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Coronary Flow Velocity Reserve in Subjects with High HDL Cholesterol

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SOUHRN

Kontext: V posledních letech se vede diskuse o tom, zda vysoké hodnoty cholesterolu v lipoproteinech o vysoké hustotě (HDL-C) jednoznačně poskytují ochranu kardiovaskulárního systému. Porovnali jsme koronární průtokovou rezervu (coronary flow velocity reserve, CFVR) jedinců s normálními hodnotami HDL-C se stejným parametrem jedinců s vysokými hodnotami HDL-C.
Metody a výsledky: Jedinci vyšetřovaní pro podezření na anginu pectoris bez patologického nálezu na klinice kardiologie istanbulské Medeniyet University v letech 2012 až 2022 absolvovali screening a při hodnotách HDL-C ≥ 50 mg/dl byli určeni k analýze; pro tento účel byli rozděleni do dvou skupin: (1) pacienti s HDL-C ≥ 70 mg/dl a (2) pacienti s HDL-C ≥ 50 a < 70 mg/dl. Skupiny byly porovnány s použitím CFVR.
Výsledky: Do studie bylo zařazeno celkem 121 jedinců (průměrný věk 37,60 ± 9,23; muži n = 46, 38 %). Devět účastníků (7,4 %) mělo hodnoty HDL-C ≥ 70 mg/dl. Při srovnání CFVR účastníků s HDL-C ≥ 70 mg/dl s CFVR jedinců s nižšími hodnotami HDL (≥ 50 a < 70 mg/dl) byly hodnoty CFVR nižší ve skupině s vysokými hodnotami HDL-C (2,20 ± 0,52 vs. 2,65 ± 0,53; p = 0,007).
Závěr: Hodnoty HDL-C ≥ 70 mg/dl mohou nepříznivě ovlivňovat koronární mikrocirkulaci.

Keywords:
Coronary flow velocity reserve
Coronary microcirculation
High HDL-C

ABSTRACT

Background: In recent years, it has been debated whether high HDL-C definitely provides cardiovascular protection. We compared coronary flow velocity reserve (CFVR) of subjects with normal HDL-C levels with subjects who have high HDL-C levels.
Methods and results: Subjects who were evaluated for angina with no pathological findings at the Cardiology Department of Istanbul Medeniyet University between 2012–2022 were screened and included to analysis if their HDL-C levels were ≥50 mg/dL. They were divided into two groups: (1) patients with HDL-C ≥70 mg/dL and (2) patients with HDL-C ≥50 and <70 mg/ dL. Groups were compared in terms of CFVR.
Results: A total of 121 subjects (mean age: 37.60 ± 9.23; male n = 46, 38%) were included. There were 9 (7.4%) participants with HDL-C levels ≥70 mg/dL. When CFVR of participants with HDL-C ≥70 mg/dL was compared with participants with lower HDL (≥50 and <70 mg/dL), CFVR was lower in the high HDL group (2.20 ± 0.52 vs. 2.65 ± 0.53, p = 0.007).
Conclusion: HDL-C levels ≥70 mg/dL may negatively impact coronary microcirculation.

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Introduction

Low high density lipoprotein cholesterol (HDL-C) has been marked as a risk factor for coronary heart disease.[1] Almost five decades ago Framingham study has shown the association between increased risk of coronary death and low HDL-C level.[2] There have been numerous scientific attempts to increase HDL-C and lower cardiovascular risk, no significant finding to support this hypothesis was achieved.[3] Recently a new trial tested the effect of apolipoprotein A1 (the main protein in HDL-C) on early cardiovascular events in patients with acute myocardial infarction[4] and found no significant difference between apolipoprotein A1 infusion and placebo.

