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Professional article
Stručni članak
UDK 616.153-008.9:577.125]-07
https://doi.org/10.2298/MPNS2306151K

CORRELATION OF THE DUTCH LIPID CLINIC NETWORK SCORE AS A DIAGNOSTIC TOOL AND LIPID PARAMETERS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

KORELACIJA DIJAGNOSTIČKOG DUTCH LIPID CLINIC NETWORK SKORA I LIPIDNIH PARAMETARA KOD PACIJENATA SA FAMILIJARNOM HIPERHOLESTEROLEMIJOM

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Summary

Introduction. Familial hypercholesterolemia is a congenital disorder of lipid metabolism. The Dutch Lipid Clinic Network score is used for early diagnosis of familial hypercholesterolemia. The aim of the study was to examine correlation between the above score and the first measured lipid values in patients who had not used lipid-lowering therapy. **Material and Methods.** 390 patients identified as familial hypercholesterolemia+ (n=247) and familial hypercholesterolemia- (n=143) according to the Dutch Lipid Clinic Network score. Family and personal history, physical examination, demographic and anthropometric characteristics and lipid status were analyzed. **Results.** The familial hypercholesterolemia+ group had all Dutch Lipid Clinic Network score components significantly higher than the familial hypercholesterolemia- group. The highest average number of points in familial hypercholesterolemia+ group carries low-density lipoprotein level and family history data. Significantly higher levels of total cholesterol, low-density lipoprotein and apolipoprotein B were found in the familial hypercholesterolemia+ group, while high-density lipoprotein was lower in the familial hypercholesterolemia- group. The Dutch Lipid Clinic Network score correlates best with level of low-density lipoprotein and apolipoprotein B ($p<0.001$). The cut-off point for low-density lipoprotein is 4.9 mmol/L (sensitivity 56%; specificity 8%), while the cut-off point for apolipoprotein B is 1.52 g/L (sensitivity 42%; specificity 12.5%) for diagnosis of familial hypercholesterolemia. **Conclusion.** Low-density lipoprotein and apolipoprotein B values significantly correlate with Dutch Lipid Clinic Network score values. Elevated values of low-density lipoprotein (>4.9 mmol/L) significantly affect the total value of the Dutch Lipid Clinic Network score and are considered components that carry large number of points for the diagnosis of familial hypercholesterolemia.

Key words: Hyperlipoproteinemia Type II; Early Diagnosis; Cholesterol, LDL; Apolipoproteins B; Decision Support Techniques; Predictive Value of Tests

Sažetak

Uvod. Familijarna hiperholesterolemija je urođeni poremećaj metabolizma lipida. Za ranu dijagnostiku koristi se *Dutch Lipid Clinic Network* skor. Cilj studije bio je da ispita korelaciju između pomenutog skora i prvih izmerenih vrednosti lipida kod pacijenata koji ranije nisu koristili terapiju za snižavanje nivoa lipida. **Materijal i metode.** Identifikovano je 390 pacijenata kao familijarna hiperholesterolemija + (n = 247) i familijarna hiperholesterolemija – (n = 143) prema *Dutch Lipid Clinic Network* skoru. Analizirali smo porodičnu i ličnu anamnezu, fizikalni pregled, demografske i antropometrijske karakteristike i kompletan lipidogram. **Rezultati.** Grupa Familijarna hiperholesterolemija + imala je sve komponente *Dutch Lipid Clinic Network* skora značajno veće nego grupa Familijarna hiperholesterolemija –. Najveći prosečni broj poena u grupi Familijarna hiperholesterolemija + nosi nivo lipoproteina male gustine i podaci o porodičnoj anamnezi. Nađeni su značajno viši nivoi ukupnog holesterola, lipoproteina male gustine i apolipoptoteina B u grupi Familijarna hiperholesterolemija +, dok je lipoprotein velike gustine bio niži u grupi Familijarna hiperholesterolemija –. *Dutch Lipid Clinic Network* skor najbolje korelira sa nivoom lipoproteina male gustine i sa apolipoproteinom B ($p < 0,001$). Granična tačka za lipoprotein male gustine je 4,9 mmol/L (osetljivost 56%; specifičnost 8%), dok je za apolipoprotein B granična tačka 1,52 g/L (osetljivost 42%; specifičnost 12,5%) za dijagnozu familijarne hiperholesterolemije. **Zaključak.** Vrednosti lipoproteina male gustine i apolipoprotina B značajno koreliraju sa vrednostima *Dutch Lipid Clinic Network* skora. Povišene vrednosti lipoproteina male gustine (> 4,9 mmol/L) značajno utiču na ukupnu vrednost *Dutch Lipid Clinic Network* skora, te se smatraju komponentom koja nosi veliki broj poena za dijagnozu familijarne hiperholesterolemije.

