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Biochemical markers and carotid intima-media thickness in relation to cardiovascular risk in young women

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Cardiovascular disease (CVD) is a major cause of death in the female population. The current study aimed to examine the relationship between CVD risk and novel endothelial dysfunction biomarkers [i.e., endocan, adiponectin and intercellular adhesion molecule (ICAM)-1] and carotid intima-media thickness (cIMT), respectively in a cohort of disease-free women of reproductive age. A total of 129 women were selected. Serum endocan, adiponectin and ICAM-1 were measured by a commercial enzyme-linked immunosorbent assay and cITM was determined by ultrasound. Cardiovascular risk score (CVRS) was calculated. The lowest endocan (p for trend = 0.051) and adiponectin (p for trend = 0.040) levels were found in a group of subjects with the highest CVRS. The cIMT values were the highest in second tertile subgroups, with the highest 75th percentile in a third tertile CVRS group, while the lowest cIMT values were detected in the lowest CVRS tertile group (p for trend = 0.001). A significant positive correlation between cIMT and CVRS (ρ = 0.307, $p < 0.001$), and a negative correlation between adiponectin and endocan with CVRS, respectively (ρ = −0.252, $p = 0.004$; ρ = −0.179, $p = 0.043$) were observed, but only endocan retained the independent association with CVRS ($p = 0.030$) in the multiple linear regression analysis. Endocan could be useful diagnostic tool in the estimation of cardiovascular risk in young women.

Keywords Cardiovascular risk, Insulin resistance, Biomarkers, Inflammation, Obesity

Cardiovascular disease (CVD) is a major cause of death in the female population[1]. The manifestation of CVD occurs later in life in women than in men. However, CVD risk in women is often unrecognized, the diagnosis is not made timely, and the therapy is often not adequate[1,2].

Although some progress has been made, the existing evidence indicates that men are still more likely than women to get guidelines-recommended cardiovascular therapy, whereas the greatest gaps occur in women of reproductive age.

The need to make further improvements and to develop sex-dependent strategies to enable adequate diagnostic/treatment care for the female population places this significant public health issue at the highest level of priority[1].

The estimation of CVD risk in women persists as a challenge, despite the existence of a variety of algorithms. Each algorithm is derived from a specific population and a variability in a sample size limits their validity. This is especially true for young women since the majority of these tools are intended for older individuals[3].

The onset of CVD starts early in life but remains clinically unrecognized until an acute cardiovascular event occurs[4]. Subclinical atherosclerosis, as a chronic inflammatory disorder, is the underlying feature of CVD[4]. Atherogenesis includes a pathophysiology of multiple different pathways of endothelial dysfunction with enhanced oxidative stress and inflammatory cascade as prominent features[4]. Several novel endothelial dysfunction

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biomarkers, such as endocan, adiponectin and intercellular adhesion molecule (ICAM-1), have gained increased attention in recent years, showing promising diagnostic accuracy in cardiometabolic disorders[5–10].

Endocan is regarded as a novel biomarker of endothelial dysfunction. It was shown to exhibit proinflammatory properties via mitogen-activated protein kinase and nuclear factor kappa B signaling pathways, thus leading to enhanced expression of ICAM-1 and other cell adhesion molecules and subsequent promoting migration of leukocytes and their adhesion to the endothelium[11].

Adiponectin, as adipose-tissue secreted adipokine, exhibits cardioprotective, anti-inflammatory, antiatherogenic, and antidiabetic properties, being lower in CVD, which might in part be explained by the deleterious effects of obesity[7]. By inhibiting lipolysis, adiponectin also regulates the metabolism of lipids[7]. Lower adiponectin levels were shown to contribute to subclinical atherosclerosis in postmenopausal women[8].

The enhanced expression of ICAM-1 on the endothelial surface occurs in response to inflammation and tissue damage[9]. ICAM-1 favors the attachment of leukocytes and monocytes to the endothelial cells, promoting their migration and accumulation into the subendothelium[12], increasing the production of oxidized low-density lipoprotein particles and initiating atherosclerosis onset. Therefore, ICAM-1 is also regarded as an early biomarker of atherosclerosis decades before the progression of manifest CVD[9].