The question of "how high" it is protective has begun to be questioned, with observational studies suggesting a possible "U" curve. Madsen et al. reported increased all-cause mortality in patients with extremely high HDL-C levels from two population based studies (n = 116508).[5] EPOCH-Japan study has shown increased cardiovascular mortality in men with HDL-C levels ≥90 mg/dL.[6] Takaeko et al. reported impaired endothelial dysfunction with low and high HDL-C levels.[7] A recent report from United Kingdom Biobank has shown an increased mortality rate in male subjects with HDL-C levels ≥80 mg/dL.[8] Dyslipidemia guideline of European Society of Cardiology warned against using extremely high HDL-C levels (>90 mg/dL) as a risk predictor.[9]

Coronary flow velocity reserve (CFVR) can be used as a surrogate marker to assess coronary microcirculation.[10] It can be used to evaluate intermediate coronary stenosis[11] and shows correlation with coronary physiology.[12] In this analysis we compared CFVR of patients with normal HDL-C levels and patients with high HDL-C levels.

Material and methods

Ethics

Ethics Committee approval was obtained from Istanbul Medeniyet University; rule number: 2022/0237.

Subjects

Subjects presented to Cardiology Department of Istanbul Medeniyet University for angina between 2012–2022 were screened. Subjects with unremarkable exercise stress test were included in the analysis if they have also undergone CFVR. Subjects who had no disease history (diabetes, hypertension, chronic kidney disease, hyperlipidemia, malignancy etc.) and no medication use were recruited if their HDL-C levels were ≥50 mg/dL and if their CFVR and/or c-IMT were measured. Subjects < 18 years old were excluded.

Their demographic data including age, sex, blood lipid profile, and echocardiographic findings were screened. Subjects with HDL-C levels ≥50 mg/dL were selected and further divided into two groups: (1) patients with HDL-C ≥70 mg/dL and (2) patients with HDL-C ≥50 and <70 mg/dL. Patients with LDL cholesterol higher than >190 mg/dl were excluded.

Echocardiographic measurements

Measurement technique of CFVR has been described previously.[13] All measurements were performed from the left anterior descending artery (LAD) by visualizing the LAD from a modified 2- or 4-chamber view when the patient was in the left lateral position. Coronary blood flow velocities were measured using pulsed wave Doppler at rest and immediately after dipyridamole infusion (0.56 mg/kg over 4 min). The 5 highest diastolic velocities recorded during the test were averaged to obtain the diastolic peak flow velocities (DPFV) at baseline, during maximal dipyridamole infusion, and 3 min after cessation of dipyridamole. Echocardiographic examinations were done with an ultrasound platform (Philips EPIQ 7G, Bothell, WA, USA) equipped with a broadband S5-1 transducer (transmission frequency: 1.7 MHz; receiver frequency: 3.4 MHz). CFVR was defined as the ratio of hyperemic diastolic peak velocity to baseline diastolic peak velocity, and a CFVR ≥2.0 was assessed as normal.

Statistical analysis

Statistical analysis was done with SPSS software version 16. Normality of the variables was tested with visual (histogram) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to analyze distribution. Kruskal–Wallis test was used for groups with less than 30 subjects and Student T test was used if normality tests showed parametric distribution. A *p* value less than 0.05 was accepted as statistically significant.

Results

There were 602 subjects with no disease history, no medication history, unremarkable exercise stress test findings and CFVR evaluation. Subjects with HDL-C <50 mg/dL and subjects with LDL cholesterol >190 mg/dL were excluded for final analysis (**Fig. 1**).

A total of 121 subjects (mean age: 37.60 ± 9.23; male n = 46, 38%) were included. Their mean total cholesterol level was 191.35 ± 29.53, mean triglyceride level was 102.97 ± 45.10, mean LDL-C level was 114.26 ± 25.54, and mean HDL-C level was 58.55 ± 8.29 (**Table 1**). There were

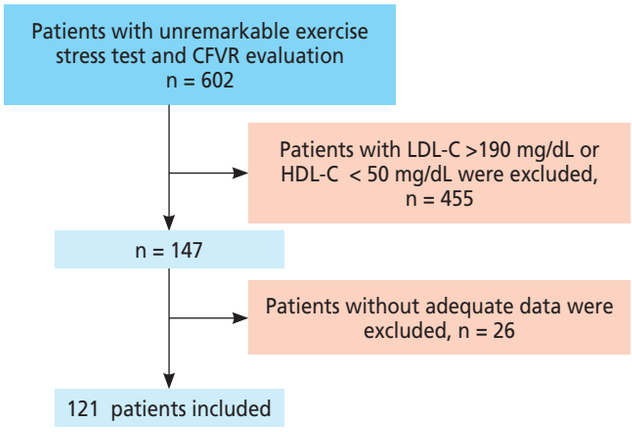

Fig. 1 – Study flowchart.

