

Proatherogenic or antiatherogenic high density lipoprotein type in acute coronary syndrome and healthy male person

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Abstrak

Tujuan: Membuat kriteria tipe HDL proaterogenik/antiaterogenik berdasarkan konsentrasi Apolipoprotein A-I (ApoA-I), Paraoxonase-I (PON-1), Neopterin dan HDL-cholesterol.

Metode: Penelitian dilakukan secara kontrol-kasus pada 52 subjek dengan sindrom koroner akut (SKA) dan 30 subjek kontrol sehat. Tipe HDL proaterogenik dan antiaterogenik ditentukan berdasarkan konsentrasi ApoA-I, PON-1, Neopterin dan HDL-cholesterol. Konsentrasi ApoA-I diukur menggunakan metode imunoturbidimetri, PON-1 diukur dengan metode kolorimetri, Neopterin diukur dengan metode ELISA dan HDL-cholesterol diukur dengan metode homogenous. Analisis regresi logistik univariat dilakukan dengan SKA sebagai variabel tergantung dan konsentrasi ApoA-I, PON-1, Neopterin dan HDL-cholesterol sebagai variabel tidak tergantung. Tipe HDL proaterogenik dan antiaterogenik ditentukan dengan menggunakan nilai cut off dan odd ratio ApoA-I, PON-1, Neopterin dan HDL-cholesterol.

Hasil: Umur subjek penelitian adalah $50,89 \pm 12,63$ tahun, konsentrasi HDL-cholesterol : $39,82 \pm 9,84$ mg/dL, Apo A-I : $119,77 \pm 32,05$ mg/dL, PON-1 : $41,26 \pm 18,19$ kU/L, Neopterin : $16,22 \pm 38,10$ nmol/L. Cut off ApoA-I, PON-1 dan Neopterin secara berturut-turut adalah 124,5 mg/dL, 40,8 kU/L, and 7,016 nmol/L. Hasil analisis regresi logistik univariat didapatkan OR untuk ApoA-I, PON-1 dan Neopterin secara berturut-turut 29,759 (95% CI : 4,074 – 217,382), 1,647 (95% CI : 0,412 – 6,586), 4,317 (95% CI : 1,098 – 16,977). Dengan sistem scoring, kami menyimpulkan total score > 18 menunjukkan tipe HDL proaterogenik, dan total score < 18 merupakan tipe HDL antiaterogenik. Dengan sistem scoring ini kami menemukan 78,85% populasi SKA termasuk ke dalam tipe HDL proaterogenik.

Kesimpulan: Disfungsi HDL atau tipe HDL proaterogenik/antiaterogenik dapat diperkirakan dengan menggunakan sistem scoring ApoA-I – PON-1 – Neopterin – HDL-cholesterol. Subjek dengan total score < 18 dikelompokkan ke dalam tipe HDL antiaterogenik, sedangkan subjek dengan total score >18 memiliki tipe HDL proaterogenik. (*Med J Indones 2010; 19:228-34*)

Abstract

Aim: To make proatherogenic/antiatherogenic HDL type criteria using Apolipoprotein A-I (ApoA-I), Paraoxonase-1 (PON-1), Neopterin and HDL-cholesterol levels, which may be useful in clinical practice.

Methods: This was a case control study recruiting 52 subjects with Acute Coronary Syndrome (ACS) and 30 control healthy subjects. HDL type was classified into antiatherogenic and proatherogenic based on the levels of ApoA-I, PON-1, Neopterin and HDL-cholesterol. Concentrations of ApoA-I was measured by immunoturbidimetry method, PON-1 was measured by colorimetric method, Neopterin was measured by ELISA, and HDL-C was determined by homogenous method. Univariate logistic regression analysis was done using ACS as a dependent variable and levels of ApoA-I, PON-1, Neopterin and HDL-cholesterol as independent variables. Proatherogenic/antiatherogenic HDL type was determined by using ApoA-I, PON-1, Neopterin and HDL-cholesterol cut off and odd ratios.

