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# LIPID RESIDUAL CARDIOVASCULAR RISK PARAMETERS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA – IMPORTANCE OF TRIGLYCERIDE TO HIGH-DENSITY LIPOPROTEIN RATIO

## *LIPIDNI PARAMETRI REZIDUALNOG KARDIOVASKULARNOG RIZIKA KOD PACIJENATA SA FAMILIJARNOM HIPERHOLESTEROLEMIJOM − VAŽNOST ODNOSA TRIGLICERIDA I HOLESTEROLA VELIKE MASE*

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**Summary**

**Introduction.** Familial hipercholesterolemia is monogenetic disorder associated with early onset of cardiovascular disease. The measurement of low density cholesterol is the primary therapeutic goal in familial hypercholesterolemia patients, but despite the lipid-lowering therapy cardiovascular disease still occurs. It became clear that it's necessary to consider residual cardiovascular risk. The aim of study was to evaluate residual cardiovascular risk in familial hipercholesterolemia. **Material and Methods.** In this cross-sectional study we included 291 familial hipercholesterolemia patients with and without previously diagnosed diabetes. Based on value of the Dutch Lipid Clinical Network score criteria, familial hipercholesterolemia patients without diabetes was further divided into: possible (3-5 points), probable (6-8 points), and definite (>8 points) familial hypercholesterolemia. Triglyceride to high density cholesterol ratio, non-HDL-cholesterol and remnant cholesterol were used as parameters of lipid residual cardiovascular risk. **Results.** We found statistically significant differences in total cholesterol, low and high density cholesterol, triglycerides and apolipoprotein B between the groups ($p>0.05$). The definite and probable group had higher non-HDL-cholesterol values than possible and familial hypercholesterolemia with diabetes ($p<0.01$) groups. Familial hypercholesterolemia with diabetes group had higher values of triglyceride to high density cholesterol ratio and remnant cholesterol than definite and probable group ($p<0.01$). Regression analysis showed that triglyceride to high density cholesterol ratio was independent predictor of appearance of coronary artery disease in addition to elevated low density cholesterol and non-HDL-cholesterol ($p<0.01$). **Conclusion.** Triglyceride to high density cholesterol ratio is the most important parameter of the lipid residual cardiovacular risk that strongly linked with cardiovascular disease in familal hypercholesterolemia patients, especially with associated diabetes.

**Key words:** Heart Disease Risk Factors; Hyperlipoproteinemia Type II; Diabetes Mellitus; Cardiovascular Diseases; Risk Factors; Triglycerides; Cholesterol, HDL

**Sažetak**

**Uvod.** Familijarna hiperholesterolemija je nasledna bolest povezana sa pojavom prematurne kardiovaskularne bolesti. Primarni terapijski cilj je nivo holesterola male molekulske mase, ali se uprkos primeni hipolipemijske terapije često razvija kardiovaskularna bolest. Stoga, postalo je neophodno uzeti u obzir rezidualni kardiovaskularni rizik. Cilj ove studije bio je evaluacija rezidualnog kardiovaskularnog rizika u pacijenata sa familijarnom hiperholesterolemijom. **Materijal i metode.** U ovu presečnu studiju uključili smo 291 pacijenta sa familijarnom hiperholesterolemijom sa i bez prethodno dijagnostikovanog dijabetesa. Na osnovu Dutch Lipid Network Clinical skora za postavljanje kliničke dijagnoze familijarne hiperholesterolemije, grupu pacijenata sa familijarnom hiperholesterolemijom bez dijabetesa smo podelili na: Moguća (3-5 poena), Verovatna (6-8 poena) i Sigurna (>8 poena) familijarna hiperholesterolemija. Odnos triglicerida i holesterola velike molekulske mase, non-HDL-holesterola i holesterolskih ostaka su korišćeni kao lipidni parametri rezidualnog kardiovaskularnog rizika. **Rezultati.** Našli smo statistički značajne razlike u ukupnom holesterolu, holesterolu velike i male molekulske mase, trigliceridima i apolipoproteinu B između grupa ($p>0,05$). Grupe definitivna i verovatna imale su veće vrednosti non-HDL-holesterola od moguće i familijarne hiperholesterolemije sa udruženim dijabetesom ($p<0,01$). Grupa familijarne hiperholesterolemije sa dijabetesom imala je veće vrednosti odnosa triglicerida i holesterola velike molekulske mase i holestrolskih ostaka od Verovatne i Definitivne grupe ($p<0,01$). Regresiona analiza je pokazala da je odnos odnos triglicerida i holesterola velike molekulske mase bio nezavisan prediktor pojave koronarne arterijske bolesti pored povišenih holesterola male molekulske mase i non-HDL-holesterola ($p<0,01$). **Zaključak.** Odnos triglicerida i holesterola velike molekulske mase je najvažniji parametar lipidnog rezidualnog kardiovaskularnog rizika snažno povezan sa nastankom koronarne arterijske bolesti kod pacijenata sa familijarnom hiperholesterolemijom, posebno u slučajevima pridruženog dijabetesa.

