

Tissue inhibitors of matrix metalloproteinases in serum are cardiac biomarkers in Emery-Dreifuss muscular dystrophy

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Abstract

Background: Tissue inhibitors of matrix metalloproteinases (TIMPs) are known to be involved in cardiovascular diseases. Hitherto, they have not been examined in dilated cardiomyopathy in the course of Emery-Dreifuss muscular dystrophy (EDMD).

Aim: To define TIMPs in serum because they might help in defining cardiac dysfunction at the early cardiological stages of this disease and detect preclinical stages of cardiomyopathy.

Methods: Twenty-five EDMD patients connected with lamin A/C (AD-EDMD) or emerin (X-EDMD) deficiency and 20 healthy age-matched controls were examined. The serum levels of the tissue inhibitors TIMP-1, -2, -3 were quantified using the ELISA sandwich immunoassay procedure with appropriate antibodies.

Results: Serum levels of TIMP-1 were normal in autosomal AD-EDMD and increased in the majority of X-linked EDMD. The level of TIMP-2 was decreased in 25%/21% of AD-EDMD/X-EDMD cases. TIMP-3 serum level was significantly reduced in all the examined patients. Receiver operating curves indicated that in terms of sensitivity and specificity characteristics the performance of TIMP-3 (less that of TIMP-2) makes them the best markers of cardiac involvement among the examined TIMPs.

Conclusions: Evidence shows that the levels of TIMP-3, and in some cases also TIMP-2, are decreased in EDMD. The decrease might be associated with an adverse effect on matrix metalloproteinases and remodelling of the myocardial matrix. The specific decrease of TIMP-3 indicates that this biomarker might help in early detection of cardiac involvement in EDMD. Up-regulation of TIMP-1 in the majority of patients with X-EDMD indicates increased myocardial extracellular matrix turnover, early onset of tissue remodelling, and may contribute to arrhythmia, frequently occurring in this form of the disease.

Key words: Emery-Dreifuss muscular dystrophy (EDMD), tissue inhibitors of matrix metalloproteinases (TIMPs), dilated cardiomyopathy

Kardiol Pol 2015; 73, 5: 360–365

INTRODUCTION

Emery-Dreifuss muscular dystrophy (EDMD) is a rare, genetically transmitted disease, which is associated with a defect in *EMD* or *LMNA* genes encoding nuclear proteins: emerin or lamin A/C, respectively. EDMD associated with emerinopathy is known as X-EDMD (X-linked EDMD), while that associated with laminopathy is known as AD-EDMD (autosomal dominant EDMD). The clinical symptoms are manifested as skeletal

muscle atrophy and weakness, joint contractures, and dilated cardiomyopathy (DCM) with conduction defects [1]. While the latter often remains clinically silent for prolonged periods, sudden death is not a rare event. The pathogenesis of DCM in EDMD is not recognised, yet. It is supposed that changes in the myocardial extracellular matrix (ECM), important for ventricular stability and alignment of cardiomyocytes [2], are responsible for the induction of matrix metalloproteinases

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Received: 12.02.2014 Accepted: 03.11.2014

Available as AOP: 30.12.2014

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(MMPs) connected with a decrease in levels of tissue inhibitors of matrix metalloproteinases (TIMPs). Potentially it may evoke DCM [3–7]. In EDMD changed values of MMPs are observed [8]. They indicate cardiac involvement and help monitoring of the DCM treatment.

Tissue inhibitors of metalloproteinases 1-4 (TIMP-1-4) are endogenous regulators of MMPs. They participate in cellular homeostasis, tissue remodelling, and adaptation. TIMPs influence cardiac fibroblasts, endothelial cells, cardiomyocytes, smooth muscle cells, and inflammatory cells, promote cell growth, and have antiapoptotic and anti-androgenic activity, and provide means of negatively controlling tissue effects of MMPs [9–11]. Changes in TIMPs are associated with heart failure. An imbalance between MMPs and TIMPs is seen in tissue destruction and degradation of ECM structural proteins. MMPs also play a role in left ventricular (LV) structural remodelling [12]. The imbalance between MMPs and TIMPs may contribute to the risk of arrhythmia and atrial fibrillation [13]. Plasma TIMPs are associated with major cardiovascular risk and indicate LV hypertrophy, systolic dysfunction, and increased mortality in congestive heart failure [14, 15]. In failing hearts MMP/TIMP production is dysregulated, and elevated TIMP content may represent a compensatory response to increased MMP activity [16].

