A new index (CHOLINDEX) in detecting coronary artery disease risk

Koroner arter hastalığı riskini belirlemede yeni bir index (CHOLINDEX)

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ABSTRACT

Objective: Coronary artery disease (CAD) risk increases with the elevation of low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and low level high-density lipoprotein cholesterol (HDL-C) levels. However, the magnitude at which CAD risk increases with every lipid parameter is controversial. We developed a new index called CHOLINDEX, in order to evaluate CAD risk, and investigated its reliability.
Methods: Three hundred and seven patients (190 males and 117 females, aged between 26-80 years, mean 53.6±10.2 years) who underwent diagnostic coronary angiography were included in the study. Risk factors and lipid profiles of all patients were noted. CHOLINDEX was calculated by using a formula as follows: CHOLINDEX=LDL-C–HDL-C (TG < 400 mg/dL), LDL-C–HDL-C + 1/5 of TG (TG ≥ 400mg/dL).
Results: Of the 307 patients, 180 had CAD. We found that age, male gender, hypertension, diabetes mellitus, smoking and CHOLINDEX were independent predictors of CAD. The logistic regression analysis showed that the CHOLINDEX had a much more significant relation with CAD (odds ratio=1.011, 95% CI=1.003-1.019) compared with other lipid parameters.
Conclusion: CHOLINDEX is a simple index which can be used reliably in prediction of CAD like other lipid parameters in daily clinical practice. *(Anadolu Kardiyol Derg 2013; 13: 315-9)*
Key words: CHOLINDEX, coronary heart disease, lipids, regression analysis

ÖZET

Amaç: Düşük yoğunluklu lipoprotein kolesterol (LDL-K), trigliserid (TG) düzeyinin yüksekliği ve yüksek yoğunluklu lipoprotein kolesterol (HDL-K) düzeyinin düşüklüğü koroner arter hastalığı (KAH) riskini artırmaktadır. Ancak bu lipit parametrelerin KAH riskini oluşturmadaki miktarı ise hala tartışmalıdır. Biz bu çalışmada KAH riskini değerlendirebilmek için geliştirdiğimiz CHOLINDEX ismindeki yeni indeksin güvenilirliğini araştırmayı amaçladık.
Yöntemler: Koroner anjiyografisi yapılan 307 hasta (190 erkek ve 117 kadın, yaşları 26-80 yıl arası, ortalama 53.6±10.2 yıl) çalışmaya alındı. Tüm hastaların risk faktörleri ve lipit değerleri kaydedildi. CHOLINDEX aşağıdaki formül kullanılarak hesaplandı: CHOLINDEX=LDL-K–HDL-K (TG<400 mg/dL), LDL-K–HDL-K + TG/5 (TG≥400 mg/dL).
Bulgular: Çalışma grubumuzdaki 307 kişinin, 180'inde KAH mevcut idi. Biz yaş, erkek cinsiyet, hipertansiyon, diyabetes mellitus, sigara ve CHOLINDEX'in KAH açısından bağımsız risk faktörü olduğunu saptadık. Lojistik regresyon analizi CHOLINDEX'in KAH ile ilişkisinin diğer lipit parametrelerinden istatistiksel olarak daha fazla olduğunu gösterdi (odds ratio=1.011, %95 CI=1.003-1.019).
Sonuç: Günlük klinik pratikte KAH riskini değerlendirmede CHOLINDEX, diğer lipit parametreleri gibi güvenilir olarak kullanılabilecek basit bir indekstir. *(Anadolu Kardiyol Derg 2013; 13: 315-9)*
Anahtar kelimeler: CHOLINDEX, koroner arter hastalığı, lipitler, regresyon analizi

Introduction

It is known that serum lipid levels are strongly correlated with atherosclerosis (1-2). Elevated levels of high-density lipoprotein cholesterol (HDL-C) provide a cardioprotective effect while a high level of low-density lipoprotein cholesterol (LDL-C) is atherogenic (2-4). In addition, many studies have shown that high triglyceride (TG) levels are associated with coronary artery disease (CAD) (5-8). However, frequency of the increase of CAD risk with each individual lipid parameter has been controversial.

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Previous studies recognizing the relation of cholesterol with atherosclerosis were performed by using the levels of total cholesterol (TC) and LDL-C. It was proposed to use LDL-C/HDL-C ratio to determine CAD risk when the role of HDL-C as cardioprotective agent was revealed (9). Since this ratio does not include TG levels, it has a limited value.