**Ključne reči:** faktori rizika srčanih oboljenja; familijarna hiperholesterolemija; dijabetes melitus; kardiovaskularna oboljenja; faktori rizika; trigliceridi; HDL holesterol

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***Abbreviations***

| | |
|---|---|
| FH | – familial hypercholesterolemia |
| Ch | – total cholesterol |
| LDL-Ch | – low-density lipoprotein cholesterol |
| LDLR | – low-density cholesterol lipoprotein receptor |
| Apo | – apolipoprotein |
| PCKS9 | – proprotein convertase subtilisin/kexin type 9 |
| LDLRAP | – low-density lipoprotein receptor adapter protein |
| DLCN | – Dutch Lipid Clinic Network |
| ASCVD | – atherosclerosis cardiovascular disease |
| CVD | – cardiovascular disease |
| CV | – cardiovascular |
| Tg/HDL | – triglyceride to high-density lipoprotein |
| CAD | – coronary artery disease |
| SE | – standard error |
| ANOVA | – analysis of variance |
| BMI | – body mass index |
| MetS | – metabolic syndrome |
| Non-HDL-Ch | – non-high-density lipoprotein cholesterol |
| DM | – diabetes mellitus |

## Introduction

Familial hypercholesterolemia (FH) is one of the most common monogenic disorders with a prevalence of 1:250 - 1:500. It is often an underdiagnosed, underestimated and untreated disease that leads to severe elevation of the serum concentrations of total cholesterol (Ch) and low density lipoprotein cholesterol (LDL-Ch). The FH is caused by three main known gene mutations such as defects in LDL receptor (LDLR) gene, less often a variant in the gene for its ligand, apolipoprotein (Apo) B, and rarely by mutation in proprotein convertase subtilisin/kexin type 9 (PCSK9) gene [1–4]. Also, the phenotypic expression with a recessive inheritance may be caused by variants in the LDL receptor adapter protein (LDLRAP) gene [5, 6].

Genetic testing is the gold standard for diagnosing FH; however, it is not always available. The European Association for Atherosclerosis recommends the Dutch Lipid Clinic Network (DLCN) criteria for clinical diagnosis of FH. The DLCN score is useful for clinical evaluation and detection of FH, but it can sometimes be compromised by the lack of information needed to quantify it. As an alternative, the criteria of United States Program - Make Early Diagnosis to Prevent Early Deaths and Simon-Broome Diagnostic criteria can be used [5–7].

