Heart, Lung and Circulation (2016) xx, 1–6
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.11.023

ORIGINAL ARTICLE

Interaction Between Vitamin D and Lipoprotein (a) on the Presence and Extent of Coronary Heart Disease

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Received 29 July 2016; received in revised form 13 October 2016; accepted 20 November 2016; online published-ahead-of-print xxx

Background Given both lipoprotein (Lp)(a) and vitamin D have been found to be associated with coronary heart disease (CHD) risk and a biochemical link between vitamin D and cholesterol on atherosclerosis has been proposed, we hypothesised there could exist an interaction between Lp(a) and vitamin D on the severity of CHD.

Methods Lp(a) and 25-OH vitamin D were measured in the plasma of 348 consecutive patients (mean age 62.4±10.5 years; 56.3% male) undergoing coronary angiography at our Heart Center. A multivariate logistic regression model was used to estimate the odds ratios (ORs) of CHD.

Results Of these patients, CHD was identified in 211 (60.6%). A multivariable logistic regression model showed multivariable-adjusted ORs (95% CI) of CHD for patients with Lp(a) ≧30 mg/dl and vitamin D <10 ng/ml, Lp(a) <30 mg/dl and vitamin D <10 ng/ml, and Lp(a) ≧30 mg/dl and vitamin D ≧10 ng/ml were 4.62 (2.04–10.46), 1.79 (1.00–3.17), and 1.70 (0.88–3.31), respectively, compared with those with Lp(a) <30 mg/dl and vitamin D ≧10 ng/ml; the multivariable-adjusted ORs of a higher Gensini Score for the above three corresponding groups were 3.48 (1.84–6.60), 1.59 (0.96–2.65), and 1.55 (0.86–2.79), respectively. The interaction term between Lp(a) and vitamin D in each of the above two models was significant (p=0.004 and p=0.005, respectively).

Conclusions Among patients undergoing coronary angiography, there existed an interaction between Lp(a) and vitamin D on the severity of CHD. Future cohort studies are warranted to confirm this finding.

Keywords Vitamin D • Lipoprotein (a) • Coronary heart disease • Coronary angiography • Interaction

Introduction

Q3 Although impressive progress has been made in medical and interventional therapeutic modalities, coronary heart disease (CHD) continues to be one of the leading causes of death in adults worldwide[1,2]. Given that traditional risk factors alone cannot explain the entire risk for CHD events, there have been significant efforts to identify other (novel) risk factors in order to improve global risk assessment for CHD[3]. Of the novel risk factors, Lp(a) and 25-OH vitamin D have been clinically linked to CHD risks by a large body of studies [4–9].

Both elevated Lp(a) and vitamin D deficiency appear to increase CHD risk even more in the presence of other risk factors[10–13]. One recent animal study revealed a biochemical link between vitamin D and cholesterol on atherosclerosis [14]. Thus, we hypothesised that a clinically relevant interaction between Lp(a) and vitamin D on CHD risk might exist.

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Please cite this article in press as: Li K, et al. Interaction Between Vitamin D and Lipoprotein (a) on the Presence and Extent of Coronary Heart Disease. Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2016.11.023

Methods

Study Population

We consecutively recruited 348 patients undergoing coronary angiography at the Heart Center of Chaoyang Hospital Affiliated to Capital Medical University between the period of September 2014 and May 2015. Relevant current diagnoses, co-morbidities, smoking habits and results of laboratory tests were identified from inpatients' medical files.

The inclusion and exclusion criteria have been reported in detail previously[15]. Briefly, we included patients who were suspected of suffering from CHD based on their typically paroxysmal symptoms of chest discomfort and/or evidence of ischaemia by a noninvasive test, such as a dynamic change of electrocardiogram or myocardial enzymes. We excluded the patients who suffered from severe liver or kidney disease, acute or chronic inflammation, or malignancy. Patients who were taking vitamin D at admission, or refused to give an informed consent were also ruled out.

