC was positively associated with Lp(a), whereas it was inversely associated only in diabetes with low HbA1c.
4. In discordant diabetes group, inverse association was found between serum creatinine and Lp(a) in women with high HbA1c, but positive association in women with low HbA1c.

**Contrasts of variables among HbA1c/glucose categories in the 2 regional groups**

In comparison of residents of the 2 combined-region groups, serum Lp(a) was uniformly lower in residents of Marm-CA than

**Table 3. Characteristics of nondiabetic, prediabetic, and diabetic participants with different glucose and glycated hemoglobin categories, stratified to 2 geographic regions (n=1167)**

| | | Marm-CA | 5-R | | Marm-CA | *Prediabetes* 5-R | | Marm-CA | *Prediabetes* 5-R | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Ngly A1c <**5.7** | Ngly A1c <**5.7** | | Ngly +A1c**5.7-6.49** | Ngly +A1c**5.7-6.49** | | IFG+ A1c**5.7-6.49** | IFG+ A1c**5.7-6.49** | |
| | **Total n** | **Mean±SD** | **Mean±SD** | ***P*** | **Mean±SD** | **Mean±SD** | ***P*** | **Mean±SD** | **Mean±SD** | ***P*** |
| | | n=185 | n=139 | | n=247 | n=190 | | n=58 | n=22 | |
| Sex, n, M/F | 414/427 | 93/92 | 77/62 | 0.36 | 121/126 | 88/102 | 0.58 | 26/32 | 9/13 | 0.75 |
| HbA1c, % | 324+437+80 | 5.38±.23 | 5.38±.23 | 0.98 | 5.93±.19 | 5.96±.22 | 0.18 | 5.94±.36 | 5.72±.56 | 0.09 |
| Fasted glucose, mg/dL | 324+437+80 | 85.7±9.6 | 87±10 | 0.28 | 88.5±12 | 88.8±9 | 0.76 | 113±16 | 109±6 | 0.096 |
| Age, years | 324+436+80 | 58.2±9.5 | 59.4±9.8 | 0.27 | 60.7±9.7 | 60.3±9.3 | 0.65 | 63.8±12.7 | 64.7±10 | 0.75 |
| Lipoprotein(a),¶ mg/dL | 291+399+76 | 12.0; 6.0-29 | 15; 4.5-28 | 0.654 | **11.0**; 5.0-30 | 15.0; 6.5-38 | 0.026 | 9.0; 3.8-24.5 | 10.5; 6.0-29.5 | 0.429 |
| Creatinine, mg/dL | 324+437+80 | 0.86±0.32 | 0.84±0.21 | 0.52 | **0.87**±0.26 | 0.79±0.17 | 0.026 | 0.89±0.27 | 0.88±0.33 | 0.91 |
| Waist circumference, cm | 324+437+80 | 95±13 | 96±11 | 0.31 | *98.0*±12 | 100.2±12.5 | 0.059 | 101±13 | 102±12 | 0.69 |
| Systolic BP, mm Hg | 324+437+80 | 129±17 | 129±21 | 0.97 | **135**±20 | 131±21 | 0.049 | 140±19 | 133.5±21 | 0.18 |
| Diastolic BP, mm Hg | 324+437+80 | 78±11 | 78±13 | 0.93 | *79.5*±11 | 82±14 | 0.059 | 81±11 | 81±14 | 0.92 |
| Total cholesterol, mg/dL | 324+437+80 | *203*±35 | 195.6±40 | 0.089 | **216**±42 | 202±42 | <0.001 | **214**±36 | 188±42 | 0.007 |
| LDL cholesterol, mg/dL | 324+423+80 | **126.2**±29 | 116.7±36 | 0.015 | **139**±37 | 124±34 | <0.001 | *136*±31 | 121±33 | 0.074 |
| HDL cholesterol mg/dL | 324+437+80 | 49±13 | 51.4±16 | 0.12 | 48.7±13.6 | 49.2±13.5 | 0.74 | 47.3±11 | 48.5±12 | 0.79 |
| F. triglycerides,¶ mg/dL | 324+437+80 | 121; 89-174 | 119; 87-190 | 0.882 | 130; 98-105 | 132.5; 98-184 | 0.783 | 138; 101-189 | 145; 100-179 | 0.775 |
| Fasting insulin, mIU/L | 301+419+79 | *8.85*; 5.59-13.2 | 8.06; 4.83-11.3 | 0.068 | **9.7**; 6.57-14.5 | 7.94; 5.42-11.3 | <0.001 | 11.5; 7.46-20.5 | 10.4; 7.6-21.6 | 0.785 |
| HOMA index,¶ | 301+419+79 | 1.97; 1.16-2.84 | 1.73; 1.06-2.55 | 0.130 | **2.13**; 1.38-3.14 | 1.72; 1.17-2.49 | <0.001 | 3.21; 2.1-5.45 | 2.72; 2.05-5.71 | 0.883 |
| Apolipoprotein A-I, g/L | 324+416+79 | 1.49±.25 | 1.46±.27 | 0.38 | **1.49**±.24 | 1.437±.27 | 0.034 | 1.51±.22 | 1.41±.24 | 0.088 |
| Apolipoprotein B, g/L | 324+416+79 | **1.066**±.25 | 0.974±.28 | 0.003 | **1.153**±.28 | 1.075±.24 | 0.03 | **1.17**±.296 | 1.00±.274 | 0.021 |
| C-reactive protein,¶ mg/L | 324+436+80 | 2.0; 1.0-3.5 | 2.0; 1.0-4.0 | 0.621 | 2.0; 1.0-4.0 | 2.0; 1.0-5.0 | 0.316 | 2.0; 1.0-4.2 | 3.0; 1.0-8.0 | 0.124 |
| Current; past smokers, % | 324+436+80 | 23.2; 22.7 | *24.6*; 23.9 | 0.90 | 23.5; 23.5 | 25.3; 19.5 | 0.65 | 12.2; 32.8 | 13.6; 27.7 | 0.68 |
| CHD prevalence, n,% | 288+379+74 | 26; 14.9 | 29; **25.7** | 0.023 | 57; 25.4 | 48; 31 | 0.24 | 15; 26.8 | 4; 22.2 | 0.70 |