However, none any of the mentioned biomarkers has yet found its application in clinical practice[13]. Hence, the inclusion of some novel atherosclerosis-related parameters in addition to traditional ones, might increase the diagnostic accuracy of age- and sex-specific CVD risk algorithms.

Namely, the majority of previous scores include traditional risk factors, such as hypertension, dyslipidemia and hyperglycemia[1,2]. However, many of them cannot be applied to the young population[14,15]. In line with this, McMahan et al.[16] developed cardiovascular risk score (CVRS) that includes traditional coronary heart disease risk factors (i.e., sex, age, hypertension, smoking, serum lipoprotein concentrations, obesity, and hyperglycemia) to predict the likelihood of advanced atherosclerotic lesions in the coronary arteries and the abdominal aorta of young individuals between the ages of 15 and 34. This CVRS[16] showed similar discrimination for the prediction of coronary heart disease events to that obtained in Framingham risk score in older adults[14].

A carotid intima-media thickness (cIMT), as a surrogate marker of subclinical atherosclerosis, has been used frequently in recent decades due to its non-invasiveness, cost-effectiveness, and easy accessibility due to its anatomical position[17,18]. However, only a weak correlation between CVD risk score and cIMT was recently confirmed[19], which needs to be explored more deeply since studies concerning this issue are scarce and contradictory[17–19].

To the best of our knowledge, no study has yet examined endothelial dysfunction biomarkers in relation to CVD risk in young women. Also, there are no studies that examined the relationship between cIMT and CVD risk in young women. Hence, the aim of the current study was to get deeper insight into the pathophysiological traits of subclinical atherosclerosis and related risk factors by examining the relationship between CVD risk and several novel endothelial dysfunction biomarkers (i.e., endocan, adiponectin, and ICAM-1) in a cohort of disease-free women of reproductive age. We also aimed to examine the potential correlation between cIMT and CVRS in young women. Additionally, we seek the sensitive and specific panel of biomarkers that could best signify the existence of subclinical atherosclerosis, since multimarker approaches that reflect different pathophysiological pathways of increased CVD risk, rather than one single biomarker, could be of great significance.

Patients and methods

Patients

This cross-sectional study included a cohort of young women free of CVD who were willing to participate in the study. All women filled in the questionnaire. Postmenopausal and pregnant women were excluded from the research, as well as those with irregular menstrual bleeding, history of CVD, diabetes and other endocrine disorders, renal and liver diseases, malignancies, inflammatory diseases and those that self-reported medications use, such as use of contraception/other hormone therapy, anti-inflammatory medications, antihyperglycemics, antilipemics, antihypertensives, etc. After excluding women who did not meet eligibility criteria, a total of 129 women (mean age 31.8 ± 7.0 years) were passed through clinical examinations and venipuncture procedure.

The study protocol was approved by the Recep Tayyip Erdogan University Education and Research Hospital Clinical and Laboratory Research Ethics Committee (dated July 17, 2015 and numbered 2015/25) and followed by the Declaration of Helsinki principles once each woman signed an informed consent for related research.

Biochemical measurements

The blood sampling was performed after an overnight fast. The following biomarkers: total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and fasting plasma glucose were measured on the Abbott Architect c16000 device (Abbott Diagnostic, Abbott Park, IL, USA) by standardized procedures. Insulin levels were determined by the chemiluminescent microparticle immunoassay on the Abbott Architect i2000 autoanalyzer (Abbott Diagnostic, Abbott Park, IL, USA).

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as FBG (mg/dL) × fasting insulin (μU/mL)/405[10].

Each examinee was administered a 75 g oral glucose tolerance test (OGTT). Blood glucose sampling was provided at 0 min and 120 min. Glucose tolerance was classified according to 2006 WHO criteria, as described previously[10].

Impaired fasting glucose (IFG) was defined as $100 \leq$ fasting glucose levels < 126 mg/dL and impaired glucose tolerance (IGT) as $140 \leq$ glucose levels < 200 mg/dL 2 h following OGTT in the presence of fasting glucose levels < 126 mg/dL.

