Clinica Chimica Acta 484 (2018) 232–236

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Establishing age and sex dependent upper reference limits for the plasma lipoprotein (a) in a Chinese health check-up population and according to its relative risk of primary myocardial infarction

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ARTICLE INFO

Keywords:
Lipoprotein (a)
Chinese Han ethnicity
Cut-off values
Coronary artery disease
Risk factors

ABSTRACT

Background: Though lipoprotein (a) (Lp (a)) has been considered as a risk factor for coronary artery disease, there is a lack of cutoff values of Lp (a) for Chinese Han ethnicity.
Methods: We included 1 population for health check-ups. Lp (a) percentile distributions were analyzed and its cutoff for Chinese Han ethnicity was also proposed according to the its relative risk of myocardial infarction.
Results: Lp (a) distributions differed between sexes, and were highly skewed towards low concentrations with a long tail towards the highest ones. The relative risks of elevated Lp (a) concentrations for myocardial infarction had an inflection in Chinese Han ethnic at the 8th decile, corresponding to 167 mg/l, where the risk was prone to be increased. In terms of Lp (a) median concentrations, per higher age quantile (5-y interval) was associated with a significant increase of 3.2 mg/l and females were on average 19.75 mg/l higher than males with a significant difference.
Conclusions: We proposed Lp (a) $<$ 170 mg/l after rounding as cut-off values for Chinese Han ethnicity. Effects of age and sex on Lp (a) concentrations were also noted. Prospective validation of these cutoff values is critically important in Chinese Han ethnicity.

1. Introduction

Lipoprotein (a) (Lp (a)) is a well-established independent risk factor for coronary artery disease (CAD) [1–6]. Guidelines from ESC/EAS and Canadian Cardiovascular Society have unequivocally recommended an Lp (a) value of 300 or 500 mg/l as cut-off values in Caucasian [7, 8]. However, there is lack of consensus in China regarding the significance of Lp (a) in atherosclerotic cardiovascular disease (ASVCD). Moreover, the statement for the characteristics and functions of Lp (a) in the 2016 Chinese guideline for the management of dyslipidemia in adults is ambiguously reported as “with a possible association with ASVCD” [9]. Application of the cut-off Lp (a) concentrations below 300 or 500 mg/l adopted in Caucasians to Chinese Han ethnicity is apparently arbitrary without supporting evidence [9]. Lp (a) concentrations are to a large extent genetically determined [10] and differ significantly in different ethnicities [5, 11–13]. The Lp (a) concentrations in Chinese Han ethnicity are much lower than in Caucasians [3, 5, 14]. Given present knowledge of race-dependent variations in Lp (a) [1], its ranges and percentiles established for individual ethnicities are recommended [15].

2. Methods

2.1. Study subjects

Health check-up population was from this institute between Jan. 1st, 2012 and Dec. 31st, 2012. Individuals with abnormal thyroid, kidney and liver functions were excluded from this study. Statin users were also excluded.

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https://doi.org/10.1016/j.cca.2018.06.004
Received 27 December 2017; Received in revised form 31 May 2018; Accepted 2 June 2018
Available online 05 June 2018

2.2. Ethics approval and consent to participate

All the study subjects were anonymized and de-identified, and the informed consents were waived by Institute Review Boards (IRB) before analysis due to the retrospective nature of the study. The study protocol was approved by the IRB of Soochow University. The current study is in line with the principles outlined in the Declaration of Helsinki.

2.3. Definitions, diagnoses and grouping

For health check-up population, kidney, liver or thyroid function abnormalities are defined as elevated serum creatinine or alanine transferase above the upper reference limit. Thyroid dysfunction is defined beyond the normal range of thyroid stimulating factor (TSH).

2.4. Lp (a) measurement and other lab examinations

The blood samples were taken on the 2nd day morning after 8 h fasting after admission. Latex enhanced immunoturbidimetric diagnostic reagent kits, with apolipoprotein (a) isoform-insensitive property, were purchased from Sekisui Diagnostic Ltd. This reagent was utilized to quantify the Lp (a) concentrations within 4 h after taking blood samples. The assay range is 10–1000 mg/l. The blood samples with Lp (a) > 1000 mg/l were diluted manually at 1:10 with saline. Thus, the Lp (a) concentrations up to 10,000 mg/l were within the security assay rang and would not mistakenly be considered as a low concentrations due to antigen excess. The Sekisui Co. Ltd., has provided the Lp (a) protein calibrator according to the IFCC PRM-2 in order to calibrate the Lp (a) examination results. Additionally, 4-time-1-y external quality assessment (EQA), presided by the Clinical Lab Examination Center of Health Ministry of PR China, has been conducted to ensure the reliability of the lab examinations. The intra- and inter-CVs for Lp (a) assay were 2.5% and 3.11%, respectively. The diagnostic reagent kits, also from Sekisui Co. Ltd., were used to quantify remaining biochemical markers and lipid profiles according to the manufacturer's specifications. Olympus AU5400 analyzer was employed for completion of the above measurements within 2 h after blood collection and serum isolation.