¶Mann-Whitney U test was used for variables with skewed distribution. Total n denotes the total number of participants in the nondiabetic, 2 prediabetic, and diabetic groups, respectively. Numbers in boldface highlight significant difference and italics indicate borderline significant difference between 2 groups

5-R - Geographic regions of Turkey excluding Marmara and Central Anatolian regions; BP - blood pressure; CHD - coronary heart disease; DM - type-2 diabetes mellitus; F - female; HbA1c - glycated hemoglobin; HDL - high-density lipoprotein; HOMA - homeostatic model assessment; IFG - impaired fasting glucose; LDL - low-density lipoprotein; M - male; Marm-CA - Marmara and Central Anatolian regions; Ngly - normoglycemia

Continued ⟶

**Continued Table 3. Characteristics of nondiabetic, prediabetic, and diabetic participants with different glucose and glycated hemoglobin categories, stratified to 2 geographic regions (n=1167)**

| | | Marm-CA | 5-R | | Marm-CA | Diabetes 5-R | | Marm-CA | Diabetes 5-R | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No DM; A1c ≥**6.5** | No DM; A1c ≥**6.5** | | DM + A1c <**6.5** | DM + A1c <**6.5** | | DM + A1c>**6.49** | DM + A1c>**6.49** | |
| | **Total n** | **Mean±SD** | **Mean±SD** | ***P*** | **Mean±SD** | **Mean±SD** | ***P*** | **Mean±SD** | **Mean±SD** | ***P*** |
| | | n=37 | n=26 | | n=29 | n=52 | | n=108 | n=74 | |
| Sex, n, M/F | 163/163 | 22/15 | 11/15 | 0.89 | 9/20 | 23/29 | 0.24 | 58/50 | 40/34 | 0.96 |
| HbA1c, % | 63+81+182 | 6.77±.36 | 6.92±.56 | 0.18 | *6.02*±.29 | 5.88±.38 | 0.069 | 8.18± 1.4 | 8.38±1.74 | 0.16 |
| Fasting glucose, mg/dL | 63+81+182 | **108.5**±29 | 95.3±15 | 0.038 | **101.4**±25 | 113.4±25 | 0.042 | 174±69 | 171±64 | 0.37 |
| Age, years | 63+81+182 | 61±8 | 60.9±9.2 | 0.95 | 65.4±9.5 | 62±10 | 0.15 | 64.6±9.6 | 62.6±8.6 | 0.75 |
| Lipoprotein(a),¶ mg/dL | 55+76+164 | 7.33; 3.42-20.9 *2.95 | 16.3; 5.86-32.7 | 0.188 | 9.75; 2.23-23.2 | 10.8; 5.2-29.2 | 0.262 | 10.4; 5-22.5 | 13.2; 4.7-41.8 | 0.131 |
| Creatinine, mg/dL | 63+81+182 | 0.88±0.20 | 0.86±0.21 | 0.73 | 0.88±0.26 | 0.90±0.68 | 0.81 | 0.877±0.26 | 1.034±1.26 | 0.30 |