When the effects of high serum TG levels on atherosclerosis were clearly identified, the nonHDL-C was proposed to use as a possible predictor of CAD. Subsequent studies showed that, nonHDL-C (TC-HDL-C) as an effective indicator of CAD more than LDL-C (10). When, the only level of nonHDL-C is examined, it is not possible to evaluate the cardioprotective effect of HDL-C. Therefore, nonHDL-C can give limited information.

In order to evaluate CAD risk, we developed a new index called CHOLINDEX. Our index is simple and includes three main cholesterol parameter; LDL-C, HDL-C and TG level. The objective of the present study was to investigate the relative contributions of several indexes of the lipid-lipoprotein profile, LDL-C, HDL-C, TG and nonHDL-C levels as well as the TC to HDL-C ratio, the LDL-C to HDL-C ratio and our index to the risk of developing CHD in a study of South Anatolia population.

Methods

Study design

This is an observational cross-sectional study.

Study population

The study population consisted of 307 patients who were admitted for diagnostic coronary angiography for the assessment of a suspected or confirmed clinical diagnosis of CAD. The patients taking cholesterol-lowering medication were excluded from the study. As a routine procedure, an informed written consent was obtained from all patients.

Definitions of risk factors

Risk factors were considered such as hypertension (HT), hyperlipidemia, diabetes mellitus (DM), cigarette smoking and family history for CAD. Patients with a sustained blood pressure equal or greater than 140 mmHg systolic and/or 90 mmHg diastolic or patients using an antihypertensive medication were considered to have hypertension (11). Diabetes mellitus was defined as hyperglycemia, requiring antidiabetic drugs or if the fasting glucose was equal or higher than 126mg/dL (12). Patients reporting cigarette use during the year prior to examination were considered as smokers.

Coronary angiography

Coronary angiography was performed by Judkins technique and images of coronary tree were obtained in routine, standardized projections. The angiograms were assessed by at least two cardiologists. CAD was diagnosed as 50% reduction of internal diameter of left anterior descending, right coronary, circumflex artery or their primary branches. Patients without angiographic lesions were considered as the patients without CAD.

Laboratory analyses and CHOLINDEX calculation

Venous blood samples were collected after 12 h fasting before angiography. Plasma was separated within 4 h and stored at -20°C. TC, LDL-C, TG and HDL-C [colorimetric method (CHOD/PAP) without sample pretreatment] were measured by enzymatic methods by an Olympus 5200 autoanalyzer (Olympus Diagnostica GmbH, Hamburg, Germany).

CHOLINDEX were calculated using the following formulas.

$$\text{CHOLINDEX} = \begin{cases} \text{LDL-C} - \text{HDL-C} & (\text{TG} < 400) \\ \text{LDL-C} - \text{HDL-C} + (\text{TG} / 5) & (\text{TG} \geq 400) \end{cases}$$

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS), version 11.0 (SPSS Inc., Chicago, Il, USA) and all values were expressed as mean±standard deviation for both genders. Student's t-test and Chi-square test were used to evaluate the mean age, plasma lipid profile and other risk factors. A p value of < 0.05 was considered significant. The differences in subjects with and without CAD were analyzed by a Chi-square and Fisher's exact tests. The stepwise logistic regression analysis was performed for the determination of the independent predictors for CAD and the odds ratios as estimators of relative risk together with their 95% approximate confidence intervals were calculated to assess the association with and without CAD. ROC analysis was performed to define the diagnostic value of CHOLINDEX in prediction of CAD.

Results

The clinical and laboratory characteristics of the study population according to the presence and absence of CAD are show in Table 1. Of the 307 cases, 180 (131 males and 49 females) had CAD at least in one coronary artery (Group 1) and the remaining 127 (59 males and 68 females) had normal coronary arteries (Group 2). The incidence of DM (19.4%), HT (47.2%) and smoking (48.3%) was significantly higher in Group 1. Compared to Group 2, Group 1 subjects had significantly higher values of TC, LDL-C, nonHDL-C, TC/HDL-C and LDL-C/HDL-C. There was no difference in HDL-C and TG levels between the groups. In addition, levels of CHOLINDEX were also found to be significantly higher in Group 1 than Group 2.