Ključne reči: familijarna hiperlipoproteinemija; rana dijagnoza; LDL holesterol; apolipoprotein B; tehnike za podršku odlučivanju; prediktivna vrednost testova

Introduction

Familial hypercholesterolemia (FH) is the most common inherited disorder of lipid metabolism. It is a monogenetic disorder characterized by high levels of low-density cholesterol (LDL-ch) from birth and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD) [1, 2].

Familial hypercholesterolemia can be an autosomal dominant or an autosomal recessive disease. Autosom-

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Abbreviations

FH	– familial hypercholesterolemia
LDL-ch	– low-density cholesterol
HDL	– high-density lipoprotein
ASCVD	– atherosclerosis cardiovascular disease
Apo B	– apolipoprotein B
DLCN S	– Dutch Lipid Clinic Network Score
Apo A1	– apolipoprotein A1
Tg	– triglycerides
Lp (a)	– lipoprotein (a)
BMI	– body mass index
BW	– body weight
BH	– body height

al dominant FH in 95% of patients occurs as a result of a mutation in the gene encoding the low-density cholesterol (LDL) receptor (LDLR) [3, 4]. In 5% patients, mutations are found in the genes for apolipoprotein B (Apo B) and pro-protein convertase subtilisin/kexin type 9 (PCSK 9), and have similar functional consequences [3]. In the autosomal recessive form of FH, there is a mutation in LDLR adapter protein 1 [5].

In FH, the basis of the pathological process is inadequate removal of LDL from plasma, which increases the concentration of LDL-ch in blood and the creation of atherosclerotic changes from birth [6]. FH can be manifested in homozygous and heterozygous forms. Patients with the heterozygous form of FH have values of total cholesterol and LDL-h between 7.75-13 mmol/L, while with the homozygous form, the values are much higher and range from 15.5-31.0 mmol/L [7].

Familial hypercholesterolemia is usually underdiagnosed and undertreated leading to premature ASCVD. Early identification of FH patients is very important in order to timely reduce lipid parameters and prevent unwanted cardiovascular disorders. The use of therapy to reduce the value of lipid parameters at a younger age reduces the occurrence of premature ASCVD contributing this way to the reduction of morbidity and mortality [1, 7].

The gold standard for diagnosing FH is genetic testing, but it is not included in routine diagnostic procedures. Therefore, the diagnosis of FH is usually based on clinical findings or validated scores that include clinical and laboratory parameters. The generally accepted scoring method in the world, but also in our country, is the Dutch Lipid Clinic Network score (DLCN S). The DLCN score includes personal and family data, as well as clinical and lipid parameters. According to DLCN score points, FH patient could be identified as definite (>8), probable (6-8), possible (3-5) or unlikely (0-2) [1].

The aim of the study is to analyze the correlation between the DLCN score and the level of lipid parameters at the time of diagnosis, as well as to identify the best individual lipid parameter that correlates with the DLCN score which in routine clinical work could be an early marker of the presence of FH.

Material and Methods

For this study, we analyzed the database and the medical records of patients with lipid disorders treated in the Lipid Disorders Unit at the Clinic of Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia (UCCS). The patients were selected according to the criteria as follows: diagnosed hyperlipoproteinemia, clearly established increased LDL-ch value (without previously applied therapy) with triglycerides level < 4.5 mmol/l, and existing data on personal and family history. Our research included a total of 390 patients who met all the above criteria.