Women diagnosed with diabetes (fasting glucose levels ≥ 126 mg/dL and/or ≥ 200 mg/dL 2 h after OGTT) were excluded from the study. A cut-off value of 2.5 was set for HOMA-IR[20].

Serum endocan, adiponectin, and ICAM-1 were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits (Boster Biological Technology Co., 3942 Valley Ave., Pleasanton, CA, USA; Shanghai LZ Biotech Co., Shangai, China and eBioscience, Vienna, Austria, respectively) according to the manufacturer's instructions. No normal values of serum endocan, adiponectin, and ICAM-1 were provided by the manufacturer.

Anthropometric measurement and blood pressure, systolic (SBP) and diastolic (DBP), were determined by a trained investigator for all women. Women with a body mass index (BMI) greater than or equal to 18.5 kg/m^2, but lower than 25 kg/m^2 were regarded as normal weight. Women with BMI $\geq$ 25 kg/m^2 and BMI $\geq$ 30 kg/m^2 were regarded as overweight and obese, respectively[10], but for simplicity reasons all of them were referred as obese group.

Carotid intima-media thickness (cIMT) measurement

A cIMT was measured as described previously[10]. The same cardiologist performed ultrasonography with a multifrequency 5–10-MHz linear probe (Siemens, Sonoline G, Erlangen, Germany). In brief, the examinee lay in a supine position with the neck extended, and the probe was placed in an antero-lateral position. Ultrasonography was applied to 3 points on the carotid arteries (the common carotid, the proximal aspect of the internal carotid arteries, and the bifurcation point). The mean maximum cIMT values were used for each carotid artery. No carotid plaques were observed in any of the examined women.

Estimation of cardiovascular risk score (CVRS)

The CVRS was calculated according to the modified Risk Score for recognition of young women with a high probability of having endothelial dysfunction, as reported by McMahan et al.[16] and reported in our previous studies[21,22] by adding the points for each risk factor (e.g., female sex, smoking, blood pressure, HDL-c, non-HDL-c, and IGT), as following: female sex (−1 points); non-HDL cholesterol, mg/dL [< 130 (0 points); 130–159 (2 points); 160–189 (4 points); 190–219 (6 points); ≥220 (8 points)]; HDL-c, mg/dL [< 40 (1 point); 40–59 (0 points); 60 (−1 points)]; smoking [nonsmoker (0 points); smoker (1 points)]; blood pressure, mmHg [normotensive, i.e., < 130/85 (0 points); hypertensive, i.e., ≥ 130/85 (4 points)]; IGT, i.e., 140 ≤ glucose levels < 200 mg/dL 2 h following OGTT in the presence of fasting glucose levels < 126 mg/dL [no IGT (0 points); IGT (5 points)]. Unlike for men, obesity is not included in CVRS calculation (i.e., BMI ≥ 30 kg/m^2 − 0 points).

Statistical analysis

Statistical analysis was performed by the statistical program SPSS version 22.0 (SPSS Inc., Chicago, USA). P levels lower than 0.05 were regarded as statistically significant. The data are presented as numbers (%), mean ± SD, or median (interquartile range). The Mann-Whitney U test and Kruskal-Wallis test were used to test the difference between groups. Spearman's nonparametric correlation was applied to examine potential correlations between CVRS and cIMT, ICAM-1, adiponectin, and endocan, respectively. Multiple linear regression analysis was applied to analyze the influence of CVRS values on examined variables.

Results

Table 1 presented the basic anthropometric and clinical data about the current study group, which included young women, nonsmokers, free of diabetes, and with a slightly lower percent of lean subjects.

We have used the calculated CVRS of young subjects for tertile values to get three subgroups with low, moderate, and high CVD risk. The results of the comparison of cIMT and 3 atherosclerosis-related biomarkers across CVRS tertiles are presented in Table 2.