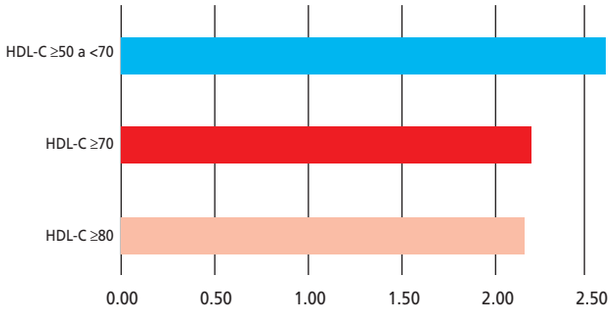

Fig. 2 – Comparison of CFVR in different HDL-C levels.

9 (7.4%) participants with HDL-C levels ≥70 mg/dL. When CFVR of participants with HDL-C ≥70 mg/dL was compared with participants with lower HDL (<70 mg/dL), CFVR was lower in the high HDL group (2.20 ± 0.52 vs. 2.65 ± 0.53, p = 0.007) (**Table 2**). Mean age between groups didn't differ (36.33 ± 12.64 for higher HDL and 37.70 ± 8.97 for lower HDL group, p = 0.757). When participants with HDL-C ≥80 mg/dL (n = 2) were compared with participants who have <80 mg/dL, low CFVR persisted however didn't reach statistical significance (2.16 ± 0.12 vs. 2.62 ± 054, p = 0.133) (**Fig. 2**). Mean CFVR of subjects with HDL-C <60 mg/dL (n = 75) was similar to subjects with ≥60 mg/dL (2.61 ± 0.43 vs. 2.61 ± 0.69, p = 0.99, respectively).

Discussion

In this study we compared CFVR of patients with high HDL-C with normal HDL-C and our findings indicate that HDL-C levels ≥70 mg/dL may have a negative impact on coronary microcirculation.

For years HDL-C has been used as a risk factor for cardiovascular risk scoring systems. Preclinical studies have shown a reduction in atherosclerotic lesions with HDL infusion,[14,15] however, human studies had conflicting data.[16,17] It is postulated that genetic conditions which increase HDL-C levels such as increased expression of *APO A-I* gene or *CETP* gene deficiency protect against cardiovascular mortality.[18] However, when medical interventions to increase HDL-C were tested, they failed to improve cardiovascular outcomes and some were early terminated.[3,19–22] Only REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid modification) study showed promising results with anacetrapib, how-

Table 1 – Demographic characteristics of the subjects

Parameters	n = 121 (mean ± standard deviation)
Age, years	37.60 ± 9.23
Male, n (%)	46, %38
BMI, kg/m^2	26.81 ± 3.44
SBP (mmHg)	119.05 ± 12.01
DBP (mmHg)	74.51 ± 6.98
Heart rate per minute	74.04 ± 7.73
Fasting glucose (mg/dL)	92.82 ± 6.43
Serum creatinine (mg/dL)	0.79 ± 0.12
Sodium (mEq/L)	139.00 ± 1.76
Potassium (mEq/L)	4.39 ± 0.41
AST (units/L)	17.40 ± 4.83
ALT (units/L)	17.30 ± 7.46
Total cholesterol (mg/dL)	191.35 ± 29.53
LDL cholesterol (mg/dL)	114.26 ± 25.54
HDL cholesterol (mg/dL)	58.55 ± 8.29
Triglyceride (mg/dL)	102.97 ± 45.10

ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; DBP – diastolic blood pressure; SBP – systolic blood pressure.