Results: Patient's age was 50.89 ± 12.63 year, HDL-C was 39.82 ± 9.84 mg/dL, Apo A-I was 119.77 ± 32.05 mg/dL, PON-1 was 41.26 ± 18.19 kU/L, Neopterin was 16.22 ± 38.10 nmol/L. Cut offs of ApoA-I, PON-1 and Neopterin successively were 124.5 mg/dL, 40.8 kU/L, and 7.016 nmol/L. On univariate logistic regression analysis showed that OR of ApoA-I, PON-1 and Neopterin respectively were 29.759 (95% CI : 4.074 – 217.382), 1.647 (95% CI : 0.412 – 6.586), 4.317 (95% CI : 1.098 – 16.977). Using scoring system, we concluded that total score > 18 was proatherogenic HDL type, and total score < 18 was antiatherogenic HDL type. With this scoring we found 78.85% had proatherogenic HDL type in ACS population.

Conclusions: Dysfunctional HDL or proatherogenic/antiatherogenic HDL type can be predicted by using ApoA-I – PON-1 – Neopterin – HDL-cholesterol scoring system. Those with score of 18 are supposed to have antiatherogenic HDL type, and those with score of > 18 were having proatherogenic HDL type. (*Med J Indones 2010; 19:228-34*)

Key words: Apolipoprotein A-I (ApoA-I), HDL-cholesterol, neopterin, paraoxonase-1 (PON-1), proatherogenic/antiatherogenic HDL

High Density Lipoprotein (HDL) particles possess potent biological activities, including cellular cholesterol efflux capacity, antioxidative, anti-inflammatory, antiapoptotic, antithrombotic and vasodilatory activities, which provide protection from atherosclerosis or may even favor plaque regression. Such functional HDL deficiency is intimately associated with alterations in HDL metabolism and structure.¹

There are many possible alterations between this dysfunctional HDL and normal functional HDL. One possibility is a change in the protein composition of HDL. Human HDL particles are quite heterogenous, encompassing a range of sizes and densities. Each HDL particle carries ApoA-I and may carry other apolipoproteins as well, such as ApoA-II, ApoA-IV, ApoE and ApoCs. In addition, HDL is associated with accessory proteins, including lecithin-cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP), PON-1, Myeloperoxidase (MPO), Serum Amyloid A (SAA) protein and platelet-activating factor acetylhydrolase (PAF-AH). Changes in HDL protein composition attributable to infection, inflammation or diabetes have been shown to be associated with decreased function. Another factor that might make HDL dysfunctional is a change in the HDL-associated lipids.²

HDL quality can be determined by its lipid contents (including oxidized lipid) and apolipoprotein in HDL, particle size and electrophoretic mobility, related enzymatic activity, inflammatory/antiinflammatory properties and ability to promote cholesterol efflux.^{3,4}

ApoA-I is thought to play a central role in cholesterol transport from macrophages to the liver, consistent with the demonstration of accelerated reverse cholesterol transport in mice overexpressing human ApoA-I.⁵

HDL plays an important role as an antioxidant by both inhibiting phospholipid oxidation within and reducing the activity of minimally modified LDL. Several components of HDL contribute to this antioxidant effect, including its major ApoA-I along with at least four enzymes, including PON-1 and LCAT. PON-1 prevents the formation of lipid hydroperoxides and oxidized phospholipids and hydrolyzes them once they are formed. In vitro, ApoA-I also reduces lipid hydroperoxides within LDL independent of PON-1.⁶

In addition, HDL-associated PON-1 enhances cholesterol efflux from macrophages via increased HDL binding mediated by ABCA1.⁷ PON-1 induced cellular accumulation of lysophosphatidylcholine, which stimulates cholesterol efflux via the ABCA1 pathway, may account for

this effect. One can hypothesize that Reverse Cholesterol Transport (RCT)-related mechanism may contribute to the antiatherosclerotic effects of PON-1 observed in vivo.⁸

The anti-inflammatory activity of HDL is illustrated by the ability of HDL to decrease cytokine-induced expression of adhesion molecules on endothelial cells and to inhibit monocyte adhesion to these cells. The ability of HDL to inhibit adhesion molecule expression may be related to the presence of ApoA-I, ApoA-II, ApoA-IV, and/or distinct molecular species of phospholipid (PL), including sphingosine-1-phosphate (S1P) and Sphingosylphosphorylcholine.⁹

The anti-inflammatory action of HDL also involves hydrolysis of oxidized lipids by HDL-associated enzymes (PAF-AH and PON-1) and is mechanistically similar to the antioxidative activity of HDL.^{10,11}