The selected risk values predictive of CAD were identified for each one of lipid parameters using the stepwise logistic regression analysis adjusted for age, sex, hypertension, diabetes mellitus and smoking (Table 2). CHOLINDEX was found to have an independent predictive value for CAD (OR=1.011, 95%CI 1.003-1.019, p=0.009). When the cardiac risk factors were evaluated all together, the stepwise logistic regression analysis indicated that HT, DM, male gender, age, smoking and CHOLINDEX

Table 1. Demographic characteristics of the patients with and without coronary artery disease

Variables	Group 1 CAD (+)	Group 2 CAD (-)	*p
Male/female, n	131/49	59/68	<0.0001
Hypertension, n (%)	85 (47.2)	45 (35.4)	0.040
Diabetes mellitus, n (%)	35 (19.4)	9 (7.1)	0.002
Smoking, n (%)	87 (48.3)	37 (29.1)	0.001
Age, years	54.9±10.2	51.8±9.9	0.008
TC, mg/dL	209.3±43.4	197.1±37.0	0.008
HDL-C, mg/dL	42.5±8.0	43.2±9.4	0.539
LDL-C, mg/dL	133.2±37.7	121.6±31.2	0.003
Triglyceride, mg/dL	171.6±88.1	164.3±73.6	0.430
TC/HDL-C	5.0±1.3	4.7±1.1	0.012
LDL/HDL-C	3.2±1.1	2.9±0.8	0.005
nonHDL-C, mg/dL	166.8±42.8	153.9±34.7	0.004
nonHDL-C–HDL-C, mg/dL	124.3±43.6	110.8±34.9	0.003
LDL-C–HDL-C, mg/dL	90.7±38.2	78.4±30.6	0.002
CHOLINDEX	93.6±40.6	79.7±30.5	0.001

Values are expressed as mean±standard deviation and number (percentage)
*Student's t-test for unpaired samples and Chi-square test
(+), present; (-), absent; CAD - coronary artery disease, HDL-high - density lipoprotein cholesterol, LDL - low-density lipoprotein cholesterol, TC - total cholesterol

Table 2. Independent contributions of lipid parameters to the risk of coronary artery disease

Model no.	Lipids included in the model	Odds ratio	95% CI	SE	*p
1	TC, mg/dL	1.008	1.001-1.014	0.003	0.024
2	HDL-C, mg/dL	1.005	0.975-1.035	0.015	0.744
3	LDL-C, mg/dL	1.009	1.001-1.017	0.004	0.026
4	Triglyceride, mg/dL	1.001	0.998-1.004	0.002	0.460
5	TC/HDL-C	1.207	0.956-1.525	0.119	0.114
6	LDL-C/HDL-C	1.301	0.972-1.743	0.149	0.077
7	nonHDL-C , mg/dL	1.008	1.001-1.015	0.004	0.023
8	nonHDL-C - HDL-C, mg/dL	1.008	1.001-1.015	0.004	0.028
9	LDL-C - HDL-C, mg/dL	1.009	1.001-1.017	0.004	0.031
10	CHOLINDEX	1.011	1.003-1.019	0.004	0.009

CI - confidence interval, HDL - high-density lipoprotein cholesterol, LDL - low-density lipoprotein cholesterol, SE - standard error, TC - total cholesterol
*Odds ratios for coronary artery disease were calculated by stepwise logistic regression analysis adjusted for age, sex, hypertension, diabetes mellitus and smoking

were found to be the independent predictors of CAD (Table 3). CHOLINDEX was found to be the most reliable formula in determining the highest risk of CAD.

ROC curve analysis revealed a cut-off value of 80 for CHOLINDEX to be predictive to evaluate CAD risk with a sensitivity and specificity of 51% and 63%, respectively (Area under curve=0.599, 95% CI=0.535 - 0.663, p=0.003) (Fig. 1).

Table 3. Multiple logistic regression analysis of coronary artery disease risk factors

	Coefficient	SE	p	Odds ratio	95% CI
Age	0.057	0.014	0.000	1.059	1.029-1.089
Gender, male	1.258	0.294	0.000	3.519	1.978-6.263
Hypertension	0.649	0.283	0.022	1.914	1.098-3.336
Diabetes mellitus	1.252	0.431	0.004	3.496	1.501-8.145
Smoking	0.978	0.301	0.001	2.660	1.475-4.796
CHOLINDEX	0.011	0.004	0.009	1.011	1.003-1.019
Constant	-5.170	0.971	0.000	0.006	

CI - confidence interval, SE - standard error
The dependent variable: The presence of coronary artery disease

Discussion

Large population studies have revealed a significant relation between the TC and LDL-C levels and cardiovascular risk (13). Existing evidence implicates LDL-C is the most important atherogenic factor. The Third Report of The National Cholesterol Education Program (Adult Treatment Panel III) guidelines (NECP ATP III) showed that LDL-C was to be the first target in treatment of high lipids (14). Besides, ATP III Guidelines indicated that in addition to high LDL-C levels, low levels of HDL are also a significant and independent risk factor for CAD (14). The same guidelines identified HDL-C levels under 40 mg/dL was to be a risk factor and levels above 60mg/dL was to be a protective factor (14). It is known that a decrease of 1 mg/dL in the mean levels of HDL-C can increase the risk of CAD by 2-3% (15). Recent studies have also shown that hypertriglyceridemia is a powerful independent risk factor for CAD (16-19).