Parameter	Number (%) or mean ± SD
Gender, female	129 (100)
Age (years)	31.8 ± 7.0
Smokers	0 (0)
Obesity, no/yes	54 (41.9)/75 (58.1)
BMI (kg/m^2)	
Normal weight	22.5 ± 2.3
Overweight/obese	36.2 ± 5.4
Insulin resistance, no/yes	75 (58.1)/54 (41.0)
SBP, mmHg	114 ± 14
DBP, mmHg	73 ± 10
Total cholesterol, mg/dL	193 ± 36
LDL-C, mg/dL	121 ± 31
HDL-C, mg/dL	50 ± 12
TG, mg/dL	109 ± 68
Glucose, mg/dL	95 ± 9

Table 1. Anthropometric and clinical patients' data. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein cholestero, *HDL-C* high-density lipoprotein cholestero, *TG* triglycerides.

Parameter	CVRS tertiles			P
	First 0–13	Second 14–17	Third 18–29	
cIMT (mm)	0.550 (0.468–0.625)	0.625 (0.550–0.700)*	0.600 (0.600–0.750)***	0.001
Endocan (pg/mL)	495 (376–586)	468 (409–616)	412 (305–489)*,##	0.051
ICAM-1 (ng/mL)	331 (300–459)	368 (284–490)	398 (340–441)	0.149
Adiponectin (mg/L)	17.1 (12.2–31.7)	12.8 (11.2–22.3)*	13.0 (11.3–18.3)*	0.040

Table 2. cIMT and selected biomarkers' concentrations in subgroups according to CVRS tertile subgroups. *CVRS* cardiovascular risk score, *cIMT* carotid intima-media thickness, *ICAM-1* intercellular adhesion molecule-1. P from Kruskal-Wallis test; *,***$P<0.05$, 0.001 respectively vs. first tertile, ##$P<0.01$ vs. second tertile (Mann-Whitney U test).

Parameter	Lean BMI: 22.0 (21.0–24.5) kg/m²			Obese BMI: 34.6 (32.0–40.0) kg/m²			P
	CVRS tertile			CVRS tertile			
	First (a) 0–13 (n = 25)	Second (b) 14–17 (n = 17)	Third (c) 18–29 (n = 11)	First (d) 0–13 (n = 22)	Second (e) 14–17 (n = 23)	Third (f) 18–29 (n = 30)	
cIMT (mm)	0.550 (0.460–0.575)	0.550 (0.500–0.600)	0.600 (0.540–0.650)[a]	0.600 (0.500–0.680)[a]	0.700 (0.625–0.730)[bbb, d]	0.620 (0.600–0.760)[d]	< 0.001
Endocan (pg/mL)	495 (385–556)	510 (427–634)	320 (268–431)[a,b]	491 (372–616)	452 (358–589)	416 (346–533)	0.057
ICAM-1 (ng/mL)	314 (281–397)	298 (273–392)	433 (354–486)[a,b]	402 (322–479)[a]	426 (335–541)[bb]	393 (329–428)	0.007
Adiponectin (mg/L)	23.9 (14.7–35.3)	16.0 (11.7–26.6)	13.0 (11.7–18.0)	15.4 (11.3–21.9)[a]	12.7 (11.0–16.8)	13.3 (11.3–20.1)	0.034

Table 3. cIMT and selected biomarkers according to obesity and CVRS status. *CVRS* cardiovascular risk score, *cIMT* carotid intima-media thickness, *ICAM-1* intercellular adhesion molecule-1. P from the Kruskal-Wallis test [a]$P<0.05$ vs. first CVRS tertile in lean group, [b, bb, bbb]$P<0.05$, 0.01, 0.001, respectively vs. second CVRS tertile in lean group; [d]$P<0.05$ vs. first CVRS tertile in obese group.

This analysis confirmed the lowest endocan and adiponectin values in a group of subjects with the highest CVRS. cIMT values were the highest in the second tertile subgroups, with the highest 75th percentile in the third tertile CVRS group, while clearly the lowest cIMT values were detected in the lowest CVRS tertile group.

Afterwards, we have divided study subjects according to their obesity status and also according to CVRS tertile subgroups, which produced 6 separate groups in order to find more subtle and more precise changes in atherosclerosis biomarkers. The results are presented in Table 3.

