The role of tenascin-C and oxidative stress in rheumatic and congenital heart valve diseases: an observational study

Tenascin-C ve oksidatif stresin romatizmal ve konjenital kalp kapak hastalığındaki rolü: Gözlemsel bir çalışma

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ABSTRACT

Objective: The aim of this study was to evaluate the association of tenascin-C (TnC) and total oxidant-antioxidant status to rheumatic or congenital heart valve diseases (HVD) in pediatric patients.

Methods: Fifty pediatric patients (25 rheumatic HVD patients and 25 congenital HVD patients) and 20 healthy age-matched control subjects, aged 3-17 years, were enrolled in this observational and cross-sectional study. Serum total antioxidant capacity (TAC), total oxidant status (TOS), oxidative stress index (OSI) and TnC levels were compared among the groups. ANOVA and Kruskal-Wallis tests were used for statistical analysis.

Results: Serum TnC level of the patients with rheumatic HVD [median 9.09 (0.94-46.30) ng/mL] was significantly higher than both congenital HVD and control groups [median 2.97 (0.66-11.80) ng/mL; $p<0.01$, 4.72±1.77 ng/mL; $p<0.05$, respectively]. However, there was no statistically significant difference between the congenital and control groups in terms of serum TnC level. The levels of serum TAC, TOS and OSI were found to be statistically similar in all groups. In addition, there were no correlations between the level of TnC, and TOS and OSI.

Conclusion: Tenascin-C can be used as a biochemical marker in the differential diagnosis of rheumatic and congenital HVD. As the oxidant and antioxidant systems were found to be in equilibrium in rheumatic and congenital HVD, oxidative stress can be thought not to have a marked role in the etiopathogenesis of rheumatic HVD during childhood. *(Anadolu Kardiyol Derg 2013; 13: 350-6)*

Key words: Children, rheumatic valve disease, congenital valve disease, tenascin-C, total antioxidant capacity, total oxidant status

ÖZET

Amaç: Bu çalışmanın amacı çocukluk döneminde romatizmal veya konjenital kapak hastalıklarının serum tenascin-C (TnC) ve total oksidan-antioksidan seviyeleri ile ilişkisini değerlendirmektir.

Yöntemler: Yaşları 3-17 arasındaki 50 çocuk hasta (25 romatizmal kapak hastası, 25 konjenital kapak hastası) ile yaşça uyumlu 20 sağlıklı birey bu enine kesitli ve gözlemsel çalışmaya alındı. Tenascin-C, total anti-oksidan kapasite (TAC), total oksidan seviye (TOS) ve oksidatif stres indeks (OSİ) değerleri gruplar arasında karşılaştırıldı. Gruplar arası karşılaştırmalarda ANOVA ve Kruskal-Wallis testi kullanıldı.

Bulgular: Romatizmal kalp hastalığı grubunun TnC düzeyleri [ortanca 9.09 (0.94-46.30) ng/mL] konjenital ve kontrol gruplarından yüksek bulundu [sırasıyla ortanca 2.97 (0.66-11.80) ng/mL, $p<0.01$; 4.72±1.77 ng/mL, $p<0.05$]. Ancak konjenital grup ile kontrol grubunun TnC düzeyleri arasında istatistiksel olarak anlamlı bir farklılık saptanmadı. Gruplar arasında TAC, TOS ve OSI değerleri açısından da farklılık saptanmadı. Tenascin-C düzeyi ile TOS ve OSI arasında da korelasyon saptanmadı.

Sonuç: Tenascin-C, romatizmal kapak hastalıkları ile konjenital kapak hastalıkları ayırıcı tanısında bir biyokimyasal marker olarak kullanılabilir. Romatizmal ve konjenital kapak hastalıklarında oksidan ve antioksidan sistemlerin denge içinde olması, çocukluk döneminde oksidatif stresin romatizmal kalp hastalığı etyopatogenezinde belirgin rolü olmadığını düşündürmektedir. *(Anadolu Kardiyol Derg 2013; 13: 350-6)*

Anahtar kelimeler: Çocuklar, romatizmal kapak hastalığı, konjenital kapak hastalığı, tenascin-C, total anti-oksidan seviye, total oksidan kapasite

