RESEARCH ARTICLE / *Araştırma Makalesi*

Ten Year Cardiovascular Risk, Serum Lipid Indices and High Sensitivity CRP in a Healthy Population

Sağlıklı Bir Popülasyonda 10 Yıllık Kardiyovasküler Risk, Serum Lipid İndeksleri ve Yüksek Duyarlı CRP

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Abstract

Introduction	It is very important to identify individuals at high risk of atherosclerotic cardiovascular diseases (ASCVD) and for this purpose, many risk calculation tools and parameters are used. In this study, we aimed to investigate the correlation between the ACC/AHA cardiovascular risk and serum lipid indices and high sensitivity C-reactive protein (hs-CRP) in a healthy population.
Materials and Methods	Our study was conducted retrospectively on individuals aged between 40 and 79 years and with sufficient data, using the hospital database. Patients with a history of any chronic disease and active infection were excluded. Individuals were analyzed by grouping them into low (<5%) and borderline to high (>5%) estimated 10-year risk of ASCVD.
Results	184 individuals with a median age of 46 and 37.5% women were included in the study. The median 10-year estimated risk of ASCVD in the study population was 3% (1.3/5.98). The low-risk group had a significantly lower atherogenic index of plasma (AIP), Castelli I risk index (CR-I), and Castelli II risk index (CR-II) compared to the borderline to high-risk group (p <0.001 for all). However, CRP was not different between groups (p: 0.683). The 10-year risk of ASCVD was statistically significantly correlated with AIP (R:0.380; p<0.001), CR-I (R:0.467; p<0.001), and CR-II (R:0.482; p<0.001), but no correlation was detected with hs-CRP (R:0.065; p:0.381).
Conclusion	The lack of correlation between ACC/AHA's risk calculation tool and hs-CRPsuggests that hs-CRP cannot be used as a high-risk indicator in these individuals or that this tool is insufficient to detect some high-risk patients.
Keywords	C-reactive protein, Cardiovascular Risk Score, Dyslipidemias

Öz

Amaç	*Aterosklerotik kardiyovasküler hastalık (ASKH) açısından yüksek risk altındaki bireylerin belirlenmesi oldukça önemlidir ve bu amaçla birçok risk hesaplama aracı ve parametresi kullanılmaktadır. Bu çalışmada, sağlıklı bir popülasyonda ACC/AHA tarafından geliştirilen kardiyovasküler risk hesaplama aracı ile serum lipid indeksleri ve yüksek duyarlıklı C-reaktif protein (hs-CRP) arasındaki ilişkiyi araştırmayı amaçladık.*
Yöntem ve Gereçler	*Çalışmamız, hastane veri tabanı kullanılarak, 40-79 yaş arası ve yeterli veriye sahip bireyler üzerinde geriye dönük olarak yapıldı. Herhangi bir kronik hastalığı ve aktif enfeksiyonu olan hastalar çalışma dışı bırakıldı. Bireyler, düşük (<%5) ve sınırda-yüksek (>%5) tahmini 10 yıllık ASKH riski olarak gruplandırılarak analiz edildi.*
Bulgular	*Çalışmaya ortanca yaşı 46 ve %37,5'i kadın olan 184 kişi dahil edildi. Çalışma popülasyonunda ortanca 10 yıllık tahmini ASKH riski %3'tü (1.3/5.98). Düşük risk grubu, sınırda-yüksek risk grubuna kıyasla önemli ölçüde daha düşük aterojenik plazma indeksi (AIP), Castelli I risk indeksi (CR-I) ve Castelli II risk indeksine (CR-II) sahipti (tümü için p <0,001). Ancak CRP gruplar arasında farklı değildi (p: 0.683). 10 yıllık ASKH riski, AIP (R:0.380; p<0.001), CR-I (R:0.467; p<0.001) ve CR-II (R:0.482; p<0.001) ile istatistiksel olarak anlamlı şekilde korele idi, ancak hs-CRP ile korelasyon saptanmadı (R:0.065; p:0.381).*
Sonuç	*ACC/AHA'nın risk hesaplama aracı ile hs-CRP arasında korelasyon olmaması, hs-CRP'nin bu bireylerde yüksek risk göstergesi olarak kullanılamayacağını veya bu aracın bazı yüksek riskli hastaları tespit etmede yetersiz olduğunu düşündürmektedir.*
Anahtar Kelimeler	*C-Reaktif Protein, Kardiyovasküler Risk Skoru, Dislipidemiler*