This part of the analysis showed significantly higher cIMT in a group of obese compared to lean subjects in the same CVRS tertile group for the first and second tertile CVRS group, while in the third CVRS tertile group the difference was not statistically significant. Endocan was the lowest in the highest CVRS tertile subgroup, and this was true for both groups, lean and obese subjects, with confirmed statistical significance only for the lean subjects' group. Significantly higher ICAM-1 in parallel with higher CVRS was evident in the lean group, while higher levels from the first to the second CVRS group were not consistent for the third CVRS subgroups among obese patients. Lower adiponectin in obese subjects compared to lean ones was significant only in the first tertile CVRS subgroup, while not significantly lower in the other two CVRS tertile subgroups. Also, lower adiponectin levels in parallel with higher CVRS were not statistically significant, and this trend is clearer for the lean subjects' group.

Spearman's nonparametric correlation revealed significant positive correlation between cIMT and CVRS, and negative correlation between adiponectin and endocan with CVRS, respectively (Fig. 1).

Multiple linear regression analysis encompassing two parameters measured in this study (endocan and logICAM) confirmed a significant influence of endocan, while logICAM-1 was not significantly independent variable for CVRS values. A whole model is influenced by 2.8% on CVRS values. Endocan had initially normal distribution, while ICAM-1 was firstly logarithmically transformed in order to reach distribution normality, which is prerequisite for multiple linear regression analysis. The results are presented in Table 4.

Discussion

Given the importance of timely recognition of increased CVD risk in young women, we have conducted this cross-sectional analysis as the first to examine atherosclerosis-related biomarkers (e.g., endocan, adiponectin, and ICAM-1) in relation to CVRS in such a population. To the best of our knowledge, no previous study examined exclusively young women free of CVD and diabetes, but rather those in the postmenopausal period and/or with diabetes or other comorbidities.

The results of this study showed the lowest endocan and adiponectin levels in a group of young women with the highest CVRS. Since obesity is independently related to CVD risk[21,22], we performed further analysis

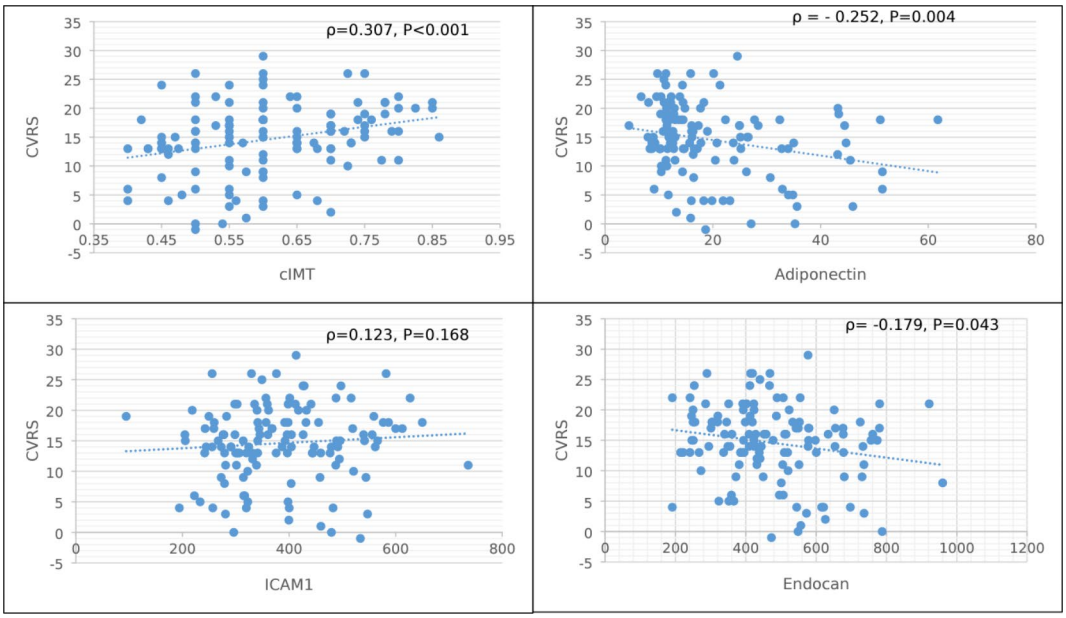

Fig. 1. Correlations between CVRS and cIMT, adiponectin, ICAM-1 and endocan. *ρ* Spearman's nonparametric correlation coefficient, *CVRS* cardiovascular risk score, *cIMT* carotid intima-media thickness, *ICAM1* intercellular adhesion molecule-1.