Ridker et al. (9) demonstrated that LDL-C/HDL-C ratio was to be superior than HDL-C or LDL-C alone in evaluating the risk of CAD. The ratio of LDL-C/HDL-C may provide a better risk assessment of CAD since it contains both atherogenic and protective lipid fractions. Nevertheless, TG levels are not considered in this ratio. Recently, Manninen et al. (20) demonstrated that elevated levels of TG in patients with high LDL-C/HDL-C ratio were a strong indicator of the short-term risk of CAD. Therefore, it is obvious that evaluating only the ratio of LDL-C/HDL-C is inadequate.

NonHDL-C may be used to evaluate the atherogenic effects of both LDL-C and TG and is calculated by subtracting HDL-C from total cholesterol. It consists of total LDL-C and VLDL-C (very low-density lipoprotein cholesterol) in serum and reflects the content of all atherogenic apolipoprotein-B containing lipoproteins. Cui et al. (10) showed that nonHDL-C is superior than LDL-C as a predictor of cardiovascular risk. However, it is not possible to observe cardioprotective effects of HDL-C if only nonHDL-C is evaluated.

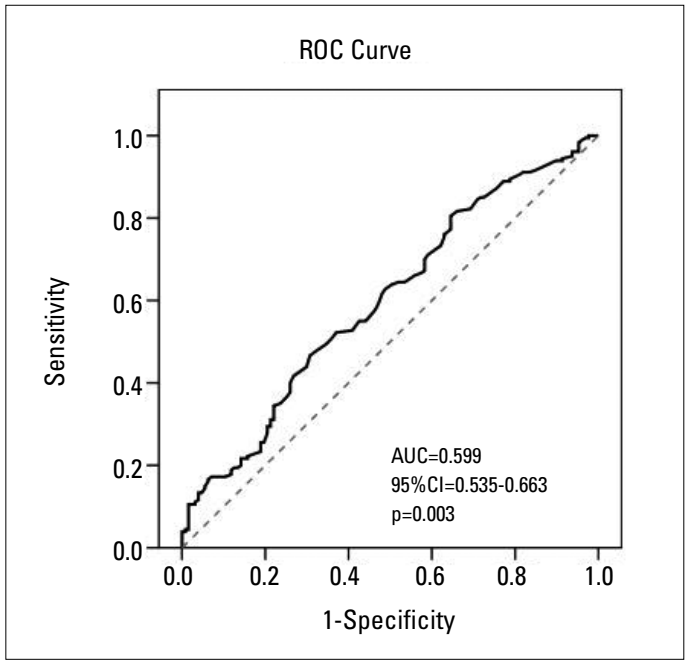

Figure 1. Diagnostic accuracy of CHOLINDEX in prediction of coronary artery disease
*ROC analysis

Serum LDL-C levels are usually estimated by the Friedewald formula [LDL-C=TC - HDL-C-(TG / 5)] that requires only the measurement of plasma TC and TG along with HDL-C (21). This calculation includes intermediate-density lipoprotein in the LDL-C fraction. As plasma TG concentrations increase, the reliability of LDL-C levels calculated by this formula progressively decrease. When the TG level is over 400 mg/dL, this formula will become useless (22).

The net effect of atherogenicity was calculated by subtracting HDL (which has cardioprotective effect) from LDL (which has the strongest atherogenic effect). Because of LDL-C levels are useless when TG levels exceed 400 mg/dL, in these cases; we decided to add TG/5 on the value as an additional atherogenic risk factor. So we developed a new index called CHOLINDEX. In our study, levels of CHOLINDEX were found to be significantly higher in CAD (+) group (p=0.001). In the all of lipid parameters, it was found most independent predictors of CAD by using the univariate logistic regression analysis (p=0.009 and odds ratio=1.011). When the stepwise logistic regression model was used in our study, CHOLINDEX levels provided the most strong relative risk value of CAD.

Formula is very simple to implement and more strongly associated with CAD than other lipid parameters considered individually. Therefore, CHOLINDEX can be used for evaluation of all lipid risk for CAD in only one parameter.

Study limitations

Our study has some limitations. Our study included a relatively small number of patients. Besides, as our hospital is a third stage health facility, our study groups may not represent the whole population in our region.

Conclusion

CHOLINDEX is a simple index, which can be used reliable in prediction of CAD like other lipid parameters in daily clinical practice. Further studies are needed in order to make this index more reliable.

Conflict of interest: None declared.

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