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REVIEW ARTICLE

CIRCULATING BIOMARKERS OF DILATED CARDIOMYOPATHY- AN ANALYSIS OF NEW POTENTIAL BIOMARKERS

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ABSTRACT

Cardiomyopathies are important causes of cardiac death in people and are responsible for arrhythmias and premature heart failure in all age groups. Although many cardiomyopathies are inherited, biochemical markers are a fundamental part of the diagnostic work-up and are useful in the prognostic and therapeutic assessment of disease. Excluding that of idiopathic DCM, there are various pathogenic pathways that can lead to DCM. Different pathways yield different biochemical substances that can be used as biomarkers. In this review, we mainly introduce some conventional and potential emerging biomarkers of dilated cardiomyopathy.

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INTRODUCTION

Cardiomyopathy refers to disease of the heart muscle which can be "acquired," meaning it develops because of another disease, condition or factor, or "inherited," meaning the gene for the disease was passed on from a parent. It is defined as a structural and functional change of the myocardium, which eventually can lead to poor function of the myocardium and thus developing heart failure. (1) These diseases have many causes, signs and symptoms depending on the severity. In order to maintain its contractile function, the heart is able to adapt to many genetic and external factors. A wide range of signaling pathways whose aim are to ensure heart contractility mediates these compensatory responses. However, persistent activation of these pathways will eventually reach a point where the heart cannot show any adequate compensatory responses, leading to cardiac dysfunction and thus cardiomyopathy occurs. (2) The heart muscle becomes enlarged, thick or rigid in cardiomyopathy, and in rare cases the muscle tissue is replaced with scar tissue. (3) As the condition worsens, the heart becomes weaker and less able to pump blood through the body and maintain a normal electrical rhythm. The result can be heart failure or arrhythmias. A weakened heart also can cause other complications, such as heart valve problems. Biomarkers, whose levels can indicate information about diseases, have become an important clinical tool in cardiomyopathy. They can be used to screen diseases, , diagnosis, monitoring state, risk stratification, to monitor effects of a therapy, to discover novel therapeutic targets and to understand molecular mechanisms underlying the disease development. There are several biomarkers which are widely employed in the evaluation of cardiomyopathy in clinic, such as B-type natriuretic peptide, C-reactive protein, cardiac troponin T, cardiac troponin I, and Apolipoprotein A-I. In recent years, some studies found more potential biomarkers, which may be used for the assessment of cardiomyopathy.

For a biomarker to be used clinically, it should fulfill some criteria set by Morrow and de Lemos: (4)

1. The measurement of the biomarker should be able to be accurately repeated clinically with cost-efficient methods.
2. Biomarkers should show more information compared to other tests already conducted.
3. Biomarkers should be clinically helpful in decision-making.

In this review, we will report the circulating biomarkers in dilated cardiomyopathy. We will emphasize more on the potential biomarkers of DCM. There is a long list that have been identified as potential biomarkers of cardiomyopathy