Parameter	B (95% CI)	SE	*P*
Endocan	−0.007 (−0.014 to −0.001)	0.003	0.030
logICAM-1	3.26 (−4.71 to 11.24)	4.031	0.419
Adjusted $R^2 = 0.028$			

Table 4. Multiple linear regression analysis for predictors of CVRS values. *SE* standard error, *CI* confidence interval, *logICAM-1* logarithmically transformed Intercellular adhesion molecule-1.

by including obesity as a potential confounding factor. Accordingly, when dividing study subjects according to their obesity status in addition to CVRS tertile subgroups in order to find more subtle and more precise changes in serum biomarkers of atherosclerosis, surprisingly more convincing results were obtained in the lean group of women. Namely, endocan was the lowest in the highest CVRS tertile subgroup, but showed statistical significance only for the lean subjects' group. Also, the trend of adiponectin's lowering in parallel with higher CVRS was clearer for the lean subjects' group. On the contrary, a significantly higher ICAM-1 in parallel with higher CVRS was evident in the lean group, whereas higher ICAM-1 was not consistent across CVRS subgroups among women with obesity.

Previous studies showed discordant results related to the mentioned biomarkers in cardiometabolic disorders. Serum endocan levels were shown to be lower in subjects with obesity[23], prediabetes[24] and metabolic syndrome[25] than in the control group.

On the other hand, no association of endocan with the CVD risk related to endothelial dysfunction was shown in women with premature ovarian insufficiency[26]. Similarly, no association between endocan and the severity of aortic stenosis was shown in individuals older than 65 years old[27].

The findings of lower serum endocan level in the higher CVRS tertile group in the current study are opposite to our previous results that showed 2.7 times higher levels of endocan in postmenopausal women with metabolic syndrome as compared to disease-free middle-aged counterparts[28]. The results of the current study are also divergent from the findings of higher endocan levels in patients with type 2 diabetes mellitus as compared to the control group[5], as well as of endocan's relation to estimated CVD risk in such patients[29]. The previous study also did not find the difference between subjects with prediabetes and controls in a population that included middle-aged subjects of both genders[5]. However, previous studies were not able to exclude some confounding factors, such as medication use (i.e., antihypertensives, antilipemics, and antidiabetics) that might affect examined serum endocan levels[11]. The different duration of obesity and related comorbidities could also influence these biomarkers, just like a variety of sample sizes of examined populations.

Endocan enhances the expression of cell adhesion molecules, such as ICAM-1, but also stimulates the secretion of proinflammatory cytokines, e.g., tumor necrosis factor-alpha (TNF-α), interleukin (IL)-8, etc. It also increases the migration of leukocytes and the permeability of blood vessels, increases the proliferation of vascular smooth muscle cells and neointima formation, thus playing an important role in atherogenesis[30].

However, the anti-inflammatory properties of endocan are also described[30]. These effects are mediated by the binding of endocan to a specific integrin in lymphocytes, so-called lymphocyte-function associated antigen (LFA-1). The latter one is linked with the endothelial ICAM-1, taking part in the regulation of the migration of leukocytes from the circulation into the tissues. Once the endocan connects with LFA-1, the interconnection between LFA-1 and ICAM-1 and subsequent recruitment of lymphocytes to the inflammation site occur, and LFA-1-dependent leukocyte adhesion/activation becomes inhibited[30].

Since the secretion of endocan and expression of ICAM-1 also occur in physiological circumstances[30], it is possible that endocan might exert anti-inflammatory properties under physiological conditions, such as in lean individuals, and shift towards pro-inflammatory properties when a pathophysiological scenario occurs.