In all patients, we analyzed demographic characteristics, lipid parameters, and all data available to determine the DLCN score. Data were collected on sex, age, body weight (BW) and body height (BH) from which we calculated the body mass index (BMI) according to the formula: BMI = BW (kg)/BH (m^2), as well as the presence of previous diseases (diabetes mellitus, ASCVD, hypertension). We have also analyzed values of the lipid parameters detected before applying any lipid lowering therapy, and that: total cholesterol, its subfractions high-density lipoprotein (HDL-ch) and LDL-ch, triglycerides (Tg) (analyzed enzymatically using commercial kit), apolipoproteins (Apo) A1 and Apo B and lipoprotein (a) (Lp(a)) (determined by immunoturbidimetry).

Dutch Lipid Clinic Network Score was use for simple diagnosis of FH based on the existing clinical and laboratory parameters. The score includes the following parameters: LDL-ch level, personal and family history (premature peripheral or cerebral vascular disease, coronary disease), presence of xanthoma and/or corneal arcus, and deoxyribonucleic acid (DNA) analysis. Based on the value of the DLCN score, the diagnosis of FH is marked as unlikely (0-2), possible (3-5), probable (6-8), or definite (>8).

The Kolmogorov-Smirnov test was used in the statistical analysis to test the normality of distribution. To compare the groups, we used either the Student's t-test or one-way analysis of variance (ANOVA with Bonferroni post hoc analysis), or the Chi-square test for nonparametric variables. The correlation of variables was tested with use of the Spearman correlation test, and cut-off points for lipid parameters were detected with use of ROC curve analysis. Results are express as mean ± standard error (SE) or as a number (percentage). The statistical significance of the difference was set at <0.05. SPSS 20.0 software was used for statistical data processing.

Results

Our research included 390 subjects, of which 159 male patients (40.8%) and 231 female patients (59.2%). From the total number of patients, 63.3% (n=247) were identified using the DLCN score as having FH (FH+ group), while in 36.7% (n=143) the diagnosis of FH (FH- group) was not confirmed (total point of DLCN score 0-2). The characteristics of the subjects included in the study are summarized in **Table 1.** The patients did not differ in age, while the majority of patients from the FH- group had diabetes, previous coronary disease and hyper-

tension, and their BMI was significantly higher in comparison to the FH+ group.

Analysis of each DLCN score component have shown that all components in the FH+ group were significantly higher than the ones in FH- group. In addition, the highest average number of points in the FH+ group carries the levels of LDL-ch and then the family data as well. At the same time, total average number of DLCN score points was almost six-fold greater compared to the FH- group **(Table 2)**.

When we analyzed the levels of the investigated lipid parameters, we found significantly higher levels of total ch, LDL-ch and Apo B in the FH+ group compared to the FH- group, while HDL-ch was significantly lower in FH- group compared to the FH+ group. At the same time, we could not find any differences in the levels of Tg, Apo A1 or Lp(a) between the two groups (data are shown on **Table 3**).

Additionally, we analyzed the mean DLCN score and lipid levels in the Group FH+ divided according to the DLCN score points. Of 247 patients with confirmed FH diagnosis, 47 patients had a definite FH diagnosis (score >8), 56 patients had a probable FH diagnosis (score 6-7) and 144 patients had a possible FH diagnosis (score 3-5). Significant difference was found between these subgroups in FH+ patients when it comes

Table 1. Demographic characteristics of the investigated patients with and without FH
Tabela 1. *Demografske karakteristike pacijenata sa familijarnom hiperholesterolemijom (FH) i bez nje*

Parameters/*Parametri*	FH+ group/*Grupa FH+* (n=247)	FH- group/*Grupa* FH- (n=143)	p/*p*
Gender (M/F)/*Pol (M/Ž)*	83/164	51/92	
Age/*Godine*	60.47 ± 1.04 [a]	59.25 ± 1.32	NS
BW/*Telesna težina* (kg)[b]	73.86 ± 0.88	78.13 ± 1.31	< 0.05
BMI/*Indeks telesne mase* (kg/m^2)[c]	26.17 ± 0.26	27.05 ± 0.33	< 0.05
Diabetes/*Dijabetes* (%)	22.0	78.0	< 0.01
Coronary disease/*Koronarna bolest* (%)	13.1	86.9	< 0.05
Hypertension/*Hipertenzija* (%)	29.9	70.1	< 0.05