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Accepted Date/Kabul Tarihi: 20.12.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 26.03.2013

doi:10.5152/akd.2013.102

Introduction

Heart valve disease (HVD) is a multifactorial process and its pathophysiology has not been fully understood. HVD is caused by the interaction of several risk factors, such as genetic, autoimmune, inflammatory, infectious, and oxidative stress (1-4). Acute rheumatic carditis is an important healthcare problem in developing countries and continues to be the leading cause of acquired heart disease in children worldwide, and acute rheumatic fever (ARF) occurs as a complication of an untreated group A β-hemolytic streptococcal pharyngitis (4, 5).

Heart valves are mainly composed of the extracellular matrix (ECM), smooth muscle cells, fibroblasts, and endothelial cells (6). Tenascin-C (TnC) is a multifunctional hexameric glycoprotein and it is a major component of the ECM. It is synthesized by interstitial fibroblasts and increases in inflammatory diseases. Only low levels of TnC can be detected in normal adult tissue, but higher levels have been reported in the areas of cancer development, cardiovascular disease, or where wounds are healing. In vitro studies have shown that a range of factors implicated in cardiovascular disease appear to be able to stimulate TnC synthesis from fibroblasts (7, 8). These factors include cytokines, growth factors, hypoxia, mechanical and oxidative stress, acidosis, angiotensin II, and hemodynamic forces (7, 8). Streptococcus pyogenes throat infection triggers an inflammatory reaction that involves several proinflammatory cytokines, such as tumor necrosis factor-α (TNFα), IL-1, and IL-6 (5). Immunohistochemical studies have shown expression of TnC in patients with congenital aortic valve stenosis (9, 10). Moreover, a recent study reported that TNFα, interferon gamma (IFNγ) and TnC concentrations in patients with rheumatic HVD were significantly higher than those with congenital valvular malformation and normal controls. Additionally, in this study it was shown that TNFα and IFNγ induced TnC transcription (11). This is the only clinical and experimental study related to TnC levels in adult patients with rheumatic or congenital HVD, until now.

The balance between the oxidant and antioxidant systems has been found to be impaired in many inflammatory diseases. Increased oxidative stress, which decreases immune system functions, is also thought to play a role in the pathogenesis of autoimmune disorders, because of apoptotic cell death (12). Consequently, oxidative stress that results from severe inflammation is thought to contribute in some way to valve damage. Rheumatic HVD has the characteristics of autoimmune diseases, but the pathogenesis of the disease remains obscure. The role of oxidative stress and systemic inflammation in rheumatic HVD are well known. Reports have indicated that oxidative modification of low-density lipoprotein by free oxygen radicals influences the initiation and progression of valve lesions (13, 14). In recent years, measurements of total antioxidant capacity (TAC) and total oxidant status (TOS) have been used in assessing oxidant and antioxidant systems in organisms (15, 16). Some previous studies have reported that oxidative stress can be either normal or increased in rheumatic HVD (17, 18).

The aim of the present study was to evaluate the association of tenascin-C (TnC) and total oxidant-antioxidant status to rheumatic or congenital heart valve diseases (HVD) in childhood.

Methods

Study design

This study was designed as cross-sectional and observational.

Study population

All patients with HVD, admitted to the Department of Pediatric Cardiology at Meram Medical Faculty of Necmettin Erbakan University in Konya between May 2011 and January 2012 were enrolled in the study. Fifty patients, aged 3-17 years with rheumatic or congenital HVD, and 20 healthy age- and sex-matched control subjects were included in the study. The study protocol complied with the principles outlined in the Declaration of Helsinki, and was approved by ethic committee of our hospital. Informed consent for participation in the study was obtained from all patients.

Study protocols

All participants were assessed with a detailed medical history, complete physical and echocardiographic examinations. All cases were examined by two pediatric cardiologists. Patients with rheumatic HVD, consisted of previously diagnosed as ARF, fulfilled the modified Jones criteria and followed-up in our clinic because of mitral regurgitation (MR) and/or aortic regurgitation (AR) that are the sequela of acute rheumatic carditis. Benzathine penicillin G was given to all non-penicillin-allergic patients to eradicate streptococci and thereafter every 3 weeks for secondary prophylaxis. Digoxin, angiotensin-converting enzyme inhibitor and diuretic were used in patients with severe carditis and heart failure.