Table 2 – Coronary flow velocity reserve (CFVR) comparison of patients with normal HDL-C and high HDL-C

Parameters (mean ± standard deviation)	Normal HDL (50–70 mg/dL) n = 112	High HDL (≥70 mg/dL) n = 9	p
Age (years)	37.70 ± 8.97	36.33 ± 12.64	0.757
LV end-diastolic volume (ml)	44.99 ± 4.15	45.73 ± 3.27	0.465
LV end-systolic volume (ml)	27.99 ± 3.09	28.44 ± 3.08	0.781
LV EF (%)	67.69 ± 3.80	67.27 ± 3.57	0.776
Interventricular septal thickness (mm)	8.61 ± 2.12	7.90 ± 3.37	0.669
Posterior wall thickness (mm)	8.21 ± 2.01	7.55 ± 3.04	0.503
Left atrial anteroposterior diameter (mm)	31.43 ± 3.10	28.71 ± 2.56	**0.035**
Mitral E wave	71.99 ± 25.24	70.22 ± 30.31	0.337
Mitral A wave	60.11 ± 21.38	55.97 ± 23.27	0.776
Mitral E/A wave	60.11 ± 31.38	55.97 ± 23.27	0.370
CFVR	2.65 ± 0.53	2.20 ± 0.52	**0.007**

CFVR – coronary flow velocity reserve; EF – ejection fraction; LV – left ventricle.

ever, it wasn't clear whether these positive findings were due to the reduction of non-HDL-C.[23] European Society of Cardiology dyslipidemia guidelines have warranted caution in patients with HDL-C >90 mg/dL.[24]

To elaborate on these findings, different hypotheses were suggested. HDL-C fractions were studied to define a fraction more beneficial than the others.[25] HDL particle number has also been tested and shown to have a better reflection of cardiovascular events than HDL-C.[26] Nowadays HDL function rather than HDL-C amount is studied as a predictor of cardiovascular risk. Especially HDL-C efflux capacity is under examination.[27] All these data show that the place of high HDL-C in cardiovascular protection is far from clear.

In our study, we tested CFVR to assess microcirculation in patients with high HDL-C. Our results indicate impairment of microcirculation after 70 mg/dL, however, we weren't able to show decreased CFVR with ≥80 mg/dL, due to a possible Type-2 error. It should also be noted that mean CFVR was lower with HDL-C ≥80 mg/dL than HDL-C levels ≥70 mg/dL. Coronary microcirculation depends on numerous physical and biochemical factors including endothelial function. Endothelial function is affected by various molecules including nitric oxide. Gomaraschi et al. has reported increased pro-oxidant and pro-inflammatory features of high HDL-C in patients with CETP deficiency which can have an impact on the NO pathway.[28]

Genetics may play a role in these findings. Scavenger receptor BI (SR-BI) is one of the key receptors of HDL-C.[29] Findings show when a loss of function mutation occurs in the gene encoding SR-BI (*SCARB1*) both HDL-C and cardiovascular heart disease risk increases.[30] In another study, Ile405Val mutation in the CETP gene was associated with high HDL-C and ischemic heart disease in women.[31] The mean HDL-C levels of these subjects were 67.67 mg/dL, which was similar to the range in our findings.

Our limitations include a low sample size, however, it is difficult to find cardiovascular healthy participants with high HDL-C , especially in a hospital setting. A larger sample size may help differentiate gender related outcomes. Also because this is a retrospective study no information regarding family history of cardiovascular disease and smoking was obtained.

In conclusion, this study presents new evidence to the possibility of a "U" curve with HDL-C. It is clear that a better understanding of the function of HDL-C at these levels is required before targeting higher HDL-C levels (>70 mg/dL).

Conflict of interest

The authors declare no conflict of interest.

Funding

No funding was received.

Ethical statement

The study was written in compliance with the Declaration of Helsinki.

Author contributions

O.T.C. designed the study and conducted the analysis, F.B.O., T.I., O.K. collected the data, R.C. contributed to writing and tables and figures, M.C. supervised the study.

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