The aim of this study was to define the value of TIMPs in serum of EDMD patients because this might identify the cardiac status in EDMD. This is because there is the possibility of unexpected cardiac decompensation and a risk of sudden death, even in young patients. Until now there were no available data on the level of circulating TIMPs in EDMD.

METHODS

Patient characteristics

A total of 25 young patients (19 males and 6 females) with EDMD were included. Ten patients had AD-EDMD and 15 had X-EDMD. Twenty age-matched healthy controls with no history of cardiac and skeletal muscle symptoms were examined as controls.

Initial diagnosis in these patients was based on the clinical status, blood creatine kinase activity, immunohistochemistry, electron microscopy, and electromyography. It was finally confirmed by *LMNA* and *EMD* gene screening. Cardiac disease was diagnosed in all patients (Table 1). In the AD-EDMD patients the progression of cardiological symptoms ranged from mild/moderate to severe/very severe. Conduction defect or impaired contractility was seen. A pacemaker had been implanted in five of the AD-EDMD patients, and a cardioverter-defibrillator in two other cases. One patient underwent heart transplantation and one patient suddenly died. In ten X-EDMD patients the cardiac involvement was either moderate or mild; in one case it was severe. Among the cardiac parameters conduction defects and atrial involvement predominated. In the majority of them (12/15) a pacemaker

had been implanted. In neither of the EDMD groups was it a straightforward matter to track the development of cardiomyopathy. Even patients with evident bradycardia had usually had their cardiac symptoms detected once the first neurological diagnosis of EDMD had been established. Skeletal muscle atrophy was diagnosed in all patients (Table 1). In AD-EDMD it was mild in two cases, moderate in four, and severe/very severe in the remaining four. In X-EDMD skeletal muscle atrophy was present in 12 cases, being either mild/moderate or severe in three cases.

Biochemical analysis

Blood was collected for routine biochemical analyses and centrifuged at 3000 rpm for 10 min. Serum was separated and frozen at -30°C until used. The levels of the biomarkers were determined using an ELISA-based one-step sandwich enzyme immunoreaction for TIMP-1 and TIMP-2 using human immunoassay kits (with anti-TIMP-1 or anti-TIMP-2 coated microplate, Chemicon Intern). To test TIMP-3 a DuoSet ELISA Development Systems with biotinylated mouse anti-human TIMP-3 (R&D) was used. The absorbance at 450 nm was then assessed using a Sigma Diagnostics EIA Microwell Reader II (Hercules, CA, USA).

Statistical analysis

Analyses were performed using a statistical software STATISTICA version 9.0 (StatSoft, Inc. Poland). The means and standard errors are presented. The analysis of variance on ranks with the Kruskal-Wallis test was done. Differences in variable values were assessed using the Mann-Whitney U test, while the relationships between variables were analysed using Spearman's correlation (ρ). The receiver operating curves (ROC) analysis, providing an index of accuracy and discrimination between normal state and probability of disease in individual subjects, was also included [17, 18]. A p value < 0.05 value was considered statistically significant.

RESULTS

The analysis of TIMP-1 in the serum of the EDMD patients showed that the level was changed in 13% of AD-EDMD patients and in 71% of the X-EDMD cases. TIMP-2 was in turn significantly decreased in 25% of patients with AD-EDMD form and 21% of the X-EDMD patients. TIMP-3 was significantly lower in all EDMD cases than in the controls (Table 2). The TIMP values were compared to those of tenascin C (TN-C), creatine kinase isoenzyme MB (CK-MB), atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), N-terminal prohormone of BNP (NT-proBNP), and MMPs, which were examined using the same serum samples and summarised in our previous paper [8]. There was a significant correlation in X-EDMD between TIMP-1, TN-C ($\rho = -0.64$, $p < 0.018$), and CK-MB ($\rho = 0.64$, $p < 0.024$). In AD-EDMD there was a correlation between TIMP-1 and NT-proBNP