The LDL-Ch is the primary target for initiating lipid-lowering therapy including statins, ezetimibe, PCSK9 inhibitors, and LDL-apheresis, in order to prevent the increase of morbidity and mortality of atherosclerotic cardiovascular disease (ASCVD) in FH patients [1, 5, 6, 8, 9]. Although LDL-Ch is a measure of CARDIOVASCULAR DISEASE (CVD) risk and lowering LDL-Ch is the primary therapeutic goal, there is evidence that despite the lipid-lowering therapy CVD still occurs, thus it is necessary to pay attention to the residual cardiovascular (CV) risk [8, 9]. The triglyceride to high-density lipoprotein (Tg/HDL) ratio is a useful marker of cardiometabolic risk strongly associated with coronary artery disease (CAD), cardiovascular events, metabolic syndrome (MetS), insulin resistance and development of diabetes mellitus (DM) [10–14].

Non-HDL-Ch value includes all the atherogenic lipoprotein particles and according to the results of primary and secondary prevention studies, non-HDL-Ch is a predictor of the lipid residual CV risk [8, 15–18].

Remnant-Ch is also proposed as a marker of residual CVD risk. It is considered that there is an association between elevated level of remnant-like particles and an increased risk for myocardial infarction [8, 16–18].

The DM is a metabolic disorder which is closely related with increased risk for CVD complications [19]. Previous studies [20, 21] suggested that patients with both hereditary dyslipidemia and DM are at significantly higher risk for unwanted outcomes of ASCVD than patients who only suffer from DM.

Considering all the above facts, the aim of the study was to evaluate the lipid residual CV risk parameters in FH patients not receiving lipid lowering therapy in order to identify patients at increased residual risk of CVD in whom treatment strategy can be adapted.

## Material and Methods

The subjects included in this cross-sectional study were selected from medical records of 291 consecutive patients with FH+ diagnosed by DLCN score. Of these subjects, we selected those without type 2 DM (FH + DM-) and subject with diagnosed type 2 DM (FH + DM+). Based on the value of the DLCN score, the FH + DM- group was further divided into three subgroups: possible FH + DM- (3 - 5 points), probable FH + DM- (6 - 8 points), and definitive FH + DM- (> 8 points). The exclusion criteria for participation were: a) individuals < 18 years; b) incomplete medical documentation; c) previous use of statins in therapy. The data collected refer to the first examination, i.e., before the start of lipid therapy.

*Dutch Lipid Clinic Network score criteria*

The DLCN score is a set of criteria including the following data: family history of early CVD (for women > 60 years, for men > 55 years), the presence of corneal arcus and xanthomas, and individuals younger than 18 years with serum LDL-Ch values above the 95th percentile for age and sex; personal history of prior coronary, cerebral, or peripheral vascular disease; blood LDL-Ch levels before initiation of therapy.

*Lipid parameters for the residual cardiovascular risk*

We used Tg/HDL ratio, non-HDL-Ch and remnant-Ch as parameters of the residual cardiovascular risk.

The Tg/HDL ratio was calculated as the quotient of serum triglyceride and HDL-Ch levels. The value of 1.0 for men and 1.3 for women was indicated as the cut-off value for identifying patients at high CVD risk. Values higher than these indicated presence of an atherogenic lipid profile, which is associated with hypertension, hypercholesterolemia and hypertriglyceridemia which are significant risks for development of CVD [14].

Non-HDL-Ch was calculated from a lipid profile (non-HDL-Ch = Ch minus HDL-Ch. Non-HDL-Ch can

be calculated in a non-fasting patient, unlike LDL-Ch measurement, which requires fasting. The optimal non-HDL cholesterol is less than 3.3 mmol/L so a higher value indicates a higher risk for heart disease [15].

Remnant-Ch was calculated from a lipid profile (remnant-Ch = Ch minus LDL-Ch minus HDL-Ch. Elevated remnant cholesterol concentrations were defined as ≥1.0 mmol/L [16, 17].

Laboratory tests and anthropometric measurements were performed at the Clinic of Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Centre of Serbia. Blood samples were collected after 12 - 14 hours of overnight fasting. Lipid status was assessed by determining Ch, HDL-Ch, and triglycerides using an enzymatic colorimetric assay for quantitative determination on Olympus analyzer. The LDL-Ch was calculated by using the Friedewald equation. Apolipoproteins (Apo) B and A1 were determined by the immunoturbidimetry method.

