Hypoalphalipoproteinemia: Prevalence and the impact of treatment on reaching HDL cholesterol target level in patients with dyslipidemia

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Abstrak

Kadar serum "high density lipoproten cholesterol" (HDL-C) yang rendah merupakan prediktor yang kuat untuk terjadinya penyakit jantung koroner (PJK). Pada populasi laki-laki dalam penelitian Framingham diperkirakan terdapat 11% orang diantaranya yang mempunyai kadar HDL-C rendah saja dan kira-kira 30% penderita dislipidemia mempunyai kadar HDL-C < 35 mg/dl (hipoalphalipoproteinemia). Di samping itu sampai saat ini masih terdapat ketidakpastian mengenai pengelolaan penderita tersebut. Di Indonesia sekarang belum ada data epidemiologi mengenai prevalensi hipoalphalipoproteinemia dan dampak pengobatan dengan anti lipid pada kadar HDL-C pada sejumlah besar penderita. Kami telah melakukan survei di 13 kota di Indonesia untuk menilai prevalensi hipoalphalipoproteinemia diantara penderita dislipidemia dan menilai dampak pengobatan dengan anti lipid pada penderita tersebut untuk mencapai kadar target HDL-C > 35 mg/dl atau lebih pada praktek dokter rutin. Sebanyak 1420 penderita dislipidemia (rata-rata usia 50 tahun, laki-laki 58%) telah diikut sertakan dalam survei ini. Prevalensi keseluruhan hipoalphalipoproteinemia dalam studi ini adalah 35.4% dan kekerapan tersebut berhubungan terbalik dengan tingkat risiko penderita yaitu 21.9% pada penderita risiko rendah (penderita < 2 faktor risiko lain), 39.6% pada risiko tinggi (penderita ≥ 2 faktor risiko lain) dan 44.3% pada penderita PJK. Setelah pengobatan 12 minggu, prevalensi tersebut menurun menjadi 12%, 20% dan 18% masing-masing pada kelompok risiko rendah, tinggi dan PJK. Besarnya perubahan kadar HDL-C mempunyai korelasi terbalik dengan kadar HDL awal. Perubahan terbesar (59%) terdapat pada kelompok HDL rendah (<25 mg/dl) dan perubahan terkecil (23%) terdapat pada kelompok HDL tertinggi (≥ 45 mg/dl). Hanya terdapat 46% dengan HDL-C < 35 mg/dl pada saat awal yang dapat mencapai kadar HDL-C sesuai target NCEP (> 35 mg/dl) setelah terapi 12 minggu. ***(Med J Indones 2001; 10: 98-102)***

Abstract

A low serum high density lipoprotein cholesterol (HDL-C) level is a potent predictor of coronary heart disease (CHD). It has been estimated that 11% of the Framingham men have isolated low HDL-C levels and about 30% of dyslipidemia patients have HDL-C level of less than 35 mg/dl (hypoalphalipoproteinemia). In addition, there is uncertainty regarding the management of these patients. There is no epidemiological data on the prevalence low HDL-C level in dyslipidemia patients and the results of treatment on HDL-C on a large number of patients in Indonesia. We conducted a survey in 13 cities in Indonesia to evaluate the prevalence of hypoalphalipoproteinemia among dyslipidemic patients and the impact of treatment with lipid modification drugs on achieving target level of HDL-C 35 mg/dl or more in routine clinical practice. A total number of 1420 dyslipidemia patients (mean age 50 years, male 58%) were included and analyzed in this report. The overall prevalence of hypoalphalipoproteinemia in our study was 35.4% and it was correlated with the risk level of the patients; 21.9% among low risk group (patients with < 2 other risk factor), 39.6% in high risk group (≥ 2 other risk factors) and 44.3% in patients with CHD. After 12 weeks treatment, the prevalence decreased to 12%, 20% and 18% in low risk, high risk and CHD patients respectively. The magnitude of HDL-C changes correlated inversely with base-line HDL-C and it was highest (59%) in the lowest HDL-C group (< 25 mg/dl) and the least change (23%) was found in group with the highest HDL-C level (≥ 45 mg/dl). Only 46% of patients with low HDL-C value at baseline achieved normal HDL-C level after treatment. In conclusion, the prevalence of low HDL-C in dyslipidemia patients was high especially in high risk group and in CHD patients. The majority of patients with low HDL-C at base-line could not reach the target level for HDL-C of 35 mg/dl or more after 12 weeks treatment with lipid modification drugs. ***(Med J Indones 2001; 10: 98-102)***