Patients with any chronic disease, associated infections, pulmonary hypertension, smoking, use of antioxidant medications, elevated acute phase reactants, abnormal serum electrolytes and renal dysfunction were excluded.

The congenital HVD group consisted of mitral valve prolapse (MVP) or bicuspid aortic valve (BAV) with valve regurgitation that without a history of previous ARF. Control group was chosen from age- and sex-matched healthy children who were referred to our outpatient clinic because of the innocent heart murmur. Also, the controls had no congenital or acquired cardiac defects except patent foramen ovale.

Study variables

Baseline demographic variables: Age, sex, body weight, height, body mass index Body mass index was calculated as weight divided by height squared (kg/m^2).

Clinical and laboratory variables: Previous history of ARF and echocardiographic findings.

Predictor variable: Presence of HVD (rheumatic or congenital).

Primary outcome variable: TnC

Secondary outcome variables: TAC, TOS, OSI

Confounding factors: Eryhrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-streptolysin-O titer (ASO).

Echocardiographic examination

Echocardiographic studies were performed with two-dimensional guided M-mode echocardiography according to the methods established by the American Society of Echocardiography with S_{2-4} probe using a Hewlett-Packard Sonos 5500 system ultrasonic imager (Andover, MA, USA). Cross-sectional and Doppler examination were used to evaluate the severity of valvular regurgitation (19). It was decided whether pathological valvular insufficiency according to World Health Organization criteria. Valvular lesions were defined as rheumatic or congenital on the basis of echocardiographic findings. Rheumatic HVD was diagnosed based on echocardiographic detection of characteristic B-mode features, such as thickening of valve leaflets and chordal apparatus, restricted leaflet separation, diastolic doming of the anterior mitral leaflet, commissural fusion or M-mode detection of diminished mitral E-F slope, and upward movement of posterior mitral leaflet in early diastole (20). In order to establish the diagnosis of bicuspid aortic valve (BAV), the valve must be visualized in systole in the short-axis view. During diastole, the raphe can make the valve mistakenly appear tri-leaflet. Additionally, the orifice has a characteristic "fish mouthed" appearance during diastole. In the long-axis view, the valve often has an eccentric closure line and there is doming of the leaflets (21). Mitral valve prolapse (MVP) was defined as superior displacement of mitral valve leaflets to the plane of mitral valve in 2D-echocardiography (22).

Blood sample collection and biochemical assay

Erythrocyte sedimentation rate, CRP, ASO, TAC, TOS and TnC were examined in every patient group. Blood samples (4 mL) were obtained following an overnight fasting. The serum was separated from the cells by centrifugation at 4,000 rpm for 10 minutes and then stored at -80°C until biochemical examination.

Tenascin-C levels were measured by commercially available kits based on enzyme-linked immunosorbent assay (ELISA) methods (Cusabio Biotech, Human Tenascin-C ELISA kit, Cat no: CSB-E13125h, Hubei Province, P.R. China). The results are expressed as ng/mL.

TAC and TOS levels were measured using commercially available kits (Rel Assay, Turkey). Level of TAC was measured using a novel automated method, which is based on the bleaching of the characteristic color of a more stable ABTS [2.2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)] radical cation by antioxidants. The results were expressed as mmol Trolox Egv./L. The level of TOS was measured by a method, in which oxidants present in the sample oxidize the ferrous-ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules abundantly present in the reaction medium. The ferric ion produces a colored complex with xylenol orange in an acidic medium. The color intensity, which was measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Egv./L). The oxidative stress index (OSI) value was calculated according to the following formula: OSI (arbitrary unit) = TOS (mmol H_2O_2 Eqv./L) / TAC (mmol Trolox Eqv./L) (23).