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are among the leading causes of death worldwide.[1] For this reason, it is very important to identify individuals at high risk for ASCVD and to take preventive measures for these individuals. Many parameters and tools have been developed to determine the risk of ASCVD.[2] In addition to classical risk factors such as smoking, hypertension, diabetes mellitus, and hyperlipidemia, many new risk factors such as PCSK9, CRP, IL-6, copeptin, cystatin-C, and various micro-RNA particles have been identified.[3] The majority of newly identified risk factors are currently unsuitable for clinical use. Castelli I risk index (CR-I), Castelli II risk index (CR-II), and atherogenic index of plasma(AIP) are factors calculated from the lipid parameters that are more widely used because of the easy accessibility and their clear relationship with ASCVD.[4] The American Society of Cardiology/American Heart Association (ACC/AHA) has developed a cardiovascular risk calculation tool using classical risk factors such as age, gender, blood pressure, diabetes, as well as lipid parameters.[5] With this tool, the 10-year cardiovascular risk can be calculated.

C-reactive protein (CRP) is an acute-phase reactant that is increased in serum and produced in the liver in inflammatory diseases.[6] Since atherosclerosis is a chronic inflammatory disease, high CRP is associated with the prevalence and severity of atherosclerotic diseases.[7] In previous studies, in addition to classical risk factors, patients with high CRP have been found to have a much higher risk of cardiovascular events.[8] In addition, it was observed that high CRP was associated with classical risk factors.[9] However, the patient groups in these studies were not homogeneous and included individuals at high risk of cardiovascular disease.

In this study, we aimed to investigate the relationship between the 10-year cardiovascular disease risk calculated by the ACC/AHA tool and the AIP, CR-I, CR-II, and high sensitivity C-reactive protein (hs-CRP) in the healthy population.

MATERIAL and METHODS

This study was approved by institutional review board. Our study was carried out retrospectively, using the records of our hospital database between the years 2015-2020. Since the 10-year risk can be calculated only in 40-79 years of age with the ACC/AHA ASCVD risk calculation tool, patients in this age group were included in the study.Individuals with a history of any cardiovascular disease, hypertension, diabetes, oncologic disease, rheumatic disease, nephrological disease, endocrinological disease, recent surgery, and active infection were excluded. Individuals who did not have sufficient data were not included in the study.

All laboratory tests were performed on fasting peripheral venous blood samples. Biochemical and hematological measurements were made using standard methods. Serum hs-CRP was measured with a C8000 Architect Abbott biochemical auto analyzer (Abbott Laboratories, Chicago, USA) and the lowest detectable level was 0.01 mg/l. The 10-year estimated risk of ASCVD was calculated with the ACC/AHA's online tool.10 Individuals were classified according to their estimated 10-year risk of ASCVD: <5% low risk, 5-7.5% borderline risk, 7.5-20% moderate risk, and ≥20% high risk. AIP was calculated by calculating the logarithm of the TG/HDL ratio from molar units, CR-I by calculating the total cholesterol/HDL cholesterol ratio, and CR-II by calculating the LDL cholesterol/HDL cholesterol ratio. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Body mass index was calculated as the ratio of body weight in kilograms to the square of the height in meters.

Statistical analyzes were performed using SPSS 22.0 statistical analysis software. The normality of the distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation,

and non-normally distributed variables were expressed as median and 25/75 quartiles. Categorical variables were expressed as numbers and percentages. Categorical variables were compared with the chi-square test. Normally distributed continuous variables were compared with Student's t-test, and those that were not normally distributed were compared with Mann Whitney U test. The relationship between the variables was evaluated with Pearson correlation analysis. All tests were two-sided and statistical significance was accepted as $p<0.05$.