The data were previously tested for normality of distribution by Kolmogorov-Smirnov test and presented as a mean ± standard error (SE) or median. The differences between FH+ DM- and FH + DM+ groups were tested by using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, while the Pearson chi-square test was used for categorical variables. In order to analyze the independent determinants of CVD, binary logistic regression analysis was used, with CVD as dependent variable. The statistical analyses were performed using SPSS software, version 20.0 and differences were considered statistically significant if $p < 0.05$.

## Results

The characteristics of subjects included in the study are summarized in **Table 1**. We found that there were statistically significant differences between groups in gender, age, body mass index (BMI) and incidence of CVD ($p < 0.05$). In all groups there were more female patients ($p < 0.01$). In our study, FH + DM+ patients were older than definite FH + DM- patients ($p = 0.01$) and probably FH + DM- patients ($p < 0.001$). Also, possible FH + DM- patients were older than probably FH + DM- patients ($p = 0.03$). We found that FH + DM+ group had a higher BMI than definitive FH + DM-, probable FH + DM- and possible FH + DM- ($p < 0.05$) groups. The possible FH + DM- and FH + DM+ patients had higher prevalence of CVD than definitive FH + DM- and probable FH + DM- patients ($p < 0.001$).

Lipid parameters in FH patients with and without diabetes are summarized in **Table 2**. We observed that there were statistically significant differences in Ch, LDL-Ch, HDL-Ch, triglycerides and Apo B between groups ($p > 0.05$). The definitive FH + DM- group had higher Ch values than possible FH + DM- and FH + DM+ ($p < 0.01$) groups. The probable FH + DM- had higher Ch values than possible FH + DM- and FH + DM+ groups ($p = 0.03$). The definitive FH + DM- group had higher LDL-Ch values than possible FH + DM- and FH + DM+ ($p < 0.01$) groups. The probable FH + DM- group had higher LDL-Ch values than possible FH + DM- and FH + DM+ groups ($p < 0.01$). The FH + DM+ group had higher triglycerides than definitive FH + DM- ($p < 0.01$) and probable FH + DM- groups ($p = 0.02$). The definitive FH + DM- group had higher Apo B values than possible FH + DM- group ($p < 0.01$). The probable FH + DM- group had higher Apo B values than possible FH + DM- group ($p < 0.01$).

Parameters of residual cardiovascular risk of lipid origin in FH patients with and without diabetes are summarized in **Table 3**. We found statistically significant differences in values of parameters of residual CVD risk of lipid origin between the groups ($p > 0.05$). The group with definitive FH + DM- had higher non-HDL values than possible FH + DM- and FH + DM+ groups ($p < 0.01$). The probable FH + DM-

**Table 1.** Patient characteristics
***Tabela 1.*** *Karakteristike pacijenata*

| | FH + DM- | | | FH + DM+ | p / *p* |
|---|---|---|---|---|---|
| | Definitive/*Sigurna* Group I/*Grupa I* | Probable/*Verovatna* Group II/*Grupa II* | Possible/*Moguća* Group III/*Grupa III* | Group IV *Grupa IV* | |
| n | 48 | 69 | 122 | 52 | |
| Gender/*Pol* (m/f/*m/ž*) | 11/37 | 18/51 | 46/76 | 19/33 | *< 0.01 |
| Age/*Starost*[a] | 53.8 ± 14.9 | 52.9 ± 16.7 | 61.4 ± 14.3 | 62.0 ± 12.8 | *< 0.001 |
| BMI (kg/m$^2$)/*ITM*[b] *(kg/m$^2$)* | 25.3 (18.9 - 34.2) | 24.8 (19.4 - 35.8) | 24.9 (18.3 - 38.5) | 28.3 (23.0 - 39.4) | **< 0.05 |
| CAD (%)/*KBS (%)* | 9.8% | 9.8% | 41.2% | 39.2% | ¶< 0.001 |

