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Original Article

Low-density lipoprotein cholesterol and metabolic syndrome in an Iranian high-risk population

Mohsen Janghorbani [a,b,*], Masoud Amini [a]

[a] Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Aim: Currently, one study support the hypothesis that low-density lipoprotein cholesterol (LDLC) is associated with metabolic syndrome (MetS) independent of pre-existing components of MetS. In this study we further evaluated the ability of the LDLC to predict prevalence and incidence of MetS in an Iranian high-risk population.

Materials and methods: We analyzed baseline ($n = 3396$) and 7-year follow-up data ($n = 865$) in first-degree relatives (FDR) of consecutive patients with type 2 diabetes 30–70 years old. We used logistic regression to estimate the odds ratio (OR) for prevalent MetS, and Cox proportional hazard models to estimate hazard ratio (HR) for incident MetS across quartiles of LDLC and plotted a receiver operating characteristic (ROC) curve to assess discrimination.

Results: The highest quartile of LDLC compared with the lowest quartile was associated with MetS in both the prevalent (OR 1.39, 95% CI 1.13, 1.70) and incident in unadjusted models (HR 1.24, 95% CI 1.03, 1.49). Adjusted for age, gender and pre-existing components of MetS attenuated association for both prevalent (OR 1.15, 95% CI 0.83, 1.59) and incident MetS (HR 1.13, 95% CI 0.93, 1.38). The area under the ROC was 52.8% (95% CI 50.7, 55.0) for prevalent and 51.8% (95% CI 47.2, 56.3) for incident MetS.

Conclusion: The results of this study highlight that LDLC level is not a robust predictor of MetS, independent of age, gender or the pre-existing components of MetS, in high-risk individuals in Iran.

1. Introduction

Metabolic syndrome (MetS), a cluster of metabolic and cardiovascular risk factors including obesity, dyslipidemia, hypertension, and insulin resistance leads to increased risk of cardiovascular diseases and type 2 diabetes [1]. It is estimated that around a quarter of the world's adult population have MetS [2,3] and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome [4]. People with MetS have a fivefold greater risk of developing type 2 diabetes [5]. Thus, having MetS means having a significantly reduced quality and quantity of life. The cause of the syndrome remains obscure but the pathophysiology seems to be largely attributable to insulin resistance, excessive flux of fatty acids, endothelial dysfunction, and a chronic proinflammatory state [1]. There is no specific treatment for MetS. Therapeutics includes lifestyle changes and pharmaceutical agents, but prevention would be preferred.

High low-density lipoprotein cholesterol (LDLC) is an established risk factor for cardiovascular disease [6] but is not included in the components of MetS, although both conditions are associated with adiposity [7].

Although there are not many supporting evidences for the association between LDLC and risk of MetS [8,9], the role of LDLC as a risk factor for MetS remains unsettled: one study reported no association [9], while a recent study performed in Japan revealed that LDLC was associated with MetS [8] and postulates that the relationship between LDLC and MetS could be attributable to

Abbreviations: BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; FPG, fasting plasma glucose; FDR, first-degree relatives; HbA1c, glycosylated hemoglobin; HDLC, high density lipoprotein cholesterol; HC, hip circumference; HR, hazard ratio; IDPS, Isfahan Diabetes Prevention Study; LDLC, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic curve; SD, standard deviation; WC, aist circumference; WHR, waist–hip ratio.

* Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel.: +98 313 233 4893; fax: +98 313 668 2509.
E-mail address: janghorbani@hlth.mui.ac.ir (M. Janghorbani).

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endothelial dysfunction and vascular inflammation, independent of adiposity or the pre-existing components of MetS. However, while Oda [8] referred to LDLC as a predictor of MetS, it is likely that genetic factors also influence LDLC and MetS. LDLC and MetS components such as adiposity are determined by genetic and early environmental influences. The first-degree relatives (FDR) of patients with type 2 diabetes which have a genetic basis are at high risk of MetS and might be more appropriate for testing this hypothesis.

In order to fill some of these gaps, the objective of this cross-sectional and longitudinal study, therefore, was to evaluate the ability of the LDLC to predict the prevalence and incidence of MetS in an Iranian high-risk population. We hypothesized that LDLC is not associated with the incidence and prevalence of MetS.

2. Subjects and methods

2.1. Data collection

This study was conducted within the framework of the Isfahan Diabetes Prevention Study (IDPS), an ongoing cohort in central Iran to assess the various potential risk factors for diabetes in subjects with family history of type 2 diabetes (one of the main risk factors for diabetes). The recruitment methods and examination procedures of the IDPS have been described before [10]. Our study sample at baseline comprised 3396 (889 men and 2507 women) first-degree relatives (FDR) of consecutive patients with type 2 diabetes. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted between the years 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed laboratory tests including a standard 75 g 2-h oral glucose tolerance test (OGTT), a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to Standard of Medical Care in Diabetes [11] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually. Tenets of the current version of the Declaration of Helsinki were followed, institutional ethical committee approval was granted, and an informed consent form was signed by each participant.