RESULTS

184 individuals who met the study criteria were included in the study. The median age of the individuals included in the study was 46, and 115 (62.5%) were male. The median estimated 10-year risk of ASCVD was 3%. Of the individuals, 128 (69.6%) were at low risk, 18 (9.8%) were at borderline risk, 36 (19.6%) were at intermediate risk, and 2 (1.1%) were at high risk. Since there were few individuals in the borderline, medium, and high-risk groups, these groups were combined and evaluated as the borderline to high-risk group. Analyzes were performed between low-risk and borderline-to-high-risk groups.

The clinical, laboratory characteristics and risk indexes of individuals according to risk groups are given in detail in the table. In the low-risk group, the age was lower, the female gender was more, active smoking was less, and diastolic blood pressure was lower (p: <0.001, <0.001, <0.001, 0.009, respectively). However, systolic blood pressure and body mass index were not different between the groups (p: 0.515, 0.960, respectively). Hemoglobin and creatinine values were lower and GFR was higher in the low-risk group (p: <0.001, <0.001, and 0.002, respectively). Glucose, leukocyte count, and hs-CRP values were not different (p: 0.294, 0.054, and 0.683, respectively). Total cholesterol, LDL cholesterol, and triglyceride were lower and HDL cholesterol was higher in the low-risk group (p:0.002, <0.001, <0.001, and <0.001, respectively). Similarly, AIP, CR-I, and CR-II were significantly lower in the low-risk group (p<0.001 for all).

The estimated 10-year risk of ASCVD was statistically significantly correlated with AIP (R: 0.380; p<0.001), CR-I (R: 0.467; p<0.001), and CR-II (R: 0.482; p<0.001), but no correlation was detected with hs-CRP (R: 0.065; p: 0.381) (Figure).

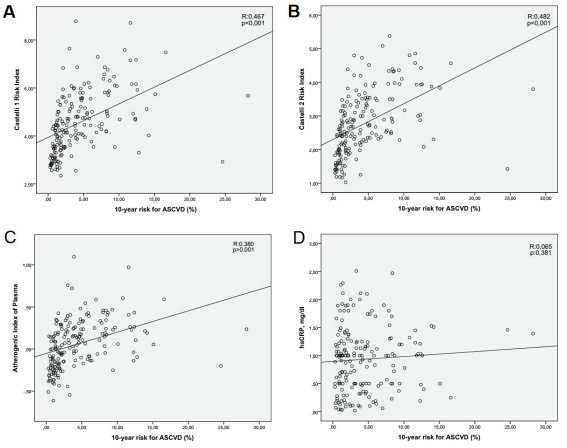

Figure: Correlation graphs of 10-year estimated risk of atherosclerotic cardiovascular disease (ASCVD) with other risk parameters A. Correlation of 10-year ASCVD risk with Castelli I risk index, B. Correlation of 10-year ASCVD risk with Castelli II risk index, C. Correlation of 10-year ASCVD risk and atherogenic index of plasma, D. Correlation of 10-year risk of ASCVD with hs-CRP

Table: Clinical and laboratory findings of groups separated according to 10-year ASCVD risk.