| Waist circumference, cm | 63+81+182 | 101±11 | 104±12 | 0.26 | **99.0**±11 | 105±12 | 0.022 | 106.5±12.5 | 108.5±11 | 0.64 |
| Systolic BP, mm Hg | 63+81+182 | 134±20 | 137±25 | 0.55 | 137±17 | 136.5±20 | 0.97 | 146±20 | 143±235 | 0.46 |
| Diastolic BP, mm Hg | 63+81+182 | *78.4*±10 | 85±15 | 0.057 | *79*.±10.6 | 82±15 | 0.32 | 81.7±10 | 83±14.5 | 0.44 |
| Total cholesterol, mg/dL | 63+81+182 | *213*±37 | 190±51 | 0.055 | 197±35 | 195±46 | 0.84 | 205±47 | 199±47 | 0.37 |
| LDL cholesterol, mg/dL | 63+79+175 | **134**±34 | 115±33.5 | 0.032 | 121±38 | 120±32 | 0.92 | 124±40 | 115±40 | 0.14 |
| HDL cholesterol mg/dL | 63+81+182 | 45±11 | 44±12 | 0.72 | 48±10 | 44.4±11.8 | 0.20 | 44.4±12.3 | 43.6±11.5 | 0.64 |
| F. triglycerides,¶ mg/dL | 62+81+182 | 162; 107-202 | 178; 105-221 | 0.722 | 137; 96-168 | 149; 104-233 | 0.261 | 158.5; 126-227 | 186; 127-248 | 0.368 |
| Fasting insulin, mIU/L | 60+81+170 | *11.93**1.75 | 9.32*2.00 | 0.14 | 12.74*2.19 | 10.12*1.80 | 0.12 | 12.4*2.24 | 13.4*2.00 | 0.28 |
| HOMA index,¶ | 60+81+167 | *2.89*; 2.17-4.39 *1.91 | 2.78; 1.11-3.64 | 0.095 | 2.53; 1.43-5.13 *2.54 | 2.76; 1.87-4.24 | 0.76 | 4.81; 2.74-8.0 | 2.30; 1.23-5.35 | 0.198 |
| Apolipoprotein A-I, g/L | 59+78+167 | 1.485±.21 | 1.39±.23 | 0.12 | **1.55**±.19 | 1.41±.21 | 0.005 | **1.49**±.28 | 1.385±.27 | 0.018 |
| Apolipoprotein B, g/L | 59+78+168 | *1.163*±.30 | 1.035±.22 | 0.076 | 1.06±.21 | 1.06±.32 | 0.98 | *1.065*±.27 | 1.065±.32 | 0.042 |
| C-reactive protein,¶ mg/L | 62+81+182 | 3.84; 1.29-8.60 | 2.24; 1.01-4.25 | 0.111 | 2.48; 1.21-4.1 | 2.52; 1.11-4.34 *3.14 | 0.875 | 2.50; 1.16-6.23 | 2.30; 1.23-5.35 | 0.738 |
| Current; past smokers, % | 63+81+181 | 40.5; 29.7 | 26.9; 23.1 | 0.26 | *6.9*; 24.1 | 26.9; 25 | 0.073 | 3.9; 33.3 | 12.3; 34.2 | 0.95 |
| CHD prevalence, n, % | 52+75+1650 | 7; 20.6 | 7; 38.9 | 0.16 | 9; 33.3 | 12; 25 | 0.44 | 42; 42 | 30; 46.2 | 0.95 |

¶Mann-Whitney U test was used for variables with skewed distribution. Total n denotes the total number of participants in the nondiabetic, 2 prediabetic, and diabetic groups, respectively. Numbers in boldface highlight significant difference and italics indicate borderline significant difference between 2 groups

