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Original article

Homocysteine and metabolic syndrome: From clustering to additional utility in prediction of coronary heart disease

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ABSTRACT

Background: The association between homocysteine (Hcy) and metabolic syndrome (MetS)-related disorders remains to be unveiled. First, the role of Hcy–MetS interaction in prediction of coronary heart disease (CHD) was assessed. Next, we investigated whether serum Hcy improves CHD risk-prediction beyond MetS and traditional risk factors (TRFs).
Design: A prospective study of 5893 community-dwelling participants (two sub-cohorts, 3286 diabetic and 2607 non-diabetic; ~8.5 years of follow-up).
Methods: Clustering of Hcy with MetS components was assessed using exploratory factor-analysis. Cox regression hazard ratio (HR) was used to predict CHD using Hcy level and MetS status. Baseline model included MetS and TRFs. Addition of Hcy and hyper-homocysteinemia (HHcy) to the baseline model was evaluated in two separate models.
Results: Hcy was correlated with MetS components, especially with systolic blood pressure. The factor linking MetS to CHD is the factor through which Hcy is linked to MetS. HHcy and MetS interacted as risk factors for CHD.
Conclusion: Hcy adds to the value of MetS and TRFs for CHD risk-prediction by reclassifying around 47.3–49.0% of the overall and 21.6–28.1% of the intermediate-risk population.

Introduction

Coronary heart disease (CHD) is among the leading causes of mortality worldwide [1]. Traditional risk factors (TRFs) contributing to a CHD event have been recognized [2]. Preventive strategies altering these modifiable risk factors can play a major role in controlling the incident cases [3]. Prediction of susceptible or at-risk subjects is the prior step to any preventive program. Scoring systems predicting the risk of CHD in prospective time frames have been designed [4,5]. Despite predictive strategies, a great number of cases remain unpredicted [3]. Moreover, among the at-risk stratified population, a majority fall into the intermediate-risk group, for whom the clinical decision remains controversial [6]. Novel strategies are mandated to unveil indeterminate cases and to enhance the precision of CHD risk-prediction models that rely on conventional risk factors [7].

Novel markers have been introduced in recent decades which can either anticipate or be associated with an incident CHD event [8]. C-reactive protein, B-type natriuretic peptide, lipoprotein (a), and homocysteine (Hcy) are to name a few [9]. Hcy is a non-essential amino acid that is known as a marker of endothelial injury [10]. Hyper-homocysteinemia (HHcy) is regarded as a risk factor for development of atherosclerotic vascular injuries including CHD [11].

Metabolic syndrome (MetS) is an entity that clusters a number of metabolic abnormalities, including abdominal obesity, impaired glucose metabolism, dyslipidemia, and hypertension [12]. MetS and its components have been strongly correlated to CHD and other thrombotic events [13]. Control of MetS can be the mainstay of preventive programs [14].

MetS components and Hcy have both been subjects of studies focused on CHD prevention [14–16]. Nonetheless, the existing relationship between them is a contentious issue in the literature [17–19]. Debates on whether they share a common linkage or not persists [17]. It seems appealing to indicate if Hcy is part of

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MetS-related disorders and if MetS components and Hcy interact in an incident CHD event.

The purpose of this study was to investigate the association between Hcy and MetS components, and to reveal their clustering pattern. Next, we assessed whether Hcy improves CHD risk prediction beyond MetS and TRFs. Finally, the extent by which Hcy measurement could assist in the prediction and prevention of a CHD event, beyond the capability of MetS and the TRFs, was estimated.

Materials and methods

Study population

This study uses the data from an Iranian prospective open cohort. Organized subject recruitment for research purposes started in 2005. Strategic preparations of the structure were performed in the years before 2005. The primary aim of the study was to investigate the natural history and the outcome of MetS and its correlates. Participants were at least 15 years old (by the time of inquiry) and were randomly selected with the aid of four local primary health surveillance centers located in the center, east, west, and south of Tehran. Details on the recruitments and extrapolation of the data to the Tehran general population are as previously described [12]. Multiple cross-sectional studies revealed characteristics of the study population from 2006 to 2012 [12,20–22]. The original cohort consists of two sub-cohorts of healthy, community dwelling participants with and without diabetes. The diabetic sub-cohort consisted of subjects who were newly diagnosed with diabetes in their entry workup. All subjects were investigated prior to their inclusion and those with recognized benign or malignant pathologies of internal organs were not included. Details on examinations and included individuals were as previously described [12]. Overall, 5893 subjects with available follow-ups until fall 2013 were included in the study. Missing values accounted for 3.4% of the values. Model-based expectation maximization method was used in handling the missing data. Hcy's main effect was confirmed to be similar to the obtained results from complete case analysis and multiple imputations. The study protocol was approved by the institutional review board of the Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences. All participants provided informed consent on their entry.