Table 1. Clinical and laboratory data in patients with Emery-Dreifuss muscular dystrophy (EDMD)

| Description | X-EDMD (n = 15) | AD-EDMD (n = 10) |
|------------------------------------|--|--|
| Family history | Familial (14) Sporadic (1) | Familial (7) Sporadic (3) |
| Age [years] | 28 ± 12 | 30 ± 11 |
| Skeletal muscle involvement | Elbow, ankle contractures, and spine rigidity (15) Generalised muscle atrophy (3) Arms, calf atrophy (5) Arm atrophy (2) | Elbow, ankle contractures, and spine rigidity (9) Generalised atrophy (6) Arms, thighs (2) Arms, calf atrophy (1) Wheelchair-bound (2) |
| Cardiac symptoms | AVB 2/3 (7) AF/AFL (5) Tachy-brady (3) | Heart failure (3) (including NYHA III (1)), NYHA II/III (2) AVB 3 (3) AF (4) SVT (3) VT (1) |
| Cardiac device/age of implantation | Pacemaker/14–33 years (11) | Pacemaker/20–41 years (5), then ICD/28–29 years (2 of these 5) |
| Mutation | 1A>G (2) 3G>A (1) 153delC (6) 192G>T, 194insC (1) 256C>T (1) 266-27del18 (1) 397C>T (1) 399+1G>C (1) 450insG (1) | 334_336del (1) 788T>C (1) 743T>C (1) 1072G>A (1) 1337A>T (1) 1357C>T (4) |

Number of patients is shown in parentheses. AF — atrial fibrillation; AFL — atrial flutter; AVB — atrio-ventricular block; ICD — implanted cardioverter-defibrillator; NYHA — New York Heart Association; SVT — supraventricular tachycardia; VT — ventricular tachycardia

Table 2. Tissue inhibitor of matrix metalloproteinases (TIMP) in serum of Emery-Dreifuss muscular dystrophy (EDMD) patients

| TIMP | AD-EDMD (normal/changed) [%] ^a | X-EDMD (normal/changed) [%] ^a | Controls |
|----------------|--|---|------------|
| TIMP-1 [ng/mL] | 43.7 ± 7.9 (87/13d) | 96.1 ± 7.0 ^{#,*} (29/71i) | 47.1 ± 3.5 |
| TIMP-2 [ng/mL] | 17.3 ± 2.4* (75/25d) | 15.1 ± 1.2* (79/21d) | 34.9 ± 3.2 |
| TIMP-3 [pg/mL] | 10.6 ± 0.4* (0/100d) | 10.4 ± 0.4* (0/100d) | 17.1 ± 0.9 |

Values are means ± standard errors; *p < 0.005 for patients vs. controls; #p < 0.002 for AD-EDMD vs. X-EDMD patients; ^aChanged values vs. controls: increased (i) or decreased (d)

($\rho = 0.86$, $p < 0.014$). A significant correlation in X-EDMD between TIMP-3, BNP ($\rho = -0.62$, $p < 0.022$), and ANP ($\rho = -0.72$, $p < 0.012$) was present. In AD-EDMD there was a significant correlation between TIMP-3 and membrane type 1 MMP (MT1-MMP) ($\rho = -0.83$, $p < 0.042$). To assess the value of TIMP estimation for the EDMD diagnosis, the

area under the receiver operating curves (AUC of ROC) was calculated (Fig. 1). In terms of sensitivity and specificity in the ROC characteristics the performance of TIMP-3 and of TIMP-2 made TIMP-3 the best marker from the TIMPs set (AUC = 0.989 for TIMP-3, AUC = 0.923 for TIMP-2, AUC = 0.758 for TIMP-1).

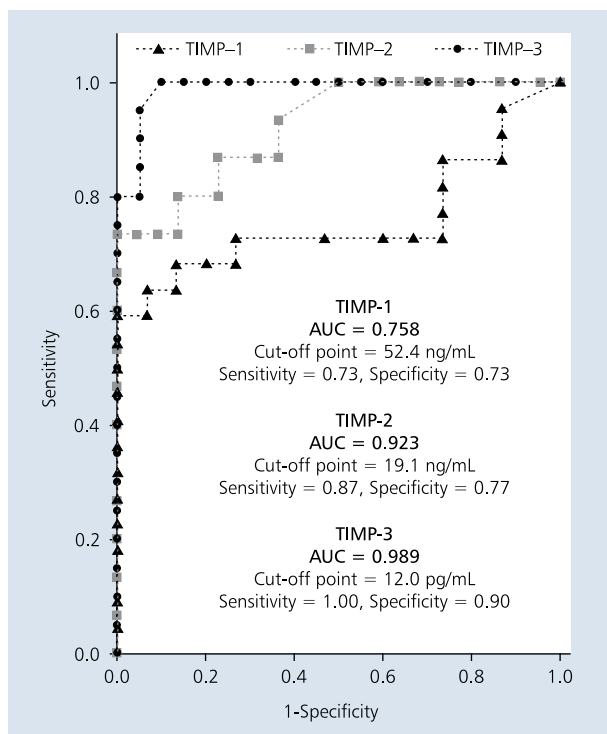


Figure 1. The receiver operating curves (ROC) for tissue inhibitors of matrix metalloproteinases (TIMPs) in Emery-Dreifuss muscular dystrophy patients; AUC — area under the ROC

