Could Serum YKL-40 Level be the New Cardiovascular Risk Prediction Model?

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SOUHRN

Cíl: Protože kardiovaskulární onemocnění jsou příčinou závažné morbidity a mortality, je třeba zjišťovat jejich přítomnost a začít je včas léčit. Proto byla pro stanovení rizika vypracována řada stupnic, v současnosti se však rutinně nepoužívá žádný biochemický marker pro stanovení kardiovaskulárního rizika. Ateroskleróza je nejzávažnější příčinou rozvoje kardiovaskulárních onemocnění a v patofyziologii aterosklerózy hraje jistou úlohu zánět cév. Řada studií prokázala, že mnoho kroků v procesu rozvoje tohoto zánětu ovlivňují hodnoty YKL-40 v séru. Evropská kardiologická společnost používá pro stanovení desetiletého kardiovaskulárního rizika skórovací systém SCORE2. V naší studii jsme zkoumali vztah mezi algoritmem pro toto riziko a hodnotou biochemického markeru YKL-40 v séru.
Materiál a metody: Do studie bylo zařazeno 87 dobrovolníků ve věku 40–70 let, kteří se dostavili na naši kliniku, v minulosti neprodělali kardiovaskulární příhodu, měli však rizikové faktory pro rozvoj kardiovaskulárního onemocnění. Pomocí predikčního modelu SCORE2 bylo stanoveno jejich kardiovaskulární riziko a současně změřeny hodnoty YKL-40 v séru. Tyto hodnoty se mění s věkem bez ohledu na přítomnost či nepřítomnost nemoci, což platilo pro naši studii stejně jako pro jiné studie. Abychom eliminovali toto paradigma, hodnotili jsme hodnoty YKL-40 v séru pomocí statistického modelu společně s věkem.
Výsledky: Naše základní analýza nezjistila významný vztah mezi hodnotami YKL-40 a všemi parametry v algoritmu predikčního modelu SCORE2. Nicméně po porovnání výsledku analýzy s výsledkem statistického modelu s použitím věku se ukázalo se, že hodnota YKL-40 představuje biochemický marker, který lze použít, podobně jako systém SCORE2, při stanovování kardiovaskulárního rizika (R^2 : 0,72; $p < 0,001$).

Keywords:
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ABSTRACT

Objective: Since cardiovascular diseases are a cause of serious morbidity and mortality, it is important to detect and treat them in advance. For this reason, many risk scales have been created, but there is currently no biochemical marker in routine use to estimate cardiovascular risk. Atherosclerosis is the most important reason for the development of cardiovascular disease, and vascular inflammation plays a role in the pathophysiology of atherosclerosis. It has been observed in many studies that the serum YKL-40 level has an effect on many steps in the development process of this inflammation. SCORE2 are used by the European Society of Cardiology to estimate 10-year cardiovascular risk. In our study, we investigated the relationship between this risk algorithm and the serum YKL-40 level, which is a biochemical marker.
Material and methods: 87 volunteers between the ages of 40–70 who applied to our clinic, who had not yet experienced a cardiovascular event but had risk factors for cardiovascular diseases, were included in the study. SCORE2 cardiovascular disease risk was calculated for the patients and serum YKL-40 levels were gaged. Serum YKL-40 levels change with age, regardless of the disease, in our study as in many studies. In order to eliminate this paradigm, we examined serum YKL-40 levels with a statistical model that evaluates them jointly with age.
Results: We could not detect a significant relationship with YKL-40 levels in the basal analysis performed by considering all parameters of SCORE2 algorithm. However, result of the statistical model that we evaluated with age, we found that the YKL-40 level is a biochemical parameter that can be used like SCORE2 in cardiovascular disease risk estimation (R^2 : 0.72, $p < 0.001$).