Legend: [a] Results are expressed as mean ± SE; [b] BW - Body weight; [c] BMI - Body mass index
Legenda: [a] Rezultati su izraženi kao srednja vrednost ± SD; [b] BW – Telesna težina; [c] BMI – Indeks telesne mase

Table 2. Average point number of DLCN S components in patients with and without FH
Tabela 2. *Prosečan broj poena komponenti DLCN skora kod pacijenata sa familijarnom hiperholesterolemijom (FH) i bez nje*

Score components/*Komponente skora*	FH+ group/*FH+ grupa*	FH- group *FH- grupa*	p/*p*
Family history/*Porodična anamneza*	1.09 ± 0.06	0.42 ± 0.04	<0.001
Personal history/*Lična anamneza*	0.60 ± 0.06	0.12 ± 0.03	<0.001
Xanthomas/*Ksantomi*	0.53 ± 0.11[a]	0.00 ± 0.00	<0.001
LDL-ch value/LDL-h[b]	3.74 ± 0.13	0.63 ± 0.04	<0.001
Total DLCN score[c]/*Ukupni DLCN skor*	5.92 ± 0.21	1.03 ± 0.07	<0.001

Legend: [a] Results are expressed as mean ± SE; [b] LDL-ch/LDL-h – Low density lipoprotein; [c] DLCN S – Dutch Lipid Clinic Network score
Legenda: [a] Rezultati su izraženi kao srednja vrednost ± SD; [b] LDL-ch/LDL-h – Lipoprotein male gustine; DLCN skor – Dutch Lipid Clinic Network skor

Table 3. Values of lipid parameters in patients with FH vs. patients with no disease
Tabela 3. *Vrednost lipidnih parametara kod pacijenata sa familijarnom hiperholesterolemijom (FH) i kod pacijenata bez bolesti*

Parameters/*Parametri*	FH+ group/*Grupa FH+*	FH- group/*Grupa FH-*	p/*p*
Total cholesterol/*Ukupni holesterol*	7.33 ± 0.13[a]	5.84 ± 0.12	<0.001
HDL-ch/ HDL-h[b] (mmol/L)	1.37 ± 0.02	1.22 ± 0.03	<0.05
LDL-ch/LDL-h[c] (mmol/L)	5.05 ± 0.12	3.62 ± 0.10	<0.01
Tg[d] (mmol/L)	2.09 ± 0.07	2.30 ± 0.13	NS
Apo A1[e] (g/L)	1.63 ± 0.02	1.55 ± 0.03	NS
Apo B[f] (g/L)	1.46 ± 0.03	1.22 ± 0.03	<0.001
Lp(a) (mg/L)	0.33 ± 0.02	0.32 ± 0.03	NS

Legend: [a] Results are expressed as mean ± SE; HDL-ch/HDL-h[b] – High density cholesterol; LDL-ch/LDL-h[c] – Low density lipoprotein; Tg[d] – Triglycerides; Apo A1[e] – Apolipoprotein A; Apo B[f] – Apolipoprotein B
Legenda: HDL-ch/HDL-h[b] – Holesterol velike gustine; LDL-ch/LDL-h[c] – Lipoprotein male gustine; Tg[d] – Trigliceridi; Apo A1[e] – Apolipoprotein A; Apo B[f] – Apolipoprotein B