Direct interaction of ApoA-I with T-lymphocytes, which can block subsequent activation of monocytes by lymphocytes, represents another plausible mechanism of HDL anti-inflammatory action.¹² In addition, ApoA-I has been reported to diminish neutrophil activation in vitro.¹³ The anti-inflammatory activity of HDL in vivo is consistent with elevated levels of CRP in subjects with hypoalphalipoproteinemia¹⁴, with negative correlation between plasma levels of CRP and HDL-C¹⁵ but also between plasma levels of intercellular adhesion molecule-1 and HDL-C.¹⁶

Neopterin, a pteridin derivative produced by activated macrophage in response to stimulation by interferon- γ is a marker of both immune activation and Coronary Artery Disease activity. Increased Neopterin is associated with the presence of vulnerable or disrupted atheromatous plaques and represents a marker of increased risk of further events in patients with ACS.¹⁷

A few studies to date have investigated the assay to determine dysfunctional HDL, but is still too laborious for routine clinical use. According to that reason, we need to study about the role of major HDL component such as ApoA-I, PON-1 and HDL-cholesterol, and Neopterin as marker of inflammation, in altering antiatherogenic HDL type to proatherogenic HDL type.

METHODS

Patients and study design

Fifty two patients with Acute Coronary Syndrome, aged 30 – 75 years (man) were enrolled in this case control

study. Thirty healthy subjects, aged 30 – 62 years (man) also were analysed. Participants signed informed consents to have personal data such as height, weight, smoking, serum measurements, blood tension, waist circumference, exercises, alcohol, drugs. The study's proposal has been approved by The Health Research Ethics Committee of The Faculty of Medicine Hasanuddin University of Makassar and Udayana University of Denpasar.

Assays of biochemical markers

ApoA-I was measured with immunoturbidimetry method (Roche), PON-1 was measured with colorimetry method (ZeptoMetrix Co), Neopterin was measured with Enzyme Linked Immunosorbent Assay kit (IBL, Hamburg) and HDL-cholesterol was measured by homogenous method (Daiichi Pure Chemicals Co). Serum were separated from whole blood after centrifugation, and immediately kept at -20°C until assays. All assays were performed according to manufacturers instruction.

For each run of ApoA-I, PON-1, Neopterin and HDL-cholesterol controls were included in the assays, and all results were within acceptable ranges.

Data analysis

Statistical analyses were performed with the SPSS for Windows version 11.5 software (SPSS Inc., Chicago, IL, USA). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov and for variance homogeneity using Leven's test. ROC Curve were made to determine ApoA-I, PON-1, Neopterin and HDL-cholesterol cut off levels. Using univariate logistic regression analysis, we found ApoA-I, PON-1, Neopterin and HDL-cholesterol odd ratios (OR) in acute coronary syndrome. HDL type (proatherogenic/antiatherogenic) was determined by using scoring system with these four parameters cut offs and ORs. The results were narrated and explained by tables and graphs. For statistical test, we used 5% to define the level of significance.

RESULTS

Patient's age was 50.89 ± 12.63 year, HDL-C was 39.82 ± 9.84 mg/dL, Apo A-1 was 119.77 ± 32.05 mg/dL, PON-1 was 41.26 ± 18.19 kU/L, Neopterin was 16.22 ± 38.10 nmol/L.

Table 1 describes the clinical and biochemical characteristics of the subjects. Table 2 showed ROC curves analysis to

find ApoA-I, PON-1 and Neopterin cut offs. For HDL-cholesterol cut off, we used cut off that approved by Perkeni (from Perkeni-consensus of lipid), and table 3 showed univariate logistic regression analysis of ApoA-I, PON-1, Neopterin and HDL-cholesterol to find ORs in Acute Coronary Syndrome. These cut off value and odd ratio will be used in scoring system for determining HDL type (as shown in table 4).

Table 1. Clinical and biochemical characteristics of Acute Coronary Syndrome and controls