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Introduction

Atherosclerotic cardiovascular diseases are the leading cause of mortality and morbidity worldwide.[1] In the prevention of cardiovascular diseases (CVD), risk assessment, and risk prediction have an important role in the management of cardiovascular diseases. Determining and controlling the risk of cardiovascular events has been shown to reduce CVD-related mortality and morbidity, especially in those at high risk. The burden of CVD is becoming more and more severe with the increase in comorbidities such as diabetes mellitus, hypertension, obesity, metabolic syndrome, malnutrition, and increased use of tobacco products such as smoking. In addition, it also significantly burdens the economy of countries. Determination of CVD risk and risk-based strategies can reduce the burden of CVDs such as sudden cardiac death, acute coronary syndrome, and ischaemic stroke, which cause both mortality and serious morbidity. CVD risk assessment can be performed systematically.[2] SCORE2 risk prediction models developed and updated by the Cardiovascular Risk Collaboration of the European Society of Cardiology, were created to identify high-risk individuals and prevent cardiovascular diseases by predicting the 10-year CVD risk across Europe.[3] It requires multiple laboratory parameters to calculate CVD risk (HbA_{1c}, total cholesterol, HDL, eGFR, etc.). In order to recalculate this currently used score, these parameters need to be studied each time, and the cost increases. Having a simple and useful quantified laboratory parameter for the determination of cardiovascular risk may provide a cost-effective and objective result. In addition, there is currently no biochemical marker in routine use for the determination of cardiovascular disease risk.

Serum YKL-40, an inflammatory glycoprotein, is also known as chitinase-3-like 1 protein, human cartilage glycoprotein-39, 38-kDa heparin-binding glycoprotein and is secreted by macrophages, synovial cells, chondrocytes, neutrophils, and vascular smooth muscle cells.[4] It is expressed by macrophages infiltrating atherosclerotic lesions and is involved in cell adhesion, migration and modulation of extracellular matrix in the vessel wall during remodeling processes during atherogenesis.[5] Studies have shown that serum YKL-40 is associated with the pathogenesis of atherosclerosis, abnormal angiogenesis and endothelial dysfunction.[6] In clinical studies, high serum YKL-40 levels were found to be associated with cardiovascular morbidity, cardiovascular and all-cause mortality.[7–9]

Material and method

Increased serum YKL-40 levels have been associated with vascular damage in many studies, and the possibility of its use as a biochemical parameter in predicting cardiovascular disease risk is of interest. There is no biochemical quantitative equivalent of cardiovascular disease risk (SCORE2) in the literature. This study aimed to evaluate the relationship between serum YKL-40 levels and SCORE2 cardiovascular disease risk and to investigate whether serum YKL-40 level is a simple and useful quantitative parameter for predicting cardiovascular disease risk.

Eighty-seven volunteers between the ages of 40 and 75 years, who had not yet experienced a cardiovascular event but had risk factors for cardiovascular diseases and applied to Atatürk University Department of Cardiology were randomly included in the study. Blood pressure arterial values of all volunteers in the sample group were measured, and cardiovascular comorbidities and HDL cholesterol, LDL cholesterol, HbA_{1c} level, total cholesterol level, and triglyceride levels were recorded. SCORE2 cardiovascular disease risk was calculated for each patient. Blood samples were collected from the same group of patients and serum YKL-40 levels were analyzed (Sunlong Biotech, Human Chitinase-3-like Protein 1, ELISA KIT). SCORE2 cardiovascular disease risk was accepted as the reference value for cardiovascular risk assessment. The data obtained were then subjected to a statistical analysis.

Statistical analysis and results

IBM SPSS 27.0 analysis program was used for statistical analysis. Initially, patients' characteristics were analyzed. The prevalence of smoking, hypertension, diabetes mellitus, and statin group drug use in different

Table 1 – Mann–Whitney U test

		N (%)	Serum YKL-40 level		SCORE2/SCORE2-OP	
			Mean rank	*p*	Mean rank	*p*
Sex	Female	31 (35.7)	43.53	0.895	36.28	0.030
	Male	56 (64.3)	44.27		48.49	
HT	No HT	47 (54)	48.77	0.056	40.88	0.212
	HT	40 (46)	38.40		47.66	
DM	No DM	65 (74.7)	45.93	0.220	42.58	0.366
	DM	22 (25.3)	38.30		48.20	
Smoking	Not using	55 (63.2)	45.67	0.418	38.84	0.012
	Using	32 (36.8)	41.13		52.88	
Statin	Not using	69 (79.3)	45.25	0.367	43.58	0.761
	Using	18 (20.7)	39.22		45.61	

