Role of Certain Pro-Inflammatory Cytokines in Pathogenicity of Cardiomyopathy in Sample of Iraqi Patients

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ABSTRACT

Background: Cardiomyopathy (CM) is a cardiac muscle disorder that can lead to heart failure (HF). It has several phenotypes, including dilated, hypertrophic, and restricted. Pro-inflammatory cytokines play a crucial part in the development and advancement of CM.

Objective: This study aimed to measure the concentration of certain cytokines [Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF-α)] in the serum of Iraqi patients with CM.

Materials and Methods: Sixty CM patients and 30 healthy individuals with age ranged from 40 to 70 years old were enrolled in this study through their presence at Iraqi Center for Heart Diseases, Ghazy Al-Hariri Hospital for Surgical Specialties in the Medical City in Baghdad. The study was conducted from November 2021 to April 2022. Blood samples were collected to evaluate the level of Interleukin IL-1β, IL-6, and TNF-α using ELISA technique.

Results: The findings revealed a highly significant (P≤0.01) increase in the level of IL-1β IL-6 and TNF-α (15.71 ±0.33 pg/ml, 65.84 ±0.73pg/ml, and 17.81 ±0.58 pg/ml) respectively in comparison with control (4.59 ±0.17 pg/ml, 7.60 ±0.18pg/ml, and 6.26 ±0.34 pg/ml) respectively.

Conclusion: It can be concluded from the current results that the pro-inflammatory cytokines play a major role in the development and severity of cardiomyopathy in Iraqi patients.

Keywords: IL-1β, IL-6, TNF-α, Cardiomyopathy, pro-inflammatory cytokines.

INTRODUCTION

Cardiomyopathy (CM) is a diverse collection of illnesses of the myocardium, typically with inappropriate ventricular hypertrophy or dilatation. It is an anatomical and pathologic diagnosis connected to muscular or electrical malfunction of the heart. It frequently results in cardiovascular mortality or progressive heart failure-related impairment and may be heart-specific or a component of a more widespread systemic illness (1).

Dilated cardiomyopathy (DCM) is a nonischemic condition that affects the myocardium and has structural and functional abnormalities. The clinical features of DCM are present if the arterial muscles of the heart are dilated at systole, resulting in valvular disease, genetically transmissible heart disease, or hypertension (2-5).

Currently, DCM is It is characterized system-related disease, resulting in various other disorders like autoimmune disease, endocrinological disease, and neuromuscular or infectious disease. It indicates if transplantation of a heart is needed or not (4). Hypertrophic cardiomyopathy (HCM) is virtually a hereditary condition and is defined by an increase in the number of heart muscle cells. This disease is caused if any mutations occur in genes responsible for the coding of sarcomeres protein, resulting in myocyte disarray which is a characteristic of HCM (5).

Nearly 70% of all deaths in hypertrophic obstructive cardiomyopathy are unexpected. HCM frequently offers a silent course. It is the most prevalent form of hereditary cardiomyopathy, and it is characterized by aberrant ventricular wall thickening in the absence of abnormal loading conditions (6).

Restrictive cardiomyopathy (RCM) is a cardiac disorder that is frequently brought on by increased myocardial stiffness and inadequate ventricular filling. The biventricular chamber size and systolic function are frequently normal or almost normal up to the latter stages of the disease. the ventricles, either the left or right. Due to increased end-diastolic pressure in the ventricles, genetic RCM is frequently characterized by a left ventricle that is almost normal in size, increased stiffness, and enlarged atria the rarest form, accounting for only 5%, however, it has the worst prognosis and treatment options of all the cardiomyopathies (7).

Cytokines are defined as pleiotropic low molecular weight polypeptides that can produce autocrine, juxtacrine, and paracrine effects. They play important role in regulating inflammatory and immune responses (8).

Cytokines that promote inflammation (such as TNF-α, IL-6, and IL-1β) and chemokines have been found in the hearts of both ischemic cardiomyopathy patients and DCM patients (9).

The