5-R - Geographic regions of Turkey excluding Marmara and Central Anatolian regions; BP - blood pressure; CHD - coronary heart disease; DM - type-2 diabetes mellitus; F - female; HbA1c - glycated hemoglobin; HDL - high-density lipoprotein; HOMA - homeostatic model assessment; IFG - impaired fasting glucose; LDL - low-density lipoprotein; M - male; Marm-CA - Marmara and Central Anatolian regions; Ngly - normoglycemia

5-R group, and proved to be significant in prediabetic individuals having normoglycemia and HbA1c of 5.7–6.49% (median 11.0 vs. 15.0 mg/dL; p=0.026) (Table 3). Among all participants having HbA1c ≥5.7%, difference in log-transformed Lp(a) assays was of borderline significance in men (10.17x2.9 vs. 12.39x3.16 mg/dL; p=0.091), but significant in women (11.05x2.98 vs. 15.23x2.84 mg/dL; p=0.005) (Fig. 1).

Both serum apoB and LDL-cholesterol levels were higher (uniformly p<0.001) in residents of Marm-CA than 5-R group in combined gender and each sex of non-diabetic sample (Fig. 1 and Table 3). Significantly higher values of apoB (112.5 vs. 103 mg/dL; p<0.001), LDL-cholesterol (134 vs. 121 mg/dL; p<0.001), fasting insulin, and HOMA index were observed in Marm-CA participants. Significantly or borderline significantly higher apoA-I was seen in prediabetes and diabetes groups. Significantly higher systolic BP and creatinine levels were found in prediabetes with normoglycemia. HOMA score was one-quarter higher (p<0.001) in Marm-CA participants in large group of normoglycemia combined with elevated HbA1c.

## Discussion

In this cross-sectional study of middle-aged and elderly Turks stratified in 2 groups according to residence in geographical region, key findings were as follows: 1) Except for individuals with discordant glucose/HbA1c for diabetes, HOMA score was uniformly inversely associated with Lp(a) in each sex, corroborating previous reports (14) and own findings (15). 2) Circulating Lp(a) was overall 23% lower in residents of Marm-CA than 5-R group, with the exception of normoglycemia, where difference was marginal. 3) ApoB/total cholesterol, HOMA index score, and apoA-I were significantly higher than in 5-R group in the non-diabetic sample. 4) Prevalence of prediabetes with normoglycemia was remarkably high (37.4%), higher than normoglycemia proper.

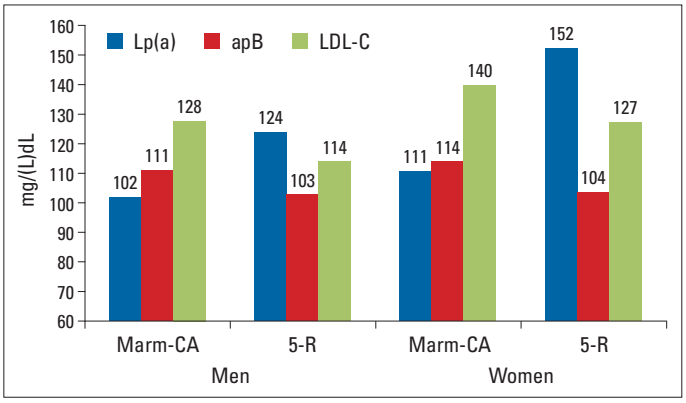


**Figure 1.** Comparison of mean levels of serum lipoprotein (a) (mg/L), apolipoprotein B and low-density lipoprotein cholesterol (LDL-C) (mg/dL) in men and women residing in Marmara-Central Anatolia (Marm-CA) regions compared to the remaining 5 regions (5-R) of Turkey. Participants having HbA1c ≥5.7% alone were considered for Lp(a) (n=770), non-diabetic individuals for apoB/LDL-C (n=867). Highly significant difference (p uniformly <0.001) exists, such that -- compared to 5-R residents -- Marm-CA participants have lower Lp(a), but higher apoB and LDL-C levels in each sex. This constellation is consistent with aggregation of Lp(a) protein alone (not including apoB) in participants of Marm-CA in prediabetic status

Collectively, these findings strongly supported the concept of operation of autoimmune processes, primarily induced by Lp(a), and modulated by both gender and residential area. Findings also suggested involvement in autoimmune complex primarily of Lp(a) protein alone, without apoB concomitantly taking part.