Parameter	Control (n=30)	ACS (n=52)	P
	Mean \pm SD	Mean \pm SD	
Age (years)	41.5 \pm 9.29	56.31 \pm 11.07	0.000
SGOT (U/L)	19.06 \pm 4.17	58.17 \pm 53.93	0.000
SGPT (U/L)	23.33 \pm 8.75	46.04 \pm 55.49	0.006
FPG (mg/dL)	85.87 \pm 8.16	101.08 \pm 30.23	0.001
Creatinin (mg/dL)	0.96 \pm 0.11	1.36 \pm 0.82	0.001
Total Cholesterol(mg/dL)	212.47 \pm 29.57	177.94 \pm 40.30	0.000
LDL Cholesterol(mg/dL)	141.53 \pm 25.70	120.79 \pm 33.55	0.004
HDL Cholesterol(mg/dL)	46.67 \pm 8.13	35.87 \pm 8.53	0.000
Triglyceride (mg/dL)	127.03 \pm 43.85	138.33 \pm 55.42	0.342
Apo A1 (mg/dL)	146.73 \pm 21.16	103.90 \pm 26.29	0.000
Neopterin (nmol/L)	6.59 \pm 2.77	22.00 \pm 47.39	0.026
PON-1 (kU/L)	49.29 \pm 18.84	36.62 \pm 16.23	0.002
hs-CRP (mg/L)	1.33 \pm 1.14	44.18 \pm 45.26	0.000
SBP (mmHg)	113.67 \pm 10.66	122.90 \pm 20.25	0.008
DBP (mmHg)	77.83 \pm 8.68	77.00 \pm 10.76	0.719
BMI (kg/m ²)	23.73 \pm 2.93	24.31 \pm 3.05	0.402
WC (cm)	85.9 \pm 7.88	89.67 \pm 8.15	0.044
GFR (mL/ menit)	95.92 \pm 22.92	68.25 \pm 25.23	0.000

Description: SGOT = Serum Glutamic Oxalacetatic Transaminase; SGPT = Serum Glutamic Piruvate Transaminase; FPG = Fasting Plasma Glucose; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; PON-1 = Paraoxonase-1; hs-CRP = high sensitivity C-Reactive Protein; SBP = Sistolic Blood Pressure; DBP= Diastolik Blood Pressure; BMI = Body Mass Index; WC = Waist Circumference; SD= Standard Deviation; p=probability "unpaired t test" result test; *=significance (p < 0.05)

From all of the variable that using in scoring system, ApoA-I showed its highest effect, with highest odd ratio (OR : 29.759; 95% CI : 4.074 – 217.382; p = 0,000), followed by HDL-cholesterol, Neopterin and PON-1. We made tabulation using ApoA-I, PON-1, Neopterin and HDL-cholesterol cut offs and ORs. Subjects with ApoA-I, PON-1 and HDL cholesterol level < cut off value would get 30, 2 and 13 respectively for the score (approximation from OR value 29.759, 1.647 and 13.286 respectively). Subjects with Neopterin level >

cut off value would get 4 for the score (approximation from OR 4.317) We made ROC analysis from these tabulation. HDL was defined as antiatherogenic based on total score < 18, and as proatherogenic based on total score > 18 (AUC : 0.899, sensitivity 83.7%, specificity 99.33%)

Figure 1 showed us scoring system to determine HDL type. From 52 ACS patients, by using this criteria we found 41 subjects with proatherogenic properties and 8 subjects with antiatherogenic properties.

Table 2. ROC Curves Analysis

Variable	AUC	Cut Off	Sensitivity	Specificity
ApoA-1	0.895	124.5	93.3 %	78.4 %
PON-1	0.699	40.8	63.3 %	61.5 %
Neopterin	0.801	7.016	76.0 %	73.3 %
HDL-cholesterol	0.816	40.5	86.7%	71.2%

Description : ApoA-I = Apolipoprotein A-I, PON-1 = Paraoxonase-1, HDL = High Density Lipoprotein

Table 3. Univariate Logistic Regression Analysis

Variable	OR	95% CI	p
ApoA-1	29.759	4.074 – 217.382	0.000
PON-1	1.647	0.412 – 6.586	0.486
Neopterin	4.317	1.098 – 16.977	0.036
HDL-cholesterol	13.286	3.566 – 49.493	0.000

Description : ApoA-I = Apolipoprotein A-I, PON-1 = Paraoxonase-1, HDL = High Density Lipoprotein

Table 4. Scoring system for determining HDL type

Variable	Cut off	OR	Score
Apo A-1 :	124.5	29.759	
Apo A-1 < 124,5			30
Apo A-1 ≥ 124,5			1
PON-1 :	40.8	1.647	
PON-1 < 40,8			2
PON-1 ≥ 40,8			1
Neopterin :	7.016	4.317	
Neopterin < 7,016			1
Neopterin ≥ 7,016			4
HDL-Cholesterol :	40	13.286	
HDL-Cholesterol < 40			13
HDL-Cholesterol ≥ 40			1