[a]Data are expressed as a mean ± SE or as a [b]median/*[a]Podaci su izraženi kao srednja vrednost ± standardna greška ili kao [b]medijana*; BMI/ITM - Body mass index/*Indeks telesne mase*; CAD - Coronary artery disease/*KBS - koronarna bolest srca*

DLCNS – Dutch Lipid Clinic Network score/*Skor*; FH + DM- – Familial hypercholesterolemia patients without diabetes/*Pacijenti sa familijarnom hiperholesterolemijom bez dijabetesa*; FH + DM+ – Familial hypercholesterolemia patients with diabetes/*Pacijenti sa familijarnom hiperholesterolemijom i udruženim dijabetesom*

Group/*Grupa I* – DLCNS > 8; Group II/*Grupa II* – DLCNS 6 – 8; Group III/*Grupa III* – DLCNS 3 – 5; Group IV/*Grupa IV* – DLCNS ≥ 3 with type 2 diabetes mellitus/*sa tipom 2 dijabetesa*

*p – One way ANOVA test for differences between Group I, Group II, Group III and Group IV/*Jednofaktorska analiza varijanse je korišćena kao test za razliku između I, II, III i IV grupe. Bonferonijev naknadni test razlike između grupa*

****p – Kruskal-Wallis test used for differences between Group I, Group II, Group III and Group IV/*Kruskal-Volisov test između I, II, III i IV grupe.*

¶p – Chi-square test between Group I, Group II, Group III and Group IV/*Pirsonov Hi-kvadratni test između grupa*

**Table 2.** Lipid parameters in FH patients with (FH + DM+) and without diabetes (FH + DM-)
***Tabela 2.*** *Lipidni parametri kod pacijenata sa familijarnom hiperholesterolemijom sa (FH+DM+) i bez dijabetesa (FH+DM-)*

| | FH + DM- | | | FH + DM+ | p/*p* |
|---|---|---|---|---|---|
| | Definitive/*Sigurna* Group I/*Grupa I* | Probable/*Verovatna* Group II/*Grupa II* | Possible/*Moguća* Group III/*Grupa III* | Group IV *Grupa IV* | |
| Total Ch/*Ukupni-h (mmol/L)*[a] | 8.48 ± 2.74 | 7.78 ± 2.03 | 6.96 ± 1.51 | 6.79 ± 1.91 | < 0.01* |
| HDL-Ch/h (mmol/L) | 1.5 ± 0.48 | 1.41 ± 1.38 | 1.5 ± 0.48 | 1.27 ± 1.36 | 0.01 |
| LDL-Ch (mmol/L) | 4.63 ± 1.35 | 5.52 ± 1.85 | 4.63 ± 1.35 | 4.46 ± 1.75 | < 0.01 |
| Triglicerydes/*Trigliceridi (mmol/L)*[b] | 1.5 (0.6 - 12.4) | 1.6 (0.5 - 7.7) | 1.8 (0.5 - 11.4) | 2.3 (0.9 - 4.1) | < 0.01** |
| Apo B (g/L) | 1.6 (0.2 - 3.0) | 1.6 (0.3 - 2.9) | 1.4 (0.5 - 2.4) | 1.4 (0. 2.7) | < 0.01 |
| Apo A1 (g/L) | 1.5 (0.8 - 2.6) | 1.7 (1.1 - 2.9) | 1.6 (1.0 - 2.7) | 1.6 (1.1 - 2.7) | > 0.05 |
| Lp (a) (g/L) | 0.3 (0.1 - 1.2) | 0.2 (0.1 - 1.6) | 0.2 (0.1 - 1.7) | 0.2 (0.1 - 1.5) | > 0.05 |