Blood pressure was measured after resting at least 10 minutes, after admission by nurses. Measurements were performed twice with 10-minute intervals and averaged. Hypertension was defined as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more (or both), or current treatment for hypertension. Diabetes was defined as a fasting glucose of >7 mmol/L or random glucose of >11 mmol/L at any time within one month of their angiogram, or if a patient was on either oral hypoglycaemic agents or insulin. The study was approved by the ethics committee at the Chaoyang Hospital and all patients provided written informed consent.

Angiographic Analysis

The coronary angiography was performed by experienced interventional cardiologists. The detailed method of performing angiographic analysis has also been reported previously[15]. Angiographic CHD was defined as greater than 50% diameter stenosis in any of the major epicardial coronary arteries or major branches. Given that the Gensini score system is the most widely used system to quantify angiographic CHD burden according to the literature [16], we also used it for the assessment of severity and extent of CHD in the present study[17,18]. Gensini score was calculated by allocating a severity score to each coronary stenosis based on the location and degree of luminal narrowing[18].

Routine Laboratory Examinations

Detailed methods of taking blood have been reported previously[15]. Fasting plasma glucose (FPG) was measured using glucose oxidase method. Direct enzymatic methods were used to determine total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and Lp(a) cholesterol. Serum 25-OH vitamin D was measured using the enzyme-linked immunosorbent assay (ELISA) method.

Sample Size

To ensure that the regression coefficients of the model were estimated with adequate precision, it would be best to enrol 20 patients with CHD per coefficient estimated by the model. In this investigation, the number of about 180 cases of CHD patients was sufficient to perform adjustment in the multivariable models, which included nine pre-specified variables.

Statistical Analysis

Descriptive statistics were shown as mean ± standard deviation or median (interquartile range) for continuous variables, and count variables were shown as percentage (%). Given that a value of 25-OH vitamin D <10 ng/ml was considered as severe hypovitaminosis D[8,19] and Lp(a) ≧ 30 mg/dl was treated as abnormal Lp(a)[20], we categorised our patients into four subgroups as follows: Lp(a) <30 mg/dl with vitamin D ≧10 ng/ml; Lp(a) <30 mg/dl with vitamin D <10 ng/ml; Lp(a) ≧ 30 mg/dl with vitamin D ≧10 ng/ml; and Lp(a) ≧30 mg/dl with vitamin D <10 ng/ml. Baseline characteristics were compared across the four subgroups using Mann-Whitney, Chi square test or one-way ANOVA. Considering both Gensini score and its transformation did not follow normal distribution, we divided it into tertiles, i.e. <6, 6–28, and ≥28, and used an ordered logistic regression model with the tertiles as a dependent variable to estimate ORs of the extent of CHD. We used a multivariable logistic regression model to estimate the presence of CHD. We first explored the independent associations of severe hypovitaminosis D and abnormal Lp(a) with the presence and extent of CHD, then treated the four subgroups as a dummy variable to assess the combined role of severe hypovitaminosis D and abnormal Lp(a) on the presence and extent of CHD. The models were first adjusted for age and sex, and further adjusted for smoking, hypertension, diabetes, systolic blood pressure and total cholesterol. We also set a multiplicative interaction term of Lp(a) and 25-OH vitamin D in a logistic regression model and tested its effect on the probability of CHD, independent of Lp(a), 25-OH vitamin D and other confounding factors. All p values were two-tailed, and a significance of 0.05 was used. All statistical analyses were conducted using STATA statistical software (StataCorp LP, College Station, Texas, USA).

Results

Of the total 348 patients, 56.3% were male and the mean age was 62.4±10.5 years (range 28–86, median 62). Coronary heart disease was identified in 211 patients (60.6%). Mean vitamin D and Lp(a) levels of these patients (median (interquartile range)) were 10.5 (7.6, 14.9) ng/ml and 20.9 (13.9, 36.9), respectively. Out of these 348 patients, there were 161 (46.3%) cases with severe hypovitaminosis D, i.e. 25-OH vitamin D <10 ng/ml, and 113 (32.5%) cases with abnormal Lp(a) (Lp(a) ≧ 30 mg/dl).

Table 1 shows baseline characteristics of the study population across the four subgroups. Compared with subgroups

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