2.2. Follow-up and ascertainment of MetS

Cases of MetS were identified according to the joint interim statement criteria released in 2009 [12]. It was considered present when at least three of the following characteristics were observed: central obesity, defined using ethnic-specific cut points of waist (waist circumference $\geq$ 89 cm in men and $\geq$91 cm in women [13]); triglycerides $\geq$150 mg/dl; HDL $<$ 40 mg/dl in men and $<$50 mg/dl in women; blood pressure (BP) $\geq$ 130/85 mmHg or on antihypertensive medication, or raised plasma glucose, defined as fasting plasma glucose (FPG) $\geq$ 100 mg/dl.

Participants with type 2 diabetes mellitus were excluded in longitudinal study because there is controversy whether the diagnosis of MetS convey additional meaning in individuals with type 2 diabetes who should already be aggressively treated due to high cardiovascular risk. Other than these, individuals who already had MetS, or subjects with history of taking antidiabetic, or lipid-lowering agents were also excluded for longitudinal study. Among 3396 persons who participated at baseline, 1472 subjects were excluded because of diagnosis of type 1 and type 2 diabetes or MetS or with history of taking antidiabetic or lipid-lowering agents at baseline and 1059 have no follow-up, leaving 865 participants with a mean age 42.0 (6.4) (range 30–70) years for the longitudinal analysis, all of whom had at least one subsequent review during a mean (standard deviation [SD]) follow-up period of 7.0 (1.6) (range 2–9) years. Attendees at the follow-up visit did not differ significantly from non-attendees regarding most baseline characteristics: height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and levels of HbA1c, LDLC, triglyceride, systolic and diastolic blood pressure (BP) and obesity. However, non-attendees had slightly lower fasting plasma glucose (FPG) (98.8 mg/dl versus 105.4 mg/dl, $P < 0.001$), plasma glucose (PG) at 30 min (145.8 mg/dl versus 152.5 mg/dl, $P < 0.001$), 60 min (151.1 mg/dl versus 161.3 mg/dl, $P < 0.001$), and 120 min (120.8 mg/dl versus 132.2 mg/dl, $P < 0.001$) and cholesterol (196.4 mg/dl versus 200.1 mg/dl, $P < 0.01$), high-density lipoprotein cholesterol (HDLC) (45.0 mg/dl versus 46.2 mg/dl, $P < 0.01$) and were slightly older (43.6 year versus 43.1 year, $P < 0.05$).

2.3. Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglycerides and BP, family and personal medical history was collected at baseline and through follow-ups. The same methodology was used for baseline and follow-up studies. The participants included siblings and children of patients with type 2 diabetes. Participants reported to clinics in the morning after an overnight fast. They were asked to abstain from vigorous exercise in the evening, and in the morning of their visit. Smokers were encouraged to abstain from smoking in the morning of the investigations. First, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothing and without shoes, height, weight, WC and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, WC, and HC were measured to the nearest 0.5 cm with a measuring tape. The waist was measured midway between the lower rib margin and the iliac-crest at the end of gentle expiration in the standing position. Hip circumference was measured over the greater trochanters directly over the underwear. The body mass index (BMI) was calculated as the weight in kg divided by square of the height in meters. Resting BP was measured after the participants had been seated for 10 min with a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. FPG was measured with the glucose oxidase method. Participants with FPG $\geq$ 200 mg/dl or pharmacological treatment were considered as persons with diabetes. If FPG was $\geq$126 mg/dl and $<$200 mg/dl, a second FPG was measured on another day. If the second FPG was also $\geq$126 mg/dl, participants were considered as persons with diabetes. Those with FPG $<$ 126 mg/dl underwent a standard OGTT (75 g glucose 2-h) at baseline and the follow-up visits. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration. Plasma samples were centrifuged and analyzed the same day. Impaired glucose tolerance (IGT) was defined as FPG $<$ 126 mg/dl, but the 2hPG concentration $\geq$ 140 and $<$200 mg/dl. If the FPG was in the range of 100–126 mg/dl and the 2hPG was $<$140 mg/dl, it was considered as impaired fasting glucose (IFG); whereas, if the FPG was below 100 mg/dl and the 2hPG $<$ 140 mg/dl, it was considered a sign of normal glucose tolerance [14].

Glycosylated hemoglobin (HbA1c) (measured by ion-exchange chromatography), total cholesterol, triglycerides, HDLC, LDLC were recorded. The LDLC levels were calculated with the Friedewald Equation [15] provided total triglycerides did not exceed 400 mg/dl. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method.