Description : ApoA-I = Apolipoprotein A-I, PON-1 = Paraoxonase-1, HDL = High Density Lipoprotein

Table 5. Type of HDL in ACS and healthy control group

Group	Antiatherogenic HDL	Proatherogenic HDL	Not identified	Total
ACS	8	41	3	52
Control	28	2	-	30
Total	36	43	3	82

Description : HDL = High Density Lipoprotein

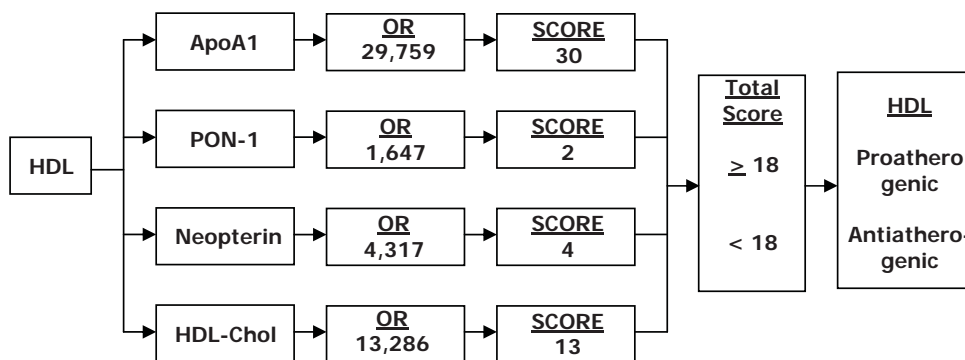


Figure 1. Scoring system to determine HDL type. HDL was defined as antiatherogenic based on total score < 18, and as proatherogenic based on total score > 18. From 52 ACS patients, by using that criteria we found 38 subjects with proatherogenic properties and 11 subjects with antiatherogenic properties.

DISCUSSIONS

Not all HDL has atheroprotective effects. HDL may become dysfunctional or even proatherogenic and thus promote atherosclerosis. The function of HDL was determined by reverse cholesterol transport activity, anti-inflammatory and antioxidant activity.

In developing new therapies to promote the biological activity of HDL, it will be important to identify the right marker of efficacy; HDL-cholesterol may not be the most effective marker to assess the potential utility of new HDL raising therapy. A number of techniques have been developed to characterize HDL structure and function. Many of these approaches still need to be

validated and standardized and the relationship between HDL characteristics and clinical outcome remains to be clearly elucidated.¹⁸ The assay for dysfunctional HDL is not yet available for routine clinical use. This study is to make proatherogenic/antiatherogenic HDL type criteria using ApoA-I, PON-1, Neopterin and HDL-cholesterol levels, which may be useful in clinical practice.

Type of HDL in ACS and healthy control group

In this study, subject were divided into ACS group (n = 52) and control group (n = 30). We use ApoA-I, PON-1, HDL-cholesterol and Neopterin levels to make proatherogenic/antiatherogenic HDL type criteria. Based on scoring system using cut off and odd ratio of Apo A-1, PON-1, Neopterin and HDL-cholesterol we determined antiatherogenic HDL type if the subject has total score < 18, and proatherogenic HDL type if the subject has total score >18.

Table 5 showed us the type of HDL in ACS and healthy control group. From 52 ACS subjects we found 41 subjects (78.85%) with proatherogenic HDL type and 8 subjects (15.40%) with antiatherogenic HDL type. From healthy control subjects we found only 2 subject with proatherogenic HDL type and 28 subjects with antiatherogenic HDL type. Three subjects could not be analysed because of 1 person having no ApoA-I data, 2 persons having very high level of Neopterin (high above limit detection that can be read by the system).

Interaction between ApoA-I, PON-1, neopterin and HDL-cholesterol in ACS

In our study, we found 40 person (76.92%) who has low level of ApoA-I and 31 person (59.62%) with low level of HDL-cholesterol in ACS group. This results show us that there are some people with normal/high HDL-cholesterol having low level of ApoA-I. By using univariate logistic regression analysis we found that in ACS ApoA-I is the best independent predictor with *odd ratio* 29.759 (95% CI : 4.074 – 217.382), p : 0,000. On the other hand based on univariate regression analysis shown that in ACS group HDL-cholesterol *odd ratio* 13.286 (95% CI : 3.566 – 49.493) p : 0,000, followed by Neopterin and PON-1 with odd ratio 4.317 (95% CI : 1.098-16.977) and 1.647 (95% CI : 0.412-6.586) respectively. It means that ApoA-I level is significantly associated and independent with ACS.