gender groups and in total were analyzed. Accordingly, 56 of the patients were male (64.3%) and 31 were female (35.7%). We evaluated whether there was a significant difference in serum YKL-40 level and SCORE2 cardiovascular disease risk in the subgroups of gender, hypertension, diabetes mellitus, and smoking variables (**Table 1**). Serum YKL-40 levels did not show a significant difference in any subgroup ($p > 0.05$). Correlation analysis was performed between serum YKL-40 levels and SCORE2 risk score (**Table 2**). In the Spearman correlation analysis, no correlation was found between serum YKL-40 levels and SCORE2 risk score ($p > 0.05$). Hierarchical regression analysis was performed to predict SCORE2 cardiovascular disease risk using serum YKL-40 level and age of the volunteers (**Table 2**). LDL level, HDL level, systolic arterial blood pressure value, HbA_{1c} level, total cholesterol level, and eGFR level were not included in the regression model because they were already used in the calculation of SCORE2 cardiovascular disease risk and were highly correlated with SCORE2 score. Age was added to the regression model together with YKL-40 levels because it is a simple value that can be known and used without the need for an additional examination (**Table 3**). According to the first model, serum YKL-40 levels alone were considered insufficient to predict the risk of SCORE2 cardiovascular disease ($p = 0.169$). According to the second model with the addition of age to YKL-40 level, age and serum YKL-40 level together explained 72% of the variance in SCORE2 cardiovascular disease risk (R^2 : 0.72, $p \leq 0.001$). According to results, it can be concluded that serum YKL-40 levels are a parameter that can be used to predict the risk of cardiovascular disease determined by SCORE2, not alone but when evaluated together with age. The equation predicting SCORE2 for model 2 can be formulated; SCORE2 cardiovascular disease risk = –17.753 – 0.004 × YKL-40 level + 0.436 × age.

Discussion

Since atherosclerosis is an inflammatory process, circulating levels of various inflammatory markers are elevated in risk individuals. After it was first recognized that C-reactive protein may be a cardiovascular marker, interest in biomarkers has increased.[10] YKL-40 expression plays an anti-inflammatory role in the atherosclerotic inflammatory cascade mediated by TNFα and IL-1.[11] In patients with stable coronary artery disease (CAD), serum YKL-40 is increased and its close association with mortality and all-cause mortality has been demonstrated.[12] It has been shown that there is a correlation between diabetes, hyperlipidemia, smoking, hypertension, age, and ethnicity and serum YKL-40, which are the parameters included in the SCORE2 scale used to calculate risk for CVD.[13–19]

Monocyte chemoattractant protein-1, which is associated with macrophage infiltration in adipose tissue in morbidly obese patients, is a strong predictor of cardiovascular death and a close association was found between YKL-40.[20] It has been suggested that it may be used as a biomarker to evaluate the pleiotropic efficacy of statins in patients with coronary artery disease.[21] Its close relationship with all these risk factors makes it inevitable that serum YKL-40 level is a determinant biomarker for cardiovascular risk.

Vázquez-Del Mercado et al. found that YKL-40 levels were correlated with age but not with disease duration in a study conducted to determine whether YKL-40 serum levels were predictive of inflammatory status.[22] In our study, similarly, the independent variable age was not correlated with SCORE2 in CVD risk prediction. In the hierarchical regression analysis including age, we revealed that YKL-40 can significantly predict CVD risk like SCORE2. Some studies have not shown a relationship between serum levels of YKL-40 and the risk of ischaemic heart disease. When we analyzed the content of these case-control studies, we found that the average age of the study groups was significantly higher than that of the control groups.[23–25]

Table 2 – Evaluation of the correlation between serum YKL-40 level and SCORE2; Spearman correlation analysis

	N	r	*p*(sig)
Serum YKL-40 levels SCORE2	88	–0.124	0.249

Conclusion

CVDs, the most common cause of death worldwide, are also one of the most challenging diseases for clinicians due to their morbidity and financial burden. Since the serum YKL-40 level we investigated is a marker of vascular damage, its use in risk assessment seems logical at first glance. Although it is not reliable to be used alone for a patient whose cardiovascular risk will be calculated for the first time due to lack of sufficient studies, it can be used as a risk assessment tool with less cost in patients whose cardiovascular disease risk is calculated at the first contact but needs to be recalculated later.

Conflict of interest
The authors declare no conflicts of interest.

Table 3 – Serum YKL-40 level and age included hierarchic regression model

	Model 1		Model 2	
	B	*p*	B	*p*
Constant	9.108	< 0.001	–17.753	< 0.001
YKL-40	–0.006 (–0.015–0.003)	0.169	–0.004 (–0.009–0.001)	0.081
Age			0.472 (0.407–0.536)	< 0.001

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Ethical statement
This study protocol was reviewed and approved by the Ataturk University Medical School Ethics Review Board with the approval number 389543.

Informed consent
All patients were enrolled by default and informed via leaflets and posters that they could decline participation at any time.

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