DISCUSSION

Most studies devoted to TIMPs in cardiac pathology have concerned DCM [19], congestive heart failure [16], acute myocardial infarction (MI) [20–22], and LV diastolic dysfunction and fibrosis in hypertension [23]. The common feature of above-mentioned pathologies is myocardial tissue remodelling of ECM and fibrosis as a consequence of biochemical stress [24], leading to ventricle dilatation and contractile dysfunction. The balance between MMPs, which degrades ECM and TIMPs, is responsible for ECM turnover. There have been no reports on TIMPs in heart disease in patients with EDMD. In our study we analysed the serum levels of TIMP-1, TIMP-2, and TIMP-3. We found changed TIMP-1 in 13% of AD-EDMD and in 71% of the X-EDMD patients. TIMP-1 is an independent predictor of cardiovascular mortality and stroke [25] and of non-response in patients treated with cardiac resynchronisation therapy [26]. An increase level of TIMP-1 was found in the acute phase of MI [20], in hypertension, and in diastolic dysfunction [23], indicating an early activation of the MMP/TIMP system in the myocardium. However, in ischaemic and dilated cardiomyopathy, cardiac expression of TIMP-1 on the mRNA and protein level was significantly reduced [16].

TIMP-2 was in turn significantly decreased in 25% of patients with AD-EDMD form and in 21% of the X-EDMD patients. Apart from inhibition of MMPs, TIMP-2 in the heart is required for cell-surface activation of MMP-2 (pro-MMP2).

TIMP-2 is unique among TIMPs because, as well as inhibiting a number of MMPs, it also causes MMP-2 activation by interacting with MT1-MMP and pro-MMP, forming a tri-molecular complex [27, 28]. Lack of TIMP-2 leads to exacerbated LV dysfunction and adverse remodelling of ECM in response to biochemical stress after pressure overload [24]. TIMP-2 is altered in different heart diseases such as hypertension and atrial fibrillation. In the end-stage of DCM TIMP-2 is unaltered or increased; it is also raised in late stages of MI [3]. The inhibitory function of TIMP-2 on MT1-MMP is a key determinant of remodelling after MI. TIMP-2 deficiency increases the severity of the disease after MI: it increases LV dilatation and induces excess degradation of ECM collagen and enhanced inflammation [24].

In our analysis in patients with EDMD we found a significant decrease of TIMP-3 in both groups: X-EDMD and AD-EDMD. This observation is consistent with reports of other authors, i.e. Li et al. [16], who found significant reduction of TIMP-3 expression on RNA and protein levels in the failing human heart. Also, Fedak et al. [19] found that TIMP-3 deficiency triggered spontaneous dilatation of LV, cardiomyocyte hypertrophy, and contractile dysfunction, consistent with human DCM. TIMP-3 differs from the other TIMPs in its direct binding with ECM components, and it models MMPs activity better than the other TIMPs. It is highly expressed in the heart and probably takes part in ECM embryonal remodelling and heart development. Reductions in TIMP-3 parallel adverse matrix remodelling in cardiomyopathic hamsters and failing human heart. TIMP-3 contributes to the regulation of remodelling in the myocardium, and its reduction is capable of promoting a transition from compensated to end-stage congestive heart failure through matrix degradation and cytokine activation. TIMP-3 deficiency impairs LV function, alters cardiac structure, and disrupts matrix homeostasis and the balance between inflammatory mediators, leading to cardiac dilatation and dysfunction [19]. TIMP-3 is critical during the early stages of recovery from MI. It is a novel marker for risk stratification in non-ischaemic cardiomyopathy. Reduced TIMP-3 levels in hearts with ischaemic cardiomyopathy, when over-expressed or supplemented with TIMP-3, may prove to be a therapeutic approach. Therapeutic restoration of myocardial TIMP-3 in patients with DCM may limit cardiac remodelling and progression to heart failure and may prove to be a therapeutic approach.