Variable	Total	Low Risk	Borderline to High Risk	p
Number, %	184(100)	128(69.6)	56(30.4)	
Age, years	46(43/51)	46(42/49)	50(45/57)	**<0.001**
Male/Female, N (%)	115(62.5) /69(37.5)	65(50.8)/63(49.2)	50(89.3)/6(10.7)	**<0.001**
Active smoker, N (%)	71(38.6)	29(22.7)	42(75)	**<0.001**
Systolic BP, mmHg	120(115/125)	120(111/125)	120(120/125)	**0.515**
Diastolic BP, mmHg	70(70/80)	70(70/80)	75(70/80)	**0.009**
Body Mass Index, kg/m2	27.5(25.6/30)	27.5(15.5/30.3)	27.2(26/29.4)	**0.960**
Hemoglobin, g/dl	14.7(13.4/15.6)	14.3(13/15.3)	15.2(14.4/15.9)	**<0.001**
Leucocyte count, x1000/µL	6.9(5.9/8.3)	6.9(5.9/7.96)	7.5(5.9/8.9)	**0.054**
hs-CRP, mg/l	1(0.5/1.26)	1(0.49/1.25)	1(0.5/1.32)	**0.683**
Glucose, mg/dl	91(85/97.8)	90(85/96)	91(86/99)	**0.294**
Total Cholesterol, mg/dl	207.9±42.1	201.5±41.6	222.4±39.7	**0.002**
HDL Cholesterol, mg/dl	47(40/54.8)	49(41/57)	42(37.2/48)	**<0.001**
LDL Cholesterol, mg/dl	125±31.5	117.9±30.4	141.3±28.1	**<0.001**
Triglyceride, mg/dl	115.5(84.3/179)	107(75/153)	168(110/212)	**<0.001**
Creatinine, mg/dl	0.79(0.7/0.87)	0.77(0.68/0.83)	0.83(0.75/0.93)	**<0.001**
Glomerular Filtration Rate, ml/min	104(95/109)	106(97/109)	100(90/107)	**0.002**
Atherogenic Index of Plasma	0.059±0.285	-0.009±0.275	0.213±0.247	**<0.001**
Castelli I Risk Index	4.55±1.28	4.18±1.13	5.39±1.21	**<0.001**
Castelli II Risk Index	2.77±0.95	2.47±0.81	3.44±0.89	**<0.001**
10-year risk for ASCVD, %	3(1.3/5.98)	1.8(1/3.18)	8.4(6.3/11.8)	**<0.001**

Categorical variables were expressed as numbers and percentages. Continuous variables that were normally distributed were expressed as mean± standard deviation, and non-normally distributed ones were as median and 25/75 quartiles.
ASCVD: Atherosclerotic cardiovascular disease, BP: Blood pressure, hs-CRP: High sensitivity C-reactive protein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, N: Number

DISCUSSION

In our study, we found that the estimated 10-year cardiovascular risk in a normotensive, nondiabetic population had a moderate correlation with serum lipid indices such as CR-I, CR-II, and AIP, but not with hs-CRP. Unlike most previous studies, our study mostly included patients at low risk of ASCVD.

The relationship between plasma lipid parameters and ASCVD has been known for a long time. However, studies have shown that AIP, CR-I, and CR-II, which are risk indices calculated from lipid parameters, make better risk predictions than lipid parameters alone.[11] Edward et al. have revealed that AIP is more successful than individual cholesterol risk parameters in estimating mortality risk in elderly patients.[11] In our study, a moderate but significant correlation was found between AIP, CR-I, and CR-II and the estimated 10-year risk of ASCVD. This relationship is expected since total, HDL, and LDL cholesterol values are also used when calculating the risk of ASCVD. However, this relationship is not strong since there are other parameters such as age, gender, smoking, blood pressure, diabetes, and drug use in risk calculation. Therefore, although these parameters reflect lipid risk factors, they are insufficient to calculate the global risk of ASCVD.

Atherosclerosis is a chronic inflammatory disease triggered by sequestration and modification of lipoproteins

in the subendothelial space.[12] The relationship between chronic elevation of CRP, an inflammation marker, with atherosclerosis has been known for a long time.[13] Recently, Yang et al.found a linear relationship between CRP level and cardiovascular diseases in a meta-analysis of 36 articles.[8] According to this meta-analysis, with each 1 mg/l increase in CRP, the relative risk of cardiovascular disease increases by 18%. In the light of these findings, some risk factors, including hs-CRP, have been developed to calculate the risk of ASCVD. Reynold risk index that incorporates hs-CRP and parental history to classical risk factors significantly improves global cardiovascular risk prediction.[14] However, hs-CRP has not been used routinely to determine the risk of ASCVD. In the 2019 cardiovascular diseases primary prevention guideline of the ACC/AHA, it was classified as a risk-increasing factor, especially in the moderate-risk patient group.[15] However, hs-CRP is not defined as a risk factor in the ESC guidelines.[1]