### Prevalence of prediabetes

Prevalence of prediabetes in TURDEP-II survey of 26,499 persons was 34.3% in women and 26.8% in men, of which impaired fasting glucose alone constituted 14.7%, IGT 7.9%, and both an 8.2% share in middle-aged adults (9). These data were based on routine application of oral GTT and use of World Health Organization criteria to define prediabetes. Our finding of 43.3% overall prediabetes prevalence is one-quarter higher than the survey figure cited. This may be ascribed to two factors: a) population sample 15 years older, b) portion of prediabetic individuals presumably had diabetes with reduced HbA1c, which may mean involvement of HbA1c in autoimmune process actually in diabetic status (not uncovered due to lack of GT testing). Huge prevalence of prediabetes (and diabetes) in this population highlights the enormous magnitude of risk of chronic diseases and problems related to their prevention.

Long-term glycemic variability was evaluated in meta-analysis comprising 13 studies on HbA1c variability in type-2 diabetes. Higher variability was associated with significantly higher risk of renal disease, macrovascular events, cardiovascular disease, and mortality, independent of HbA1c level (16). Though there was inconsistency in definition of HbA1c variability, it is likely that it may represent transient changes in autoimmune activation-inducing variability.

### Central role of Lp(a)-aggregation in insulin resistance

An important finding was significantly *inverse* (not positive) independent association between Lp(a) and HOMA index in total prediabetic and diabetic sample. This paradoxical observation cannot be a true finding and corroborates our hypothesis of aggregation-induced autoimmune activation rendering escape of Lp(a) from immunoassay (7). Hong et al. (17) suggested a critical role of serum $\gamma$ –glutamyltransferase (GGT) in pathogenesis of impaired fasting glucose, based on finding an association with body mass index (BMI) mainly among persons with the 2 highest GGT tertiles, in agreement with our demonstration that elevated serum GGT confers risk of hypertension, metabolic syndrome, and type-2 diabetes, additively to BMI (18). In the combined sample, apoB and total cholesterol levels were variably associated with serum Lp(a), suggesting that aggregation of Lp(a) was at times -- but not uniformly -- accompanied by aggregation of apoB.

Our observation that inverse association between HOMA index and Lp(a) existed in females, even in normoglycemia group, but in males only from prediabetic status onwards, supports concept that pro-inflammatory state and autoimmune activation is more pronounced and early-appearing in women.

**Table 4. Comparison of relevant metabolic variables between 2 regional groups**

| | **Marmara-Central Anatolia group (vs. 5-region group)** | |
|---|---|---|
| | **Rule** | **Exception** |
| Serum lipoprotein(a) | Uniformly lower (by 23%), significantly so in discordant pre-diabetes (40% of sample) | Marginally lower in normoglycemia |
| Serum apoB-containing lipoproteins | Significantly higher | Diabetes |
| Apolipoprotein A-I | Significantly higher | Normoglycemia (28% of sample) |
| HOMA index | Significantly higher | Concordant pre-diabetes |
| Serum creatinine | Significantly higher in discordant pre-diabetes | |
| Waist circumference | Significantly lower in DM with low A1c and discordant pre-diabetes | |
| Systolic blood pressure | Significantly higher in discordant pre-diabetes | |

Discordant prediabetes signifies predominant group with HbA1c 5.7-6.49% accompanied by normoglycemia; concordant prediabetes defined as HbA1c 5.7-6.49% accompanied by impaired fasting glucose. Apo - apolipoprotein; DM - diabetes mellitus; HbA1c - glycated hemoglobin; HOMA - homeostatic model assessment

**Summary of regional distinctions in metabolic variables**

Table 4 is a summary of salient differences across members of the 2 geographic groups. Foremost, is 23% significantly lower mean Lp(a) concentration in non-normoglycemic Marm-CA sample. This was accompanied by generally significantly higher HOMA index score, serum apoB, total cholesterol, and apoA-I levels in residents of Marm-CA. This constellation in residents of Marm-CA is consistent with concept of obesity-mediated autoimmune activation involving Lp(a) (rendering apparently "lower" levels). HOMA index, apoB, and total cholesterol behave in discordantly this process with Lp(a). Autoimmune process comprising Lp(a) in prediabetes and diabetes thus induces increase in insulin resistance and is not linked to complex formation involving apoB. Reasons for regional differences found remain to be elucidated in future studies, but may lie in genetic characteristics related to ethnicity. It is known that racial differences exist in terms of higher serum Lp(a) values in black Americans (19) (not much susceptible to autoimmune activation), compared to white populations and to Native Americans with lower serum Lp(a) values and high susceptibility to diabetes.