[a]Data are expressed as mean ± SE or as [b]median; [a]*Podaci su izraženi kao srednja vrednost ± standardna greška ili kao* [b]*medijana*;
DLCNS – Dutch Lipid Clinic Network score/*Skor*
Group/Grupa I – DLCNS > 8; Group/*Grupa* II – DLCNS 6 – 8; Group/*Grupa* III – DLCNS 3 – 5; Group/*Grupa* IV – DLCNS ≥ 3 with diabetes mellitus type 2/*Sa tipom 2 dijabetesa*
Total Ch/*Ukupni-h* – Total cholesterol/*Ukupni holesterol*; HDL-Ch/h – High density cholesterol/*Holesterol velike molekulske mase*; LDL-Ch/h – Low density cholesterol/*Holesterol male molekulske mase*
* p - One way ANOVA test between Group I, Group II, Group III and Group IV. *Jednofaktorska analiza varijanse je korišćena kao test za razliku između I, II, III i IV grupe. Bonferonijev naknadni test razlike između grupa*
**p – Kruskal-Wallis test between Group I, Group II, Group III and Group IV/*Kruskal-Volisov test između I, II, III i IV grupe.*

**Table 3.** Parameters of the residual cardiovascular risk in FH patients with (FH + DM+) and without diabetes (FH + DM-)
***Tabela 3.*** *Parametri rezudualnog kardiovaskularnog rizika kod pacijenata sa familijarnom hiperholesterolemijom sa (FH+DM+) i bez dijabetesa (FH+DM-)*

| | FH + DM- | | | FH + DM+ | p/*p* |
|---|---|---|---|---|---|
| | Definitive/*Sigurna* Group I/*Grupa I* | Probable/*Verovatna* Group II/*Grupa II* | Possible/*Moguća* Group III/*Grupa III* | Group IV *Grupa IV* | |
| Non-HDL cholesterol/ *holesterol* (mmol/l)[b] | 7.5 (1.8 - 12.4) | 6.5 (2.9 - 11.4) | 5.7 (2.0 - 9.8) | 5.6 (2.5 - 11.8) | *< 0.01 |
| Remnant-cholesterol *Rezidualni holesterol* (mmol/l) | 0.7 (0.3 - 8.5) | 0.7 (0.2 - 8.1) | 0.8 (0.2 - 9.8) | 1.1 (0.5 - 2.6) | *< 0.01 |
| Tg/HDL ratio/*odnos* | 1.1 (0.4 - 9.1) | 1.2 (0.3 - 8.5) | 1.5 (0.3 - 12.3) | 1.7 (0.8 - 4.2) | *< 0.01 |

Data are expressed as [b]median;*Podaci su izraženi kao* [b]*medijana*
Group/*Grupa I* – DLCNS > 8; Group/*Grupa* II – DLCNS 6 – 8; Group/*Grupa* III – DLCNS 3 – 5; Group/*Grupa* IV – DLCNS ≥ 3 with diabetes mellitus type 2/*Sa tipom 2 dijabetesa*
*p – Kruskal-Wallis test between Group I, Group II, Group III and Group IV/*Kruskal-Volisov test između I, II, III i IV grupe*

group had higher non-HDL-Ch values than possible FH + DM- and FH+DM+ groups (p = 0.03). In our study, the FH + DM+ group had higher values of remnant-Ch than definite FH + DM- and probable groups (p < 0.01). We found that the FH + DM+ group had higher Tg/HDL ratio than definitive FH + DM- and probable FH+DM- (p < 0.01) groups.

In order to evaluate the effects of the investigated determinants on the incidence of CVD in FH+ patients with and without type 2 DM, we performed a binary logistic regression analysis with CVD as a dependent variable and found that the Tg/HDL ratio is a strong independent predictor of CVD in the whole sample and in FH + DM+ patients **(Figure 1)**.