Confusing results have been obtained in studies in terms of the contribution of CRP to classical risk factors in detecting cardiovascular events. Juonolo et al. evaluated 1617 people in 2001, who had CRP measurements in 1980 when they are aged between 3-18 years.[16] In their study, they found that the childhood CRP value showed a weak but significant correlation with the adult CRP value, but not with the adulthood carotid intima-media thickness (CIMT). They found that the classical risk factors of childhood, BMI, HDL-C, smoking, LDL-C, blood pressure, and adulthood CIMT were significantly related. In the JUPITER study, rosuvastatin significantly reduced cardiovascular events in patients with CRP above 2 g/l and LDL-C below 130 mg/dl.[17] Although the protective effects of rosuvastatin were demonstrated in individuals with high hs-CRP in this study, a proportional relationship with CRP was not observed. In an analysis of the Heart Protection Study, 20376 people aged 40-80 years at high cardiovascular risk were evaluated for the protective effects of simvastatin based on baseline CRP levels.[18] As a result of this analysis, it was determined that simvastatin provided a significant reduction in major vascular events, but its protective effects were not proportionally related to baseline CRP levels. In the study conducted by Koening et al. on 3435 German men aged 45-74 years, they found that CRP provides prognostic information in addition to the Framingham risk score.[19] However, in the meta-analysis of Shah et al., it was seen that CRP alone did not perform discrimination better than the Framingham risk score, and when added to this risk score, it made a small and inconsistent contribution to the risk calculation.[20]

In the study of Sharif et al., they investigated the relationship of low level of hs-CRP increase with death and cardiovascular events in a mean follow-up of 7.8 years in 1679 type 2 diabetic patients. In this study, they found a low level of inflammation to be associated with all-cause and vascular mortality, but not with vascular events.[21] Buila et al. studied CRP and classic cardiovascular risk factors in 335 pilots and air traffic control workers.[22] In this study, they found that CRP was associated with factors such as age, smoking, metabolic syndrome and physical inactivity, and adding CRP to the classical risk factors improved cardiovascular risk calculation.

Our study reveals that the estimated 10-year risk of ASCVD calculated by ACC/AHA's tool in normotensive and non-diabetic individuals is not associated with hs-CRP levels. Since vascular inflammation in the presence of atherosclerosis causes hs-CRP elevation, unlike classical risk factors, high CRP is an indicator of active inflammation in the presence of atherosclerosis, rather than being a risk factor for the development of atherosclerosis. However, the population of our study consists mostly of low-risk individuals. In this patient group, the probability of atherosclerosis and associated hs-CRP elevation is low. Therefore, individuals may not have an atherosclerotic disease that may cause CRP elevation in this period, regardless of the estimated 10-year risk of ASCVD. This finding is consistent with the study of Juonolo et al., which did not find a relationship between childhood CRP level and CIMT.[16]

Another possible explanation for this finding may be that the 10-year estimated ASCVD risk calculation tool of ACC/AHA in this group of patients is insufficient to detect some individuals who may be at high risk.

The most important limitation of the study is that it was conducted retrospectively. Although we excluded conditions that may have an effect on CRP with strict criteria, we may not have been able to detect some factors due to the retrospective design. Another limitation is the small number of cases for an epidemiological study. A reevaluation of the association of hs-CRP and estimated cardiovascular risk in a larger case group will provide a clearer result. In addition, a study with long-term follow-up will provide a better understanding of the relationship between hs-CRP, estimated risk of ASCVD, and future cardiovascular events.

Conflict of Interest

None of the authors has a conflict of interest to declare.

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Ethical consent

This study was approved by the Baskent University Institutional Review Board's decision dated January 25, 2022 and numbered E-94603339-604.01.02-97632.

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Declaration of Contribution

Concept- S.A., E.A.; Design- S.A., E.A.; Data Collection- S.A., E.A.; Analysis and interpretation- S.A., E.A.; Literature review- S.A., E.A.; Writing- S.A.

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