Statistical analysis

The Statistical Package for Social Sciences (SPSS for Windows Version 16.00, Chicago, IL, USA) program was used for assessment of the results. The distribution of data analyzed using the Shapiro-Wilks test according to which suitable parametric and non-parametric tests were selected. The parametric data are given as arithmetic means±standard deviation (SD) and non-parametric data are given as median (minimum-maximum). Pearson Chi-square test was used to compare categorical variables. In the comparison of the groups, the one way-ANOVA analysis of variance was used in variables with normal distribution, while the Post Hoc test (Tukey-HSD) was used as a secondary test in multiple comparisons. The Kruskal -Wallis test was used for analysis of variables which were not normally distributed, and the Mann-Whitney U test was used in cases showing a statistical difference between the two groups. The correlation between TnC and TOS levels of the patients has been analyzed by Pearson's correlation test. In the statistical evaluations, a p value of <0.05 was regarded as significant.

Results

Baseline characteristics

Demographic characteristics and anthropometric values of patients are presented in Table 1. There were no differences in sex and anthropometric values between the patient and control groups ($p>0.05$). However, the age and anthropometric values of congenital HVD group were significantly lower than rheumatic HVD group ($p<0.05$, Table 1).

In rheumatic HVD group, the percentages of mitral regurgitation, aortic regurgitation, and MVP were 88%, 40% and 32%, respectively. Mild mitral stenosis was determined in only one patient (4%). In congenital HVD group, the percentages of MVP and BAV were determined as 56%, 44%, respectively. Mild aortic stenosis (gradient: 16-36 mmHg) was detected in 96% of the patients with BAV.

Tenascin-C and oxidative stress parameters

Serum TnC level of the patients with rheumatic HVD was significantly higher than both congenital HVD group and control subjects ($p<0.01$, $p<0.05$, respectively, Table 2, Fig. 1). However,

there was no statistically significant difference between the congenital HVD and control groups in terms of TnC.

The levels of serum TAC, TOS and OSI were found to be statistically similar (p>0.05) in all groups (Table 2). Additionally, there was no correlation between the serum TnC level, and the levels of TAC, TOS and OSI in all groups.

No statistically significant difference was detected between the patients with MVP and BAV in terms of serum TnC, TAC, TOS levels and OSI value (p>0.05). The ESR, CRP levels and ASO titers were similar between groups (Table 2).

Discussion

The present study was the first to investigate TnC and oxidative system in children with rheumatic and congenital HVD. In this study, serum TnC level was detected to be significantly higher in the patients with rheumatic HVD than in the congenital HVD and control individuals. Therefore, TnC can be suggested as a biomarker of rheumatic HVD. In addition, we found similar oxidative stress parameters (TAC, TOS and OSI) between groups.

As the rheumatic HVD is seen in children during their developmental years and affects their life expectancies, the diagnosis, follow-up, and treatment of this disease have become very important. For pediatric cardiologists, differentiating rheumatic HVD from congenital HVD is not always possible when there is no known history of ARF. Indeed, there is no previous history of ARF in 30%-40% of adult patients who have rheumatic HVD, and recurrences may even be asymptomatic (4). Also, patients with congenital HVD are at risk of developing rheumatic HVD as well. Furthermore, MVP has often been reported in patients with rheumatic carditis, as a long-term sequela; several studies have found the prevalence to be 14%-45% (24, 25). In the present study, MVP was observed in 32% of the patients who had rheumatic HVD. An accurate diagnosis for secondary prophylaxis of rheu-

Table 1. Demographic characteristics of the groups

Variables	Rheumatic HVD (n=25)	Congenital HVD (n=25)	Control (n=20)	§F	p
Sex, female/male	12/13	13/12	10/10		p>0.05ε
Age, years	13.52±2.71a	10.91±4.19	11.65±2.91	3.74	p>0.05§
Body weight, kg	45.88±12.51a	35.92±15.12	38.10±14.10	4.48	p<0.05§
Height, cm	157.16±13.18a	142.44±23.20	146.10±17.30	4.26	p<0.05§
Body mass index, kg/m2	18.92±3.47a	16.57±3.17	17.38±3.14	4.36	p<0.05§