## Discussion

Despite the significantly elevated LDL-Ch and non-HDL-Ch in all FH patients, the results of our study show that, if the Tg/HDL ratio is elevated there is a significantly higher risk for early development of CAD. Moreover, our results imply that this association is especially pronounced if there is also DM along with FH. Additionally, of the three investigated residual risk parameters, our results indicate that Tg/HDL is the most important parameter of the lipid residual CV risk, suggesting that in addition to routinely measured LDL-Ch levels in FH patients, attention needs to be paid to the residual risk, as well as the timely diagnosis of DM in those patients.

The CAD is the most common heart disease and represents a consequence of a partial or total vessel obstruction of coronary arteries caused by lipid accumulation and atherosclerotic plaque formation below the tunica intima [22]. Although the high cost of multiple markers of lipid panels which are strongly associated with development of CAD and necessity

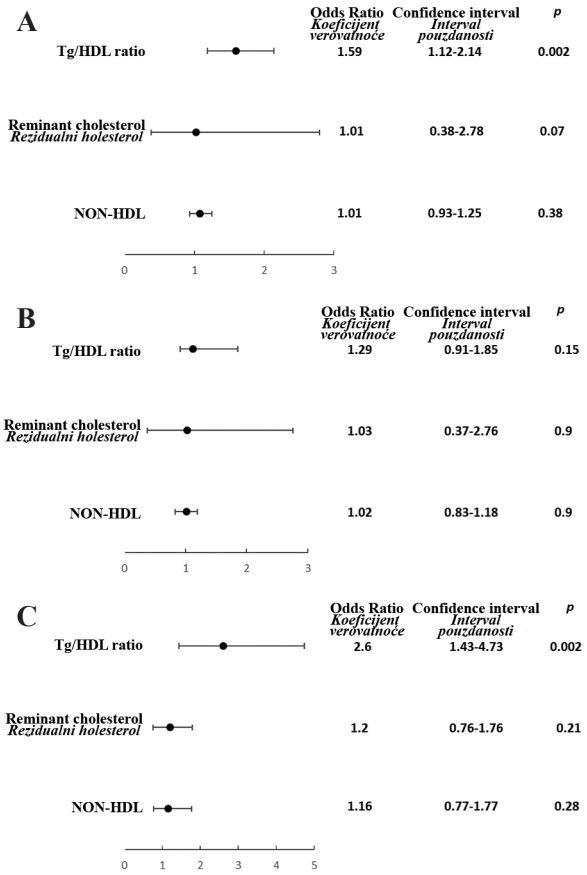


**Figure 1.** Binary logistic regression analysis of the lipid residual risk determinants in the prediction of CAD in all investigated patients with FH (A), in patient with FH without DM (B) and in patients with FH and DM (C)
***Slika 1****. Binarna logistička regresiona analiza determinanti rezidualnog lipidnog kardiovaskularnog rizika za predikciju koronarne bolesti srca kod svih pacijenata (A), kod pacijenata sa familijarnom hiperholesterolemijom bez dijabetes melitusom (B) i kod pacijenata sa familijarnom hiperholesterolemijom bez dijabetes melitusa (C)*

for technical expertise render, researchers have focused to find more affordable atherogenic indices [10].

Previous studies, including our own, show that a high percentage of patients with FH do not reach the recommended LDL-Ch target values, but also that there is a high residual CV risk [3, 9]. Gaziano et al. [13] were the first to point out in a case-control study that Tg/HDL ratio strongly predicts the risk of myocardial infarction, while other studies associate high values of the Tg/HDL with CAD [10–12], degree of coronary atherosclerosis [12] and metabolic syndrome (MetS), so it could be a good marker of increased residual CV risk [10]. In our study, the highest values of Tg/HDL ratio were found in FH patients with associated type 2 DM, and this group also had a high prevalence of CAD. Our results are consistent with the results of numerous studies that have closely linked the high values of Tg/HDL ratio with adverse CV events.