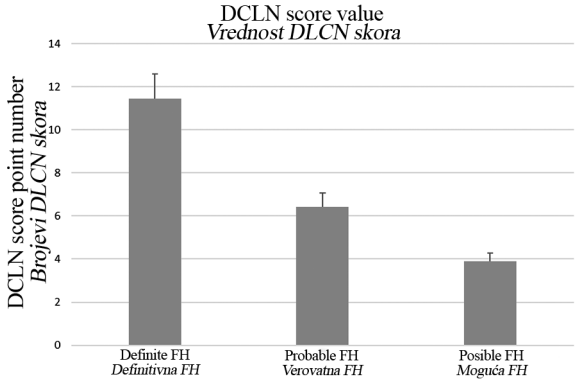

Figure 1. Mean value of total DCLN score in FH+ patients with definite, probable and possible FH
Slika 1. *Srednja vrednost ukupnog DLCN skora kod FH + pacijenata sa definitivnom, verovatnom i mogućom dijagnozom familijarne hiperholesterolemije*

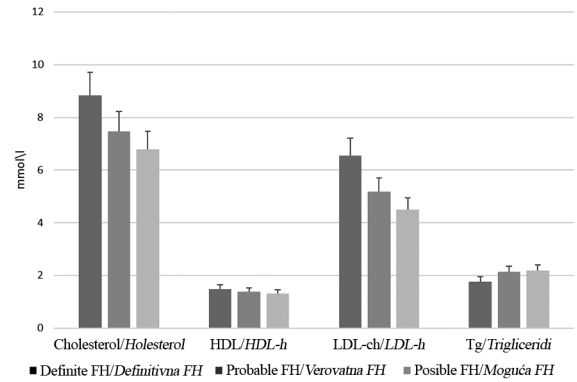

Figure 2. Mean value of lipid parameters in FH+ patients with definite, probable and possible FH
Slika 2. *Srednja vrednost lipidnih parametara kod FH+ pacijenata sa definitivnom, verovatnom i mogućom dijagnozom familijarne hiperholesterolemije*

to DLCN score values ($p<0.05$) **(Figure 1)**. Patients with a definite FH diagnosis had the highest DLCN score mean value (11.45±0.44), which was significantly higher compared to patients with a probable FH (6.43±0.06) or possible FH diagnosis (3.90±0.06; $p<0.05$ respectively) **(Figure 1)**.

Regarding the values of lipid parameters of subgroups (probable, possible, and definite) within the FH+ group, we found that total cholesterol (8.83± 0.37 mmol/l) and LDL-ch (6.55± 0.34 mmol/l) were significantly higher in with the definite FH subgroup in comparison to other two subgroups (total ch: 7.47± 0.25; 6.79± 0.12; LDL-ch: 5.18± 0.24; 4.5± 0.11 mmol/l; $p<0.01$ respectively), while we could not find any differences in HDL-ch and Tg levels **(Figure 2)**. Similarly, Apo B level was significantly higher in the definite FH subgroup (1.8± 0.09 g/l) compared to the other two subgroups (1.53± 0.06; 1.33± 0.03 g/l; $p<0.05$ respectively), while the level of Apo A1 was similar in all three subgroups **(Figure 3)**.

Finally, correlation was made between the total calculated value of the DLCN score and the level of the investigated lipid parameters. According to our results,

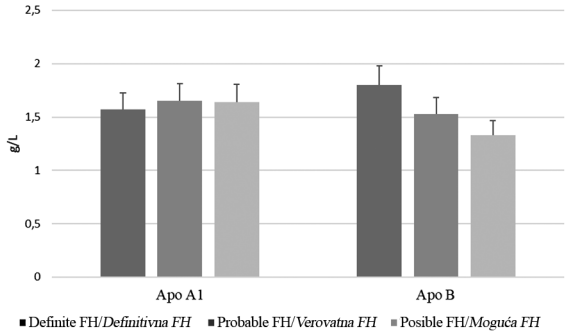

Figure 3. Mean value of Apo A1 and Apo B in FH+ patients with definite, probable and possible FH
Slika 3. *Srednja vrednost apolipoproteina A1 i B kod FH+ pacijenata sa definitivnom, verovatnom i mogućom familijarnom hiperholesterolemijom*

the DLCN score highly statistically and best correlates with the LDL-ch level ($r=0.463$; $p < 0.001$), followed by Apo B ($r=0.364$; $p < 0.001$). We performed the ROC curve analysis to investigate the LDL-ch and Apo B threshold levels that have the highest probability to diagnose FH with use of the DLCN score. The results showed that the cut-off point for LDL-ch is 4.9 mmol/l with 56% sensitivity and 8% specificity, while the cut-off point for Apo B is 1.52 g/l with 42% sensitivity and 12.5% specificity for the diagnosis of FH.