Data are presented as mean±standard deviation and numbers
εPearson Chi-square test, §ANOVA - test; a-posthoc Tukey test: rheumatic HVD vs. congenital HVD p<0.05
HVD - heart valve disease

Table 2. Comparison of serum tenascin-C, total oxidant status, total anti-oxidant status, oxidative stress index, acute phase reactants levels and anti-streptolysin-O titers between the groups

Variables	Rheumatic HVD (n=25)	Congenital HVD (n=25)	Control (n=20)	p	Chi-square/F
Tenascin-C ng/mL	9.09a,b (0.94-46.30)	2.97 (0.66-11.80)	4.72±1.77	p<0.01¥	12.47
TOS µmol H2O2 Eq/L	12.42 (8.23-31.76)	12.45 (8.77-20.88)	13.78±2.40	p>0.05¥	1.28
TAC mmol Trolox Eq/L	4.21±0.27	3.82±0.28	3.91±0.18	p>0.05§	1.39
OSI arbitrary unit	2.92 (2.18-7.03)	3.26 (2.46-6.0)	3.51±0.54	p>0.05¥	3.39
ESR, mm/hour	9.72±4.42	9.08±4.01	7.25±3.71	p>0.05§	2.13
CRP, mg/L	1.99 (1-7.8)	1.77 (1-5.93)	1.62 (1-7.5)	p>0.05¥	0.201
ASO IU/mL	109 (30.5-79)	90.70 (25-876)	89.50 (25-751)	p>0.05¥	0.292

Data are presented as mean±standard deviation for parametric test, median (min-max) value for nonparametric test
§ANOVA - test, ¥Kruskal-Wallis test, a, bMann-Whitney U test
aRheumatic HVD vs. congenital HVD p<0.01
bRheumatic HVD vs. control group p<0.05
ASO - anti-streptolysin-O, CRP - C-reactive protein, ESR- erythrocyte sedimentation rate, HVD - heart valve disease, OSI - oxidative stress index, TAC - total antioxidant capacity, TOS - total oxidant status

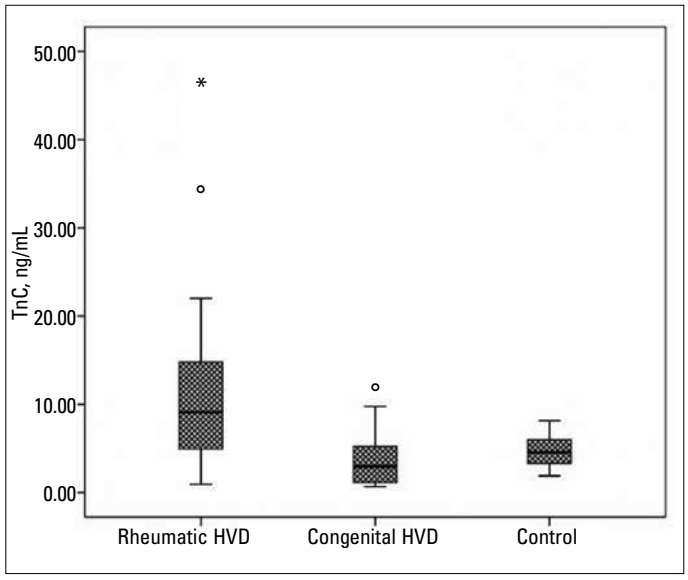

Figure 1. Comparison of serum tenascin-C levels between the groups

matic carditis is particularly important for these patients. However, treating children who have rheumatic HVD with benzathine penicillin G, intramuscularly, every three weeks for at least ten years to provide secondary prophylaxis puts them at risk of developing allergic reactions and is also quite painful. In addition, the fact that patients with congenital HVD have a risk of rheumatic heart disease as well makes differentiating between congenital and rheumatic HVD particularly important. Unfortunately, although studies have been undertaken to find a novel biochemical marker to use in diagnosing rheumatic carditis in patients who are incidentally detected to have valve insufficiency, no laboratory indicators have yet been found for practical use (4).