We previously provided epidemiological evidence that "reduced" Lp(a) levels predicted NOD (10) and (especially in women) hypertriglyceridemic-waist phenotype, which in turn strongly predicted type-2 diabetes (20). Low Lp(a) levels were predictor of development of diabetes also in the Women's Health Study (21) and the European Prospective Investigation into Cancer-Norfolk study (22).

Implications: Recent criteria for definition of prediabetes using HbA1c shed light on several problems for Turkish adults, on whom oral GTT is uncommonly performed. First, current findings allow estimation of over 10 million adults with prevalent prediabetes, a huge number. A similar trend has been observed in other populations, notably in the USA and Korea (23, 24). One-third lower prevalence of undiagnosed diabetes was found with use of HbA1c than with fasting glucose or oral GTT in the National Health and Nutrition Examination Survey (23), suggesting a shift in means to identify prediabetes in the absence of post-challenge.

Second, a sizeable portion of our prediabetic participants may actually represent cases of NOD with fasting normoglycemia and "reduced" assays of HbA1c consequent to concomitant autoimmune process. This is supported by TURDEP-II data reporting that HbA1c could recognize only 40% of NOD cases, whereas the 2 glucose tests did so in 56% and 65% of cases (9). Furthermore, mean HbA1c in NOD measured with fasting glucose was lower, and even lower than proposed cut-off levels, when oral GTT was used (9). In line with this, 43% of subjects with diabetes defined by the 2 glucose and HbA1c criteria in a large population-based study of Chinese adults displayed HbA1c <6.5% (25), suggesting that these might have been largely classified as prediabetes, had oral GTT values not been available. It was demonstrated in study with 19 European cohorts that among individuals with both fasting and 2-hour plasma glucose within the normoglycemic range, those with high 2-hour glucose harbor increased risk of insulin resistance and cardiovascular mortality (26).

Third, residents of the Marm-CA regions are more prone than those in 5-R group to apoA-I dysfunction, insulin resistance, and autoimmune activation involving Lp(a) protein, a process which may require specific approach in identification, prevention, and management, shown herein to be partly independent of adiposity. Finally, inference may be drawn that involvement of Lp(a) in autoimmune activity with low assays is a basic mechanism in prediabetic and diabetic Marm-CA residents.

## Study limitations

The absence of use of oral GTT in the current study to define prediabetes and diabetes is a major limitation; however, it is used in few epidemiological studies due to lack of practicality. Prediabetes is defined in most patients in clinical practice without administering oral GTT as well. Though sample size was somewhat limited, it was larger than other studies on the topic. Availability of data pertaining to anthropometry, insulin resistance, lipoproteins, apolipoproteins, and multivariable linear analysis of potential covariates of Lp(a) were strengths permitting elucidation of the latter's role in prediabetes and diabetes, and detection of nuances in residents of different regional groups.

## Conclusions

Hallmark of overall prediabetic and diabetic glycemia/HbA1c categories seems to be an independent inverse association between Lp(a) protein (yet not of apoB) and HOMA score, this being so primarily in residents of Marm-CA regions. ApoB-containing lipoproteins were inversely related to Lp(a) assays among non-diabetic residents of Marm-CA regions. Collectively, these observations strongly support the notion that prediabetic status is modulated by both sex and region of residence in Turkey.

**Funding statement:** This work was supported by the automotive company TOFAŞ, Istanbul, Turkey.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – A.O.; Design – A.O.; Supervision – H.Y.; Funding – A.O., H.Y.; Materials – A.K., F.Ö.K.; Data collection &/or processing – Y.K., S.K., F.Ö.K.; Analysis and/or interpretation – G.C., A.K., H.Y.; Literature review – G.C., Y.K., A.K.; Writing – A.O.; Critical review – All authors.

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