Keywords: *hypoalphalipoproteinemia, dyslipidemia, routine practice, anti lipid drugs*

Many studies in the past three decades have established the correlation of dyslipidemia with the risk of coronary heart disease (CHD). The triad of high triglycerides, low high-density lipoprotein cholesterol (HDL-C), and elevated low-density lipoprotein cholesterol (LDL-C) were the most important factors in predicting risk of CHD. It has also been long known that HDL-C concentration is

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inversely associated with atherosclerosis risk.[1] Low level of HDL-C (hypoalphaproteinemia) could predict an increased incidence of CHD, independent of other risk factors.[2,3]

Although LDL cholesterol has been the main target in lipid-lowering therapy,[4] in fact, a high LDL cholesterol was not the most prevalent lipoprotein phenotype in many population with high CHD rates. Low HDL cholesterol alone or reduced HDL combined with increased remnant lipoproteins are the more common phenotypes.[5] Data from the Munster Heart Study (PROCAM) showed that, after follow-up at 8 years. HDL-C level below 35 mg/dl was associated with a fivefold increase in risk of CHD compared to normal HDL-C values even if total cholesterol lay between 200 and 300 mg/dl.[6]

Two primary prevention trials (the Lipid Research Clinics Primary Prevention Trial and the Helsinki Heart Study) both demonstrated that increasing HDL cholesterol levels reduced CHD events independent of the effect on LDL lowering. Furthermore the recent Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that treatment with the fibrate gemfibrozil resulted in a significant 22% reduction in fatal CHD and non-fatal myocardial infarction in patients with CHD whose primary lipid abnormality was a low HDL cholesterol level (mean baseline levels were 32 mg/dl). In VA-HIT gemfibrozil-treatment patients achieving an on-treatment HDL cholesterol level above 35 mg/dl had the lowest CHD event rate and this was seen even in the presence of high triglyceride levels. The American Heart Association (AHA) guidelines on the primary and secondary prevention of CHD recommended that the secondary goal for lipid management is to increase HDL-C level to > 35 mg/dl.

In Indonesia there is no study that evaluated the prevalence of low HDL-cholesterol and the impact of lipid modification treatment on reaching target goal of HDL-cholesterol level in routine clinical practice. In view of the VA-HIT and Framingham data, we wanted to evaluate to what extend treatment was able to raise levels of HDL cholesterol to above 35 mg/dl.

The aim of this study is to evaluate the prevalence of low HDL-C in patients with dyslipidemia and the results of anti lipid treatment on HDL cholesterol in routine clinical practice.

METHODS

Study Design and Population

This was a retrospective study in 13 cities in Indonesia which invited the participation of physicians who regularly treated patients with dyslipidemia. These physicians were asked to enroll about 10 consecutive dyslipidemia patients who received lipid modification therapy. Adult patients with primary dyslipidemia who received the same anti-lipid therapy for at least 12 weeks were eligible in the study if they did not have major trauma, surgery that required anesthesia, or myocardial infarction within the past 12 weeks prior to the study. Those who had an acute infection that required current antibiotic therapy or a recent or abrupt change in their usual diet or exercise within the preceding month were excluded. Women who were pregnant, breast-feeding, or < 6 months post partum were also excluded.

Case Record Form (CRF)

Physicians who participated in this study were required to fill standardized CRF for each patient. The CRF contained patient's ID, age, sex, CHD risk factors, prevalence of CHD, metabolic liver or kidney disease, baseline and after treatment lipid profile and lipid modification drugs used.

Risk Factor Assessment and Risk Groups

Risk factors were determined for each patients, and based on the sum of the risk factor (s) he/she had, the patient was categorized in one of the three risk categories : low-risk group, high-risk group and CHD patients. Patients without CHD and have fewer than 2 risk factors other than dyslipidemia are categorized as low-risk group, while patients without CHD with 2 or more risk factors other than dyslipidemia are categorized as high-risk group. CHD patients are those who have clinical manifestations of coronary heart disease, i.e.: angina pectoris, history of myocardial infarction and surgical or non surgical or non surgical intervention for CHD.

Risk factors assessment were done following the NCEP definition of risk factors. Age risk factor was defined as > 45 years for male and > 55 years for female. Family history was considered positive if the patients father or brother died suddenly or of CHD

below 55 years of age, and for mother or sister died suddenly or of CHD below 65 years of age. Smoking was defined as current smoking, while hypertension was indicated as blood pressure > 140/90 mmHg or on anti hypertensive medication. Low HDL-C level was < 35 mg/dl and diabetes mellitus was defined as history of diabetes mellitus or under anti diabetes medication or random blood glucose > 200 mg/dl.