The pathogenesis of rheumatic HVD is complex and involves genetic factors that predispose a person to the development of autoimmune reactions (4, 5). The relationship between heart valve damage and the pathogenesis of valve fibrosis with immuno-inflammatory response is well known (1, 2). Degenerative valve lesions have many features that are characteristic to active pathobiological processes, including chronic inflammation, lipoprotein deposition, active calcification, and activation of the renin-angiotensin system. The course of rheumatic carditis is characterized by the expression of immunological and biochemical disorders (1, 2, 5, 26). Increased expression of TnC has shown to be positively linked to a range of other cardiovascular pathologies, including acute myocardial infarction, atherosclerosis, pulmonary artery hypertension, neovascularization, the peri-infarct repair process following stroke, angiotensin II-induced cardiac fibrosis, vasospasm following subarachnoid hemorrhage, and vascular calcification etc. (8). Expression of TnC has also been shown to play a major role in the development of fibrosis during tissue repair (7, 8).

Previous studies have shown that TnC can be used for diagnosing myocarditis, and dilated cardiomyopathy (7, 8). In rheumatic carditis, the development of leaflet fusion after the formation of granulation tissue and fibrosis results in valve insufficiency as well as stenosis. Valve insufficiencies and stenosis result from fibrosis of the valves, which occurs because of the inflammation in patients with rheumatic carditis (4, 5). In addition, the inflammatory response still persists in the chronic phase of rheumatic HVD (2, 3, 18). A recent study reported that the TnC levels in the serum and tissue of adults with rheumatic aortic stenosis were higher than in those of patients with non-rheumatic aortic stenosis and of the control groups (11). More IFNγ and TNF receptors were found being expressed on rheumatic aortic valves interstitial cells than on non-rheumatic ones (11). Similarly, in the present study, the serum TnC level of children with rheumatic HVD was found to be higher than both of the congenital HVD and the control groups. Furthermore, the levels of acute phase reactants were normal in patients with rheumatic HVD. We believe that higher serum TnC levels in patients with rheumatic HVD were associated to more IFNγ and TNF receptors. However, in another study of patients with non-rheumatic aortic stenosis found a positive relationship between the severity of stenosis and the TnC expression at tissue level (10). Based on these findings, it can be said that HVD is a progressive disease, and also that the inflammation and remodeling persist for a long time. In addition, we suggest that the serum TnC level can be used for the probable diagnosis of rheumatic HVD.

Tenascin-C plays a significant role in tissue remodeling, and increased TnC expression has been found to be associated with the initiation of fibrosis in the early process of tissue repair. The deposition of TnC before the composition of mature collagen fibers indicates that TnC interacts with other ECM proteins to form collagen fibers (7, 8). TnC is a profibrotic molecule that is thought to cause valvular calcification, by leading to intercellular interaction with ECM in rheumatic aortic stenosis. In addition, excessive TnC expression has indicated an active process of valvular mineralization in non-rheumatic aortic stenosis (10, 11). The overexpression of TnC was also found to be associated with the basement membrane, beneath the endothelial cells, in normal valves. However, no such expression was detected in stenotic valves, although immunoreactivity was found in the deeper layers of the valves. This reactivity was associated with characteristics that are typical of the stenosing process and the increased mechanical loading caused by hypertension (10). In addition, it has been shown that TnC, together with matrix metalloproteinase-2, can play an important role in the pathogenesis and progression of congenital aortic stenosis (9). In this study, higher serum TnC levels in the rheumatic HVD group, compared to those with congenital HVD and the control groups, suggest that TnC may play a role in the pathogenesis of rheumatic HVD. In terms of serum TnC level, no statistically significant difference was found between the congenital HVD group and the control group, due to the small numbers of patients with BAV and mild aortic stenosis.