CONCLUSIONS

In the presented study we have provided evidence for TIMP behaviour in DCM in EDMD. No data in the literature are available at present. Abnormalities in TIMPs in EDMD have already been suggested in previously published results on increased activity of MMPs, which might indicate decreases in the action of TIMPs [28]. In the analysed group of patients with both types of EDMD we observed a significant decrease

in TIMP-3. This might promote a transition from compensated to end-stage cardiomyopathy, and may be associated with adverse remodelling of the myocardial matrix. Therefore, the serum level of TIMP-3 might be a candidate biomarker of cardiac involvement in EDMD, especially in early cardiac asymptomatic patients. Reduction in TIMP-2, and changes in TIMP-1, although found in a smaller number of patients, could indicate an imbalance between TIMPs and MMPs, which disturbs the architecture of the ECM and contributes to LV remodelling and the subsequent deterioration of LV performance. On the other hand, up-regulation of TIMP-1, present in the majority of patients with X-EDMD, might suggest an increased ECM turnover and early onset of tissue remodelling and may contribute to arrhythmia, frequently occurring in this form of EDMD.

Acknowledgements

Ethical approval: the study protocol was approved by the Ethics Committee of the Medical University in Warsaw; No KB/2/2005.

Conflict of interest: none declared

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Tkankowe inhibitory metaloproteinaz macierzy w surowicy jako biomarkery kardiologiczne w dystrofii mięśniowej Emery'ego-Dreifussa

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Streszczenie

Wstęp: Tkankowe inhibitory metaloproteinaz macierzy (TIMPs) są zaangażowane w patogenezę chorób układu sercowo-naczyniowego. Dotychczas nie badano stężenia TIMPs u pacjentów z kardiomiopatią rozstrzeniową w przebiegu dystrofii mięśniowej Emery'ego-Dreifussa (EDMD).

Cel: Celem badania było określenie stężenia TIMPs w surowicy pacjentów z EDMD w celu rozstrzygnięcia, czy mogłyby stanowić biomarker dysfunkcji mięśnia sercowego na wczesnych etapach choroby i pomóc w wykrywaniu kardiomiopatii w okresie przedklinicznym.

Metody: Zbadano 25 pacjentów z EDMD związaną z mutacją w genie laminy A/C (AD-EDMD) lub w genie emeryny (X-EDMD) oraz 20 zdrowych osób z grupy kontrolnej, dobranych pod względem wieku. Stężenia TIMP-1, -2, -3 w surowicy określono za pomocą testu immunoenzymatycznego ELISA z odpowiednimi przeciwciałami.

Wyniki: Stężenia TIMP-1 w surowicy były prawidłowe u chorych z AD-EDMD, a zwiększone u większości pacjentów z X-EDMD. Stężenie TIMP-2 w surowicy było obniżone u 25% i 21% chorych, odpowiednio, z AD-EDMD i X-EDMD. Stężenie TIMP-3 było znamienne obniżone u wszystkich badanych pacjentów. Krzywe ROC wskazywały, że spośród wszystkich zbadanych TIMPs pod względem czułości i specyficzności TIMP-3 (a w mniejszym stopniu TIMP-2) jest najlepszym biomarkerem uszkodzenia mięśnia sercowego u chorych z EDMD.

Wnioski: Uzyskane wyniki wskazują, że u chorych z EDMD stężenia TIMP-3 w surowicy, a w niektórych przypadkach także TIMP-2, są obniżone. Obserwowany spadek może się wiązać z niekorzystnym wpływem na metaloproteinazy macierzy oraz remodelowaniem macierzy miokardium. Specyficzny spadek stężenia TIMP-3 w surowicy chorych wskazuje, że biomarker ten mógłby być użyteczny we wczesnej detekcji zajęcia mięśnia sercowego w EDMD. Regulacja w górę TIMP-1 u większości pacjentów z X-EDMD wskazuje na zwiększony obrót macierzy zewnątrzkomórkowej, zaś obserwowane remodelowanie tkanki może uczestniczyć w rozwoju zaburzeń rytmu serca, często stwierdzanych w tej postaci choroby.

Słowa kluczowe: dystrofia mięśniowa Emery'ego-Dreifussa (EDMD), tkankowe inhibitory metaloproteinaz macierzy (TIMPs), kardiomiopatia rozstrzeniowa

Kardiologia 2015; 73, 5: 360–365

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Praca wpłynęła: 12.02.2014 r.

Zaakceptowana do druku: 03.11.2014 r.

Data publikacji AoP: 30.12.2014 r.