Relationship between study results and epidemiological data

In our study, we found 21/52 (40.38%) individu in ACS group and 27/30 (90%) individu in healthy

control subjects having HDL level > 40 mg/dL. This results was similar with Navab et al report. Navab et al, calculated that about 44% of Coronary Heart Disease in the Framingham Heart Study occurred in patients with normal HDL-cholesterol levels, suggesting that factors other than HDL-cholesterol levels were important.

Proatherogenic HDL type was found in 78.85% ACS group and in 6.70% healthy control subjects. Our study found that most of ACS patients were having proatherogenic HDL type, even with normal or high HDL-cholesterol.

Analysis of the interaction of variables in the incidence of HDL type change from antiatherogenic to proatherogenic by pathobiological approach

A growing body of evidence supports the notion that some HDL is dysfunctional or proinflammatory, facilitating leukocyte recruitment and cellular activation phenotypes. Navab and Ansell found that HDL isolated from patients with coronary artery disease and plasma HDL levels in the normal or high range promoted rather than inhibited monocyte chemotaxis in response to oxidized low-density lipoprotein (LDL), suggesting a possible mechanism for why normal levels of HDL are not always protective.¹⁹

The role of HDL to protect from atherosclerosis is not apart from the role of Apo A-1. Apo A-1 ability to promote reverse cholesterol transport and remove *seeding molecule* from LDL (important in oxidized phospholipids formation, originate from LDL *inflammatory*) contribute to inverse relationship between HDL-cholesterol level and susceptibility to atherosclerosis.¹¹

HDL can bind and neutralize lipopolysaccharide, giving the role in acute and chronic inflammation modulation. Flowcytometry analysis showed that ApoA-I-associated-HDL, inhibit monocyte activation by binding to T lymphocyte, inhibit TNF-a and interleukin-1b production, an essential component in immunoinflammatory disease pathogenesis. It was hypothesized that the increase of HDL-cholesterol level will influence antiinflammation action.¹⁵

From our ACS patients we found 78.85% were having proatherogenic HDL type dan only 15.38% were having antiatherogenic HDL type. If we pay attention to HDL-cholesterol level per se, we found 65.38% were having HDL-cholesterol < 40 mg/dL. It means that there are several ACS patients having HDL-cholesterol level more than 40 mg/dL but the type is proatherogenic. Meanwhile, in healthy control subjects we found 6.67% proatherogenic HDL type. So, high levels of HDL-cholesterol are not always protective in subjects, suggesting that not all HDLs function to prevent atherosclerosis.

Laboratory test development giving easy quantitation, reproducible and accurate for all antiatherogenic HDL properties will help assessing cardiovascular risk in the near future more aggressive and accurate.

There was very interesting finding that if we didn't use PON-1 in the scoring system, only ApoA-I, Neopterin and HDL-cholesterol, we would get the same results as using PON-1. So in our study we found that the role of PON-1 in determining HDL type can be neglected. Our study also suggest that ApoA-I is the best marker to describe HDL type, better than Neopterin, PON-1 even HDL-cholesterol, showed by highest OR (OR : 29.759, 95% CI = 4.074 – 217.382). Future studies are clearly warranted to investigate whether ApoA-I can be used as a single marker to determine the HDL type. The good point is ApoA-I measurement is available for routine clinical use.

In conclusion, From our study there were some important points. The quality of HDL may be more important than HDL-cholesterol levels. Functional characterization of HDL is a promising method for assessment of cardiovascular risk and effectiveness of risk reduction. Simple assay for dysfunctional HDL type is not available yet. We can estimate the HDL type by measuring its major components like ApoA-I, HDL-cholesterol and PON-1. They describe the reverse cholesterol transport, antioxidant and anti-inflammatory activity of HDL. Neopterin was used to predict inflammatory effect of HDL.

By using the scoring system, using cut off and odd ratios for ApoA-I, HDL-cholesterol, PON-1 and Neopterin, we found that subject with score > 18 tend to have proatherogenic HDL type and subjects with score < 18 are having antiatherogenic HDL type. ApoA-I should have more attention than HDL-cholesterol in reducing the risk of cardiovascular disease, showing by having the highest odd ratio to ACS. ApoA-I levels may be more reliable marker of cardiovascular risk than the more commonly measured HDL cholesterol.

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