2.5. Statistical analysis

Continuous variables, failing to conform to normal distribution, were expressed as median (inter quartile range, IQR), and compared using Krusal-Wallis rank test or Ranksum test as appropriate. Categorical variables were expressed as frequencies and percentages and compared using Likelihood ratio χ^2 test. Age was divided into 12ths in increments of 5 y. Individuals < 30 y and > 80 y were combined as the bottom and top age quantiles, respectively, because of small number of sample size. Multiple linear regression was used for analyzing the effects of age decile and sex on Lp (a) median concentrations for health check-up population. Their average effects were reported. Non-parametric method was used for analyzing the Lp (a) distributions.

Statistical analyses and graphics were completed with STATA 13.0. Two-tailed $P < .05$ was considered to be statistically significant.

3. Results

A total of 11,900 consecutive "normal" individuals undergoing serum Lp (a) examination between Jan. 1st, 2012 and Dec. 31st, 2012, were included for potential analysis. Sixty-seven were excluded because of liver function abnormality; 138, because of kidney abnormality; 29, because of failure to examine the liver function; 12, because of failure to examine the kidney function; 2354, because of statin use; 59, because of repeat check-ups; and 3, because of younger age < 16 y. Thus, a total of 9238 healthy individuals were included for final analysis.

Table 1
Characteristics of health check-up population.

Variables	Values
Male n (%)	5569 (60.28)
Female n (%)	3669 (39.72)
Age, mean ± SD y	49.37 ± 14.75
LDL-C, median (IQR) mmol/l	2.74 (2.27–3.22)
TC, median (IQR) mmol/l	4.58 (4.06–5.20)
TG, median (IQR) mmol/l	1.28 (0.89–1.93)
Lp (a), median (IQR) mg/l	56 (28–132)
Sugar, median (IQR) mmol/l	5.12 (4.73–5.58)
HDL-C, median (IQR) mmol/l	1.23 (1.05–1.45)
Apo A1, median (IQR) mmol/l	1.41 (1.30–1.53)
Apo B100, median (IQR) mmol/l	0.94 (0.82–1.06)
Apo A1: apo B100	1.50 (1.30–1.77)

TC, total cholesterol; TG, triglycerides; Lp (a), lipoprotein (a); Apo A1, apolipoprotein A1; apo B100, apolipoprotein B100.

3.1. Baseline characteristics for health check-up population

The characteristics for health check-up population were listed in Table 1.

3.2. Correlations of Lp (a) concentrations with other lipid profiles plus age and sex

Lp (a) was significantly, but weakly associated with sex, age, LDL-C, TC, HDL-C, apo A and apo B. See Table 2.

3.3. Age and sex differences with respect to plasma Lp (a) median concentrations in health check-up population

Lp (a) median concentrations increased stepwise with increasing age quantiles, with a significant increase of 2.03 mg/l per higher quantile in men, 6.82 mg/l in women before age quantile 7, and 3.20 mg/l in total. In women after age quantile 7, however, Lp (a) median concentrations kept at a steady state subsequently with an insignificant increase of 0.71 mg/l. In total, females were on average 19.75 mg/l higher than males in terms of the Lp (a) median concentrations, with a significant difference ($P < .0001$) after adjusting for age. Table 3 and Fig. 1.

3.4. Characterization of Lp (a) distributions

Typical distributions of Lp (a) in Chinese Han ethnicity are shown in Fig. 2: plasma Lp (a) concentrations are similar in men and women and are highly skewed towards low concentrations with a long tail towards the highest concentrations. Lp (a) concentrations vary by > 1000-fold between individuals. The Lp (a) median concentrations are 67 mg/l in women, 51 mg/l in men and 56 mg/l in total. The 80th percentile of Lp

Table 2
Correlations of Lp (a) levels with other lipid profiles plus age and sex.

Variables	Partial corr.	Semipartial corr.	Corr. squared	Corr. squared	*P*values
Sex	−0.10	−0.09	0.0094	0.0088	0.0000
Age	0.05	0.05	0.0024	0.0022	0.0000
LDL-C	0.03	0.03	0.0011	0.0010	0.0017
TC	−0.07	−0.07	0.0051	0.0048	0.0000
TG	−0.02	−0.02	0.0004	0.0003	NS
Sugar	−0.01	−0.01	0.0001	0.0001	NS
HDL-C	0.11	0.11	0.0132	0.0123	0.0000
Apo A	−0.05	−0.05	0.0025	0.0023	0.0000
Apo B	0.10	0.10	0.0109	0.0102	0.0000
Apo A to apo B	0.02	0.01	0.0002	0.0002	NS