Measurements and laboratory tests

Individuals' demographics including age, gender, and medications were recorded by history taking. Weights and heights were measured in light clothing and without shoes. Waist circumference was measured in the middle point of iliac crest and rib cage. After resting in supine position for 10 min, systolic and diastolic blood pressures were measured twice with a 15-min interval. The average of these measurements was used for the analysis. After 12 h overnight fasting, blood samples were collected for laboratory testing. Fasting plasma glucose (FPG) and 2-h post-prandial plasma glucose levels were assayed by glucose oxidase method. Lipid profile including total cholesterol, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by direct enzymatic method (Parsazmun, Karaj, Iran). Fasting insulin levels were assessed by radioimmunoassay (the antibody had no cross-reactivity with pro-insulin and C-peptide; Immunotech, Prague, Czech Republic). C-peptide was measured by radioimmunoassay (Immunotech), and serum creatinine level was determined by the Jaffe method (Parsazmun). Hemoglobin A_{1c} was determined using high performance liquid chromatography (HPLC; DS5 Pink kit; Drew, Marseille, France). Hcy level was measured using HPLC by our designated laboratory.

Definitions and outcome measures

For the current study, first CHD was set as the primary outcome; definitions and ascertainments were done according to established protocols [23] and our previous investigations [20,22]. CHD was defined as evident episodes of myocardial infarction, angina pectoris, coronary insufficiency, or CHD death. All events were adjudicated by our center's physicians. All subjects were scheduled to be visited every 3 months. Trained research assistants completed the follow-up visits in case of missed visits. Date of each event was recorded. In non-event cases, date of the last visit was recorded. Data updates are performed annually. Cigarette smoking was defined by self-reported use of cigarettes in the year preceding the entry. Diabetes was defined according to the American Diabetes Association guidelines [24]. Diabetic subjects began initial treatment with metformin, glibenclamide, or both. Subjects requiring use of insulin for glycemic control at the time of diagnosis as well as subjects diagnosed with type I diabetes mellitus or pancreatitis-related diabetes, were not included in the cohort. Body mass index (BMI) was computed using the weight (kg)/height^2 (m) equation. The homeostasis model assessment-insulin resistance (HOMA-IR) index indicating insulin resistance was estimated as FPG (mg/dL) × fasting insulin (U/L)/405. According to the nationally modified version of the International Diabetes Federation criteria [12], patients with abdominal obesity (waist circumference ≥90 cm in both genders) along with any two or more of the following were considered to have MetS: FPG ≥ 100 mg/dL or previously diagnosed diabetes; elevated blood pressure [systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg]; TG ≥ 150 mg/dL; low HDL-C levels (<50 mg/dL in females and <40 mg/dL in males).

Statistical analysis

One-way ANOVA was used to describe the baseline characteristics of the study population. A *p*-value for trend was derived to compare each variable in consecutive Hcy levels (<10 μM/L, 10–15 μM/L, and ≥15 μM/L).

Clustering of Hcy with MetS components

Correlation of MetS components with Hcy was assessed using Pearson bivariate correlation analysis. An exploratory factor analysis was performed to extract the principal components of MetS, with and without addition of Hcy. The choice of MetS components was based on a number of previous studies [12,25]. Waist circumference, HOMA-IR, TG, HDL-C, and SBP were chosen as MetS components. Factors with an eigenvalue ≥ 1 were included as principal components. Components with a factor loading of >0.40 were considered to be significantly enrolled on the corresponding factor. A Varimax rotation was applied. Receiver operating characteristic (ROC) curve demonstrated the prediction of CHD by each factor. Area under the curve (AUC) was used to compare the derived factors.

Prediction and reclassification of CHD risk

Analysis of the CHD-free survival was performed using Cox regression analysis. The assumptions of proportionality were tested using Shoenfeld residuals. TRFs other than MetS components were considered as possible confounders including age, sex, BMI, smoking, LDL-C, family history of CHD, and therapeutic interventions [2]. Therapeutic interventions including the use of lipid-lowering agents were coded as nominal variables, similar to the Framingham risk score for prediction of 30-year risk of cardiovascular disease [26]. The baseline model was considered to include MetS and TRFs for CHD. Afterwards, Hcy and HHcy were added in two separate models, to investigate whether they add a significant