Determination of Lipid Profile

Measurement of total cholesterol, triglycerides and HDL-C were made at baseline and at least 12 weeks after treatment. LDL-C values were calculated using Friedewald formula. Measurement of baseline lipid profile were carried out with enzymatic immuno-assay method (Chod-pap) using automatic photometer equipment (Hitachi).

Data Analysis

Because of the uncontrolled nature of treatment in this study that precludes the use confirmation statistics, all data were analyzed and are presented using descriptive methods.

RESULTS

Baseline Patient Characteristics

There were 1633 patients enrolled in this study, but because of incomplete data 283 patients were excluded. In total 1420 patients had completed CRF and all of them were included in this report. Table 1 shows the baseline characteristics of the study participants. At baseline 25.7% of the patients belong to low risk group, 66.0% to high risk group and 18.3% patients with CHD. As expected, patients with CHD and patients with more than 2 risk factors (high risk group) were more likely than the low risk group to be older and to have low HDL-C levels.

CHD Risk Profile in Relation to Baseline HDL-C levels

Five hundred and three out of the total study participants (35.4%) had HDL-C level of less than 35 mg/dl. Patients with low HDL-C level had less risk factors than patients with HDL-C level of equal or more than 35 mg/dl (Table 2).

HDL-C changes After Treatment by Risk Group

Table 3 shows HDL-C level changes after treatment by risk group. It is apparent that the increase of HDL-

Table 1. Patients demographics and base line lipid profile

	Low risk (n = 366)	High risk (n = 939)	CHD patients (n = 115)	Total (n = 1420)
Mean Age (SD) yrs	43.1 (9.6)	52.4 (10.1)	54.3 (11.5)	50.3 (0.9)
Male (%)	51.3	61.0	59.6	58.4
Female (%)	48.7	39.0	40.4	41.6
BMI (kg.m2)	23.3 (2.8)	25.2 (3.0)	25.1 (2.6)	24.8 (3.1)
Lipid Profile (mg/dL)	271	267	270	268
Total cholesterol	(54)	(47)	(58)	(50)
LDL-C	192 (47)	187 (46)	198 (58)	189 (47)
HDL-C	44.3 (13.8)	39.9 (11.5)	39.0 (10.7)	41.1 (12.2)
Low HDL-C (%)	21.9	39.6	44.3	35.4
Triglyceride	207 (98)	232 (105)	237 (99)	226 (104)

Table 2. Prevalence of risk factors in patients with high and low HDL-C at baseline

Risk factor	HDL-C < 35 mg/dl (N = 503)	HDL-C > 35 mg/dl (N = 917)
Age	139	576
Smoking	89	318
Hypertension	89	420
Family history	48	149
Diabetes mellitus	32	154
Obesity	6	43

C level was greater in high risk group. CHD patients showed the greatest changes in HDL-C level, followed by high risk group and least change in HDL-C values was found in the low risk group.

Percentage of Patient Achieving Normal HDL-C level (HDL-C > 35 mg/dl) After Treatment

The effect of treatment on HDL cholesterol stratified according to baseline levels in shown in Table 4. Significant increases in HDL-C were seen in all cumulative baseline group, the effect being iversely related to the baseline level of HDL cholesterol.

Hence the largest proportional increase in HDL cholesterol (59%) was seen in the group with the lowest mean baseline levels (< 25 mg/dl) and the least increase (2.6%) was seen in group with HDL cholesterol levels ≥ 45 mg/dl. After 12 weeks treatment with lipid modification drugs, only 46% of patients with baseline HDL-C levels of less than 35 mg/dl achieved HDL-C target of 35 mg/dl or more. The properties of patients who did not reach target level of HDL-C in those, with HDL-C at baseline of < 25 mg/dl, between 25-29 mg/dl and between 30-34 mg/dl were 70%, 72% and 44% respectively.

DISCUSSION

Low levels of HDL cholesterol are associated with an increase risk of coronary artery disease events, and high levels of HDL cholesterol are associated with protection from coronary artery diseases.

Recent findings indicate that low HDL-C (with normal LDL-C) occurs in up to 30% of patients with CHD and may represent a larger proportion of the CHD population than do those with isolated high LDL-C.[4] A biologically plausible mechanism has been proposed to explain how HDL-C exerts its antiatherogenic effect.