Discussion

The results of this study showed that the level of LDL-ch and Apo B in our cohort of patients with FH correlate most strongly with DLCN score values during the diagnosis. In addition, our results imply that finding of elevated LDL-ch (> 4.9 mmol/l) and/or Apo B (> 1.52 g/l) values during the routine clinical work strongly suggest that the DLCN score should be performed on the patients in order to diagnose FH.

The presence of FH leads to atherosclerotic changes in blood vessels and increases the risk of premature coronary disease [8]. Despite the mentioned facts, the FH is often underdiagnosed in most countries. Early detection of the disease is important for early application of treatment and prevention of atherosclerosis. The goal of our research was to try to improve the diagnosis in order to apply the appropriate therapy. Previous studies, including our research, show that statins were prescribed to patients with FH in only 48% cases and the administered dose was not sufficient to reduce the LDL-ch level according to the recommended guidelines [8–11].

The analysis of all the DLCN score components in our patients showed that there is a significant difference between the patients having the disease (FH+) and the ones not having the disease (FH-), which is in accordance with earlier studies [7–9, 12, 13]. The higher value of mean score points in the DLCN score in our results was found for LDL-ch followed by family data, which strongly suggests that FH should be suspected in patients with elevated LDL-ch and a positive family history (premature ASCVD or high cholesterol in a family member).

At the University of Catania in Italy, in 2017, studies were conducted with a large number of patients (n=1575), which showed that the DLCN score is a very sensitive method that can be used to identify patients with probable FH (score value >6), after which the patients were referred for genetic testing. The high sensitivity of the test is evidenced by the fact that as much as 90.5% of patients had a genetic mutation [9]. In our country, genetic testing is not an everyday clinical practice, so simpler methods such as the DLCN score are used for diagnosis. However, DLCN is a reliable method only if all information is available to calculate its value [9].

We wanted to see with our research if there is a statistically significant difference when it comes to lipid parameters in FH+ and FH-. The results show that there is statistical significance when it comes to total cholesterol, LDL-h, and ApoB, and the diagnosis is easier if these parameters are elevated during lab tests. In the further course of the research, we compared the mean values of lipid parameters between the three groups that we defined based on the DLCN score as definitely, probably, and possibly FH. The results show that patients with a definite FH diagnosis (> 6 mmol/l) had the highest mean value of LDL-ch, while that value was around 5 mmol/l in all patients with FH. Previous research has shown that the value of LDL-ch 5.9 mmol/l represents a value that is associated with the presence of mutation [8], and the diagnosis of FH can be made with great certainty based on the measured LDL-ch between 5.7 and 7.7 mmol/l [14]. Our results are in line with these recommendations and suggest that there is safe diagnosis of FH with high probability in patients with LDL-ch greater than 6 mmol/l, but may also be present with lower LDL-ch values (cut-off >4.9 mmol/l) (which are often overlooked in routine clinical work), and it is also necessary to calculate this simple DLCN score with such patients.

Conclusion

Our research shows that low-density cholesterol values, as well as apolipoprotein B, significantly correlate with Dutch Lipid Clinic Network score values. Elevated low-density cholesterol values (>4.9 mmol/l) significantly affect the total Dutch Lipid Clinic Network score value and are considered components that carry a high number of points for the diagnosis of familial hypercholesterolemia. We want the results of our work to improve diagnosing of familial hyprcholesterolemia and thus prevent unwanted cardiovascular diseases in those patients.

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Rad je primljen 29. VIII 2023.
Recenziran 16. IX 2023.
Prihvaćen za štampu 17. IX 2023.
BIBLID.0025-8105:(2023):LXXVI:5-6:151-155.