Tenascin-C has been believed to play a role in the immunologic system or in the pathogenesis of inflammatory diseases. It is thought that, in the future, TnC will perform a key role in treatment (7, 8). Jiang et al. (11) have shown that mechanical stress and increased levels of TNFα and IFNγ lead to elevated levels of TnC in rheumatic aortic stenosis and have also suggested that the target treatment of this disease should be with anti-IFNγ and anti-TNFα. Proinflammatory cytokines such as TNFα and IFNγ, which are known to contribute to the pathogenesis of rheumatic carditis, cause increases in TnC production (5, 11). TNFα and IFNγ are proinflammatory and immune-regulator cytokines that have critical importance in the pathogenesis of various inflammatory and autoimmune diseases. Therefore, anti-TNFα, and anti-IFNγ have been used for the treatment of some autoimmune diseases (27, 28). Treating rheumatic diseases with anti-IFNγ and anti-TNFα has been reported to be effective (27). Additionally, TnC levels have been shown to decrease with treatment using steroid or non-steroidal anti-inflammatory drugs (7, 8). A previous study suggested that anti-inflammatory treatment in rheumatic HVD could reduce the progression of the disease, as well as both the mortality and morbidity (2). In future, TnC may be able to be used in therapeutic strategies, once its role in the pathogenesis of rheumatic carditis is better understood. Therefore, further prospective studies are needed to show the efficacy of the anti-inflammatory treatment on TnC levels in rheumatic HVD.

In vitro, hemodynamic changes (volume load), mechanical stress, myocardial trauma, and inflammation have been shown to increase the TnC levels from cardiac fibroblasts (7, 8, 29). Furthermore, oxidative stress may also increase the levels of TnC (7, 30, 31). Previous studies have shown increased oxidative stress in ARF and rheumatic HVD and have also suggested that this plays a role in the pathogenesis of rheumatic carditis (18, 32, 33). Increased oxidative stress in ARF has been reported to be the result of the increase in several oxidative stress indicators and also the decrease in antioxidant parameters (32-34). One study found that both malonyldialdehyde and several antioxidant enzymes were increased in ARF (35). Chiu-Braga et al. (18) detected that the levels of advanced oxidation protein products were significantly elevated in patients with rheumatic HVD, compared to the controls. Therefore, oxidative stress may be considered to play a role in the high TnC levels of those with rheumatic HVD. Another study reported normal plasma and tissue OSI levels in rheumatic HVD, in spite of low tissue TAC levels (17). On the other hand, increased oxidative stress levels were demonstrated in the tissue and serum of patients with degenerative MR (26, 36). In the present study, the levels of serum TAC, TOS, and OSI were found to be statistically similar in both the rheumatic and the congenital HVD groups. However, we did not find any correlations between the TOS or OSI and serum TnC levels in any of the groups. Our study found that either oxidative status has no pronounced influence on congenital or rheumatic HVD etiology during childhood or is currently prevented through unknown mechanisms.

Study limitations

There are some limitations, because this study was conducted with a small group. Also, we did not investigate the TNFα, IFNγ and other cytokines, which increase in patients with rheumatic HVD. Therefore, further prospective studies that include larger series with long-term follow-up evaluation are necessary to clarify the clinical utility of serum TnC level in children with rheumatic and congenital HVD.

Conclusion

Our findings suggest that the levels of serum oxidative and antioxidative parameters are similar in patients with rheumatic and congenital HVD. Hence, oxidative stress may be considered as having no obvious role in the pathogenesis of rheumatic HVD during childhood. However, we believe that TnC may have a marked role in the etiopathogenesis of rheumatic HVD, and that it can be used as a novel biochemical marker for diagnosis. Further studies are needed to determine whether TnC is a promising marker in the differential diagnosis of rheumatic from congenital valve diseases and also in the pathogenesis of rheumatic HVD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Acknowledgment

This study was financially endorsed by our Medical Faculty Scientific Study Research Commission. This study was partly presented as a poster in 46th Annual Meeting of the Association for European Paediatric and Congenital Cardiology (AEPC) in İstanbul-Turkey at 23-26 May 2012.

Authorship contributions: Concept - Z.K., H.A.; Design - Z.K., T.B.; Supervision - Z.K., T.B.; Resource - Z.K., H.A.; Materials - Z.K., H.Ç.; Data collection&/or Processing - Z.K., F.S.; Analysis &/or interpretation - Z.K., H.Ç.; Literature search - Z.K., T.B.; Writing - Z.K., F.S.; Critical review - Z.K., T.B.

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