There are several classess of anti lipid drugs available for physicians including bile acid binding resins, niacin,3-hydroxy-3 methyl glutaryl coenzyme A (HMG-CoA) reducatase inhibitors (statins), fibric acid, probucol and estrogens.

The 1993 National Cholesterol Education Program Adult Treatment Panel II guidelines place primary emphasis on LDL cholesterol levels, however it stated that HDL-C level < 35 mg/dl is an independent risk factor for CHD and the need for HDL cholesterol screening in all adults. In this guidelines, no statement was made as regard to the importance of raising low level of HDL cholesterol in both primary and secondary prevention of CHD. The American College of Physicians and the Joint Task Force of European and other Societies on Coronary Prevention do not also formally stated low HDL cholesterol as a specific target of therapy.

Tabel 3. Percentages changes of HDL-C after treatment by risk group

Risk group	HDL-C mean (SD) (mg/dL)			% Change	% Patients with low HDL-C	
	N	Before	After		Before	After
Low risk	366	44.3 (13.8)	48.7 (13.09)	+ 12.15 (23.45)	21.9	12.06
High risk	939	39.92 (11.52)	44.50 (11.96)	+ 14.56 (27.77)	39.6	20.34
CHD	115	39.04 (10.72)	44.86 (10.86)	+ 21.05 (53.10)	44.3	18.26
Total	1420	41.06 (12.18)	45.62 (12.31)	+ 14.47 (29.71)	35.4	18.04

Tabel 4. Percentages of patients achieving HDL-C > 35 mg/dl after treatment by baseline HDL-C

Baseline Level HDL-C (Mg/dl)	HDL-C mean (SD) (mg/dL)			Mean HDL-C changes (%)	% Patients with HDL-C > 35 mg/dl after treatment
	N	Before	After		
< 25	43	20.71	32.90	58.86	30.32
25-29	91	26.80	33.26	24.10	27.47
30-34	245	31.54	38.13	20.89	55.92
35-39	334	36.57	41.81	14.33	91.02
40-44	246	41.08	46.54	13.29	97.15
≥ 45	459	54.17	55.56	2.56	96.73

All of the patients included in our study were patients treated with anti lipid drugs in routine clinical practice in 13 cities in Indonesia. They were 58% men and 42% women, mean age 50 years. Most of them (72%) belong to high risk group (patients with 2 or more CHD risk factors other than dyslipidemia) and CHD patients.

The prevalence of low HDL cholesterol level in our study (< 35 mg/dl) varied from 16% in low risk group to 30% in high risk group and 33% in patients with CHD (overall prevalence 35%). This figure is lower than the prevalence of low HDL cholesterol level in CHD patients reported in Framingham Study, i.e. 57%. However, similar study is Germany found that 2078 out of 7097 dyslipidemia patients (about 29%) treated in clinics had HDL cholesterol level of < 35 mg/dl. The mean increase in HDL cholesterol levels from baseline for the total population was 15% and the most pronounced effect (59% increase from baseline) was observed in those patients who were in the lowest baseline HDL cholesterol group. Although these are not placebo-corrected data the changes in lipid fraction which occurred in those randomized to placebo in the large clinical trials were trivial and hence, placebo correction is unlikely to significantly effects the size of these reported changes in HDL cholesterol.

The results of the present study showed that there were still many patients with low HDL-C level at baseline who did not reach target HDL cholesterol level of 35 mg/dl or more after treatment. About 18% of patients with CHD 20% of high risk group and 12% of low risk group (overall patients 18%) had low HDL cholesterol leve after treatment. This is in contrast to the results of several large drug monitoring programmes in Europe in which fibrate was used for the treatment of dyslipidemia patients. These studies showed that all patients had HDL cholesterol levels of more than 35 mg/dl after treatment regardless the baseline HDL-C levels.[10,11] In our survey, 76% of the dyslipidemia patients were treated with statin and 21% with fibrate. It is known that fibrate can increase HDL cholesterol better than statin. The effects of fibrate on HDL cholesterol are mediated, at least in parts, through changes in transcription of genes encoding for proteins that control lipoprotein metabolism.[9]

In conclusion, this study has shown that within everyday clinical setting among dyslipidemic patients in Indonesia, the prevalence of patients with low HDL cholesterol levels is comparable to the Western countries. Many patients still had HDL cholesterol level of less than 35 mg/dl despite anti-lipid treatment.

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