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including enzymes, hormones, cytokines, neurotic markers, cardiac stressors and other biological agents. However, more research need to be conducted to determine whether these biomarkers meet the criteria set by Morrow and de Lemos and are of diagnostic, prognostic or risk stratification value clinically.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM), occurring mostly in adults 20 to 60, is the most prevalent form of cardiomyopathy occurring in 1 in 2,500 individuals.(2, 5, 6) The ratio of incidence between male and female is approximately 3:1.(7, 8) The reason for this discrepancy between male and female remains unclear but it can be explained by sex hormones that may have an effect on cardiac structure and function.(8) DCM is usually diagnosed from patient's history and by echocardiography or cardiac magnetic resonance showing evidence of both dilation and poor contraction of the left ventricle (EF <40%) or both ventricles.(1, 9-12) Enlarged ventricular sizes and impaired systolic functions are the characteristics of DCM.(1) An increased in left ventricular mass with structural changes manifest macroscopically.(13) A histological triad of myocyte hypertrophy, myocyte degradation, and interstitial fibrosis features microscopically.(14) Main phenotypes manifesting in DCM are ventricular chambers enlargement and thinning of ventricular walls. As the heart chambers dilate, there is deterioration of muscular structure resulting in abnormal contraction of the heart that has a high correlation with heart failure and mortality. (2) After developing symptoms of DCM, 50% of people with DCM die within five years. (15, 16) The phenotype of DCM can be accounted to many causes. It is classified as primary if of unknown etiology, also known as idiopathic DCM. Among the idiopathic cases, one third can be attributed to familial DCM that is transmitted autosomally either in a recessive or dominant manner though maternal mitochondrial DNA, or as an X-linked mutation.(17, 18) At least 50 genes have been linked to familial DCM.(19-22) Secondary causes of DCM includes diseases and conditions such as coronary heart disease, hypertension, viral infections of the heart, alcohol, drugs, toxins and so on. Biomarkers of DCM can be different based on the different causes, pathophysiology, and severity of the disease. Different biomarkers seen in DCM are described according to different mechanisms and hence it is quite challenging to categorize these biomarkers. In this review, we will concentrate more on different type of useful potential biomarkers that can aid in the screening, diagnosis or response to therapy in DCM patients.

Biomarkers of Heart Failure in DCM Patients

Brain Natriuretic Peptide (BNP) and N-terminal Brain Natriuretic Peptide (NT-pro BNP)

BNP is a cardiac peptide of 134-amino acid preprohormone synthesised by the human gene NPPB and is secreted in response of ventricular muscles stress such as volume expansion and pressure overload.(23-25) Both BNP and NT-proBNP are widely used biomarkers for diagnosis, screening and prognosis of heart failure.(26) However, NT-proBNP, being larger with a longer half-life than BNP, is a better clinical predictor.(23, 27, 28) A cohort study conducted in 622 DCM patients in Fuwai Hospital concluded that NT-proBNP is a strong predictor of mortality in DCM patients.(23, 29)

High-Sensitivity Cardiac Troponin T

Both Cardiac Troponin T and I are valuable biomarkers of myocardial injury and are used clinically in assessment of ACS.(30) A new generation of troponin biomarker namely hs-cTnT, can now be used to detect cardiac injury to the minimal extent. An increase in hs-cTnT serum concentration predicts ongoing myocardial damage.(31) A recent study conducted by Yuichi Baba and team demonstrated that hs-cTnT serum concentration provides better risk stratification in DCM patients.(30)

Soluble ST2

ST2 is a protein encoded by the IL1RL1 gene and is used as a cardiac biomarker to predict the extent of cardiac remodeling and tissue fibrosis in heart failure, myocardial infarction or acute coronary syndrome cases. (32, 33) An important characteristic of soluble ST2 as a cardiac biomarker is that unlike other biomarkers such as BNP, NT-proBNP, hs-troponin among others, is independent of age, BMI, impaired renal function, heart failure history or sex.(33) Hence, it is considered as a superior biomarker. ST2 when used in combination with NT-proBNP, has better clinical value is assessment of patient with heart failure.(34)

Inflammatory Biomarkers in DCM

CRP (C-Reactive Protein) and hs-CRP

CRP is an acute phase protein, which is produced by the liver in response to IL-6 and whose blood plasma level rise in response to inflammation.(35) Studies have concluded that CRP level can independently predict outcome of disease in DCM patients.(36, 37) CRP is an important biomarker of inflammation as well as a causative factor of endothelial dysfunction.(38-40) Endothelial dysfunction has in turn been demonstrated to be involved in the pathogenesis and prognosis of CHF(41) and therefore since CRP itself causes endothelial dysfunction, it can be used as a prognostic indicator of CHF patients with DCM. Moreover, the combination of hsCRP along with BNP can be used to predict mortality and be useful in the management of CHF patients with DCM.(42) This is further confirmed by the study conducted by Xiaopin Li *et al*. that demonstrated high level hs-CRP and NT pro-BNP are associated with higher mortality rate and that they are independent predictors of mortality in CHF patients with DCM.(43)