Adiponectin is known for its cardioprotective properties[31,32]. This adipokine favors the uptake of glucose by enhancing glycolysis, reducing gluconeogenesis, and stimulating fatty acid oxidation in the liver. Adiponectin enhances AMP-activated protein kinase (AMPK) phosphorylation/activation in skeletal muscles, thus favoring beta-oxidation[32]. Adiponectin suppress TNF-α and IL-8, while increases the expression of IL-10 levels, thus exhibiting antiinflammatory properties[31]. The treatment with adiponectin led to inhibition of the atherosclerotic plaques development[33]. However, some meta-analyses showed no association between serum adiponectin levels and coronary artery disease events[34,35]. In our study, although adiponectin was negatively correlated with CVRS in Spearman's correlation analysis, this association was not retained in the multiple linear regression analysis.

ICAM-1 stimulates the recruitment of leukocytes and monocytes into the subendothelium[12], initiating the onset of atherosclerosis, being regarded as an early biomarker of atherogenesis[9]. However, the results of the current study did not confirm the association between ICAM-1 and CVRS, which is in line with a recent study[12] in patients with obstructive sleep apnea, thus questioning its reliability in estimating CVD risk.

We have confirmed a positive correlation between cIMT, as a surrogate marker of endothelial dysfunction, and CVRS in Spearman's correlation analysis. We have also shown significantly higher cIMT in a group of obese compared to normal weight individuals in the same CVRS tertile group for the first and second CVRS tertile groups, which could in part be explained by the fact that cIMT is associated with both obesity and cardiovascular risk[36]. However, similarly as for adiponentin in the current study, the association between cIMT and CVRS was not retained in the multiple linear regression analysis, which might in part be explained by a relatively small sample size of the study. To our knowledge, this is the first study that examined the association between cIMT and CVD risk in exclusively young disease-free females. Only a weak correlation between CVD risk score and cIMT was recently shown in a recently published study that included older patients and both genders[19].

The obtained results in the current study suggest that in addition to traditional CVD risk markers (i.e., obesity, dyslipidemia, and hyperglycemia), the importance of including some novel biomarkers should not be neglected.

The evaluation of CVD risk in a population of young women of reproductive age is one of the strengths of this study since the former is often under-recognized in this population group[1].

The CVRS is a noninvasive, cost-effective, and simple algorithm with sufficient discriminative ability to identify young adults with high CVD risk factors (such as hyperglycemia, obesity, hypertension, hyperlipidemia, and smoking) and the risk of CVD later in life[16]. The cluster of previously mentioned abnormalities, rather than each of them as a single parameter, might enable a clearer picture of CVD risk itself. The CVRS could also be used for the monitoring of the response to modification of these risk factors[16].

Moreover, we have included several atherosclerosis-related indices to get a deeper insight into the early atherogenesis onset, both imaging diagnostic methods, such as cITM, and serum biomarkers, such as endocan, adiponectin, and ICAM-1. Another strength of our study is the fact that we included only disease-free women, free of medications, and nonsmokers in an attempt to diminish, at least in part, several confounding factors that might significantly affect the examined biomarkers. One of the limitations of this study is its cross-sectional nature, which makes it impossible to establish a causal relationship between investigated atherosclerosis-related indices and CVD risk. We were also limited with data regarding reproductive history—menarche, as well as with the number of births and potential complications in pregnancy. Moreover, we were limited in the evaluation of sex hormones, especially estrogen, which might add further clarifications in relation to CVD risk and examined indices in the young female population. Longitudinal studies are needed to explore the link between CVRS, examined novel parameters, and cardiovascular events.

Conclusion

Endocan independently correlated with CVRS, which suggests that it could be a useful diagnostic tool in the estimation of cardiovascular risk in young women. Longitudinal research with a larger sample size is of utmost importance to further investigate this significant public health challenge.

Data availability

The data will be available upon reasonable request (contact persons: filizmercantepe@hotmail.com and aleksandranklisic@gmail.com).

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Author contributions

A.K. wrote the main manuscript text. J.K.S. performed statistical analysis. F.M. S.G. and S.B.S. performed material preparation, data collection and laboratory analyses. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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