According to our results, patients with FH and type 2 DM had the highest values of triglycerides and the lowest value of HDL-Ch. Our results are consistent with early studies which proved atherogenic lipid profile in diabetic subjects. Insulin deficiency and insulin resistance, two underlying conditions in type 2 DM, lead to dyslipidemia by affecting hepatic lipoprotein production, particularly very low-density lipoprotein and triglyceride-rich lipoproteins. Also, insulin resistance, obesity, MetS and type 2 DM are associated with increased production of serum triglycerides which are associated with low levels of HDL-Ch. Atherogenic dyslipidemia in such conditions is typically characterized by lipid abnormalities such as hypertriglyceridemia, reduced levels of HDL-Ch and increased level of small density LDL particles and Apo B, but often without significant elevation of LDL-Ch [23, 24]. Large-scale epidemiological studies indicated that, regardless of the use of statin therapy, elevated triglycerides levels may be the cause of adverse cardiovascular events. Atherogenic dyslipidemia underlies the residual CV risk that exists despite lowering LDL-Ch to target values [11].

Interestingly, in our results, the possible FH group had higher prevalence of CAD than probable and definite FH groups. Although there were no statistically significant differences in Tg/HDL values, the possible FH group had higher mean value of this ratio than definite and probable FH groups. This result can be explained by the fact that due to unavailable genetic testing for FH, this group may include individuals who do not actually have true hereditary hypercholesterolemia, but MetS. The most common lipid abnormalities associated with MetS are hypertriglyceridemia and low HDL-Ch values as a lipid profile seen in diabetic individuals [25]. The mentioned study [25] showed that Tg/HDL ratio could be an excellent novel marker for effective risk prediction for MetS and CVD.

The results of our study show that the highest remnant-Ch levels were in the group of FH patients with diabetes and it was associated with a high incidence of CAD. Earlier studies [16–18] showed that elevated remnant-Ch level was a significant and independent risk factor for CAD and type 2 DM. Due to small size, remnant-Ch passes easily through the endothelium, then binds to connective matrix in sub-endothelium and promotes chronic low-grade inflammation of smooth muscle cells, thus playing a crucial role in pathological process of atherogenesis [18]. Residual CV risk has been pointed out by various associations, such as the American College of Cardiology, American Heart Association, European Society of Cardiology, and European Atherosclerosis Society. The recommendations of these associations are based on finding a secondary treatment target that may indicate more intensive lipid-lowering therapy. The LDL-Ch remains the primary treatment target, but secondary treatment targets depend on the calculated risk of fatal ASCVD estimated by the score system (very high, high, moderate or low) and also by the associated diabetes [15]. The highest levels of non-HDL-Ch in our study were in the definitive FH group.

The obtained results are the consequence of the highest concentration of LDL-Ch and total-Ch in definitive FH group. Moreover, our study shows that despite the highest levels of LDL-Ch and non HDL-Ch unwanted cardiovascular events were not the most prevalent in this group. A possible reason is that the diagnosis of FH in definitive and probable FH groups was made more often due to the characteristic stigmata (tendon xanthomas, arcus cornealis) than to abnormality in laboratory test results and positive family history (they are not index cases).

Studies [20, 21] also confirmed that FH subjects with diabetes confer a substantial increase in the incidence of adverse CV outcomes than individuals who have only hereditary hypercholesterolemia or only type 2 DM. Due to all of the above, timely diagnosis of these disorders is extremely important, as well as the definition of therapeutic goals with special reference to the residual CV risk [20].

## Conclusion

Data from the present study suggest that, regardless of significantly elevated low density lipoprotein and non-high-density lipoprotein cholesterol in all familial hypercholesterolemia patients, if the triglyceride to high-density lipoprotein ratio is elevated, there is a significantly higher risk of coronary artery disease. In addition, our results show that triglyceride to high-density lipoprotein is the most important parameter of the lipid residual cardiovascular risk implying that its measurement is very important in the assessment of overall cardiovascular risk in patients with familial hypercholesterolemia, especially in cases with associated diabetes.

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