Cytokines: TNF –α

Many cells are able to release cytokines in response to injury or as part of immune response. Cytokines have been speculated to play a role in the pathogenesis of cardiomyopathies. TNF –α secreting B cells are elevated in DCM patients from myocarditis and are involved in myocardial fibrosis.(44) This shows that B cells are involved in the pathogenesis of DCM. Furthermore, studies have demonstrated that TNF –α is involved in the pathogenesis of DCM by inducing iNOS in the heart.(45) Nitric oxide have a negative inotropic effect on heart, hence resulting in low cardiac output due to reduced heart contractility(46) and also increases risk for thromboembolism. Hence the finding of iNOS and TNF –α within myocardium in DCM does imply that TNF –α is involved in the pathogenesis of DCM.

New Emerging Potential Biomarkers in DCM: EPC-Epithelial Progenitor Cells

DCM is said to be a two hit disease(9) for involving both cardiac muscle alteration and defective vascularization.(47) Several studies have shown an elevated circulating level of EPC in cardiovascular diseases such as $CD34^+$ cells, $CD34^+$/ $CD133^+$/$VEGFR2^+$ cells.(48) According to Thesis *et al*., there is an increase number of $CD34^+$ cell in DCM as compared to controls and ischemic heard disease patients.(49) This can be explained by endothelial dysfunction in DMC(50), which will trigger the cytokine cascade, hence triggering release of circulating progenitor cells. Hence there exists a relation between circulating EPC level and progression of DCM.

Chemerin

Chemerin is an adipokine secreted by adipose tissue(51) and is implicated in inflammatory and immune response.(52-54) It is secreted in response to inflammatory stimulation such as TNF-alpha and Il-1B.(55, 56) Many inflammatory markers including TNF-alpha, CRP among others was showed to increase in DMC. A recent study conducted by Ou Zhang and team, first reported that chemerin is involved in DCM. Their study concluded that plasma chemerin level was significantly raised in DCM patients.(54) Moreover, a positive relationship between chemerin and LVEF was established.(54, 57)

Bispherol A

Bispherol A (BPA) is a widely used chemical in many plastic products. BPA can be detected in tissues and body fluid.(58) It has been shown that a high exposure to BPA can lead to cardiovascular disorders, including that of dilated cardiomyopathy. A recent study conducted shows that DCM patients have higher serum BPA level as compared to healthy patients.(8) This finding is further confirmed by the experiment carried out on rats, where long-term BPA exposure induces cardiomyopathy in male rats through impairment of mitochondrial function and disturbing methylation of PGC-1α.(59). Pascual-Fgal *et al*. demonstrated from his study that there exists an association between level of SHBG with severity of heart failure and higher risk of cardiac death. (60)Very interestingly, a positive relation between BPA and SHBG has been established by various studies in male population.(8, 61, 62). This can probably explain the higher incidence rate of DCM in male.

Th 22 Cells

T helper type 22 (Th22) cells, a subset of human CD4+cell, primarily secrete IL-22, IL-13, and TNF-alpha. A recent study showed that Th22 might be a potential biomarker, which may have a role to play in the pathogenesis of DCM.(12)The study concluded that DCM patients who were ANT antibody-positive showed a significantly elevated level of Th22. Furthermore, there was a relation between Th22 cells and CRP level according to the study. More interestingly, BNP which is a strong predictor of mortality in DCM(63), seems to correlate positively with percentage of Th22 cells. These observations indicate that Th22 cells may be used as a potential biomarker for predicting cardiac events in DCM. Another study demonstrated that cytokine IL22 secreted by Th22, have protective role in preventing myocardial fibrosis.

Neutrophil/Lymphocyte ratio (NLR)

Leukocytes play an important role in the pathogenesis of heart failure.(64) Studies have shown that increased level of leukocytes and certain subtypes are related with increased mortality in heart failure patients.(65, 66) A positive correlation between NLR, LVEF and anatomic parameters like LVEDV, LVESV, LVEDD, LVESD and LAD has been established in a study conducted by Anil Avci *et al*.(67) LVEF, which is clinically used as a measure of left ventricular systolic function, can be a good indicator of cardiac remodeling.(68) This implies that NLR is associated with left ventricular dysfunction in those with idiopathic DCM. Thus, NLR may be a noninvasive and inexpensive useful marker to evaluate chronic heart failure in DCM patients.

Circulating microRNAs levels

There is a possible relationship between the expression of miRNAs and DCM.(69, 70) Increase up-regulated expression of miR-423-5p has been demonstrated in DCM patients according to Thomas Thum's study.(71) A possible mechanism of increase expression of miRNAs could be by ANP.(72) So the plasma miR-423-5p levels are elevated in DCM. Moreover, there exists a positive correlation of plasma level of miR-423-5p with NT-proBNP level.(73) Hence circulating miR-423-5p has potential diagnostic value and can be used as diagnostic biomarker for heart failure caused by DCM.

IL-10 Secreting B cells

Bregs cells produce cytokines such as IL-10 which are important suppressors of inflammation and involve in autoimmune responses.(74) Hence IL-10 Bregs cells are involved in autoimmune diseases. Several subsets of B cells secreting IL-1β, IL-6, IL-10, IL-17, and TNF-α are seen in DCM.(44) A study conducted by Yujie Gua *et al*. demonstrates that DCM patients exhibit high circulation IL-10 secreting B cells.(75) This suggests that IL-10-secreting B cells may be involved in the pathogenesis of DCM. Studies need to be done how B cells differentiate into IL-10 secreting B cells and their role in DCM.

Myosin Binding Protein-C (MyBP-C)

MyBP-C is involved in the pathogenesis of DCM though eliciting an autoimmune response, resulting in production of autoantibodies. Fragment release of C0C1 following proteolysis of MyBP-C post-MI elicits production of autoantibodies. These autoantibodies against cardiac contractile protein are believed to play in role in the onset of autoimmune myocarditis, which can ultimately progress, to DCM and heart failure.(76) Studies have attributed the presence of cardiac protein autoantibodies to onset of autoimmune myocarditis and DCM.(77) Presence of MyBP-C-reactive AAbs in the sera of DCM patients was first observed by Kasahara *et al*.(78)

Heart-type fatty acid binding protein (H-FABP)

H-FABP, a cytoplasmic protein released from myocytes following ischemic conditions, has been shown to be a novel prognostic biomarker in DCM.(79) Release of H-FABP may be attributed to myocardial damage associated to DCM.(80)

Both H-FABP and BNP elevation in DCM predicts a worse prognosis. Patients with HFABP concentration value at or above the median of 5.4ng/ml has lower survival rate than those below the median value. (79)

Additional Biomarkers in DCM

Table 1. Other Biomarkers in DCM

Inflammatory marker
IL-6(81, 82)
TNF-related apoptosis inducing ligand (TRAIL)(83, 84)
TNF-related apoptosis inducing ligand (TRAIL)(83, 84)
Cardiotrophin-1(85)
Neurohormones
Norepinephrine(86)
Renin(86, 87)
Aldosterone(88)
Biomarkers of Extracellular Matrix Remodeling in DCM- Structural
Matrix Metalloproteinases(89)
Biomarkers of Oxidative Stress in DCM
Oxidized-low Density Lipoprotein(90)
Myeloperoxidase (MPO)(91, 92)
Renal Markers in DCM
NGAL(93, 94)
Beta-trace Protein (BTP)(95)

Conclusion

In this review, new potential biomarkers were selected, as they are associated with diagnostic, prognostic and therapeutic importance. Measurement of biomarkers even if they are not specific to DCM remains an important clinical tool. They provide a deeper insight about the pathogenesis of heart failure. Cardiomyopathy is an important cause of heart failure and death, so finding more circulating biomarkers with high specificity and accuracy is very important. Deeper knowledge about use of biomarkers of cardiomyopathies is of great importance to find potential therapies to prevent disease progression. Sometimes only one biomarker is not enough for a clinical approach. Nowadays, the use of biomarkers model scoring system is emerging and studies are trying to set up biomarkers scoring system for a better clinical approach in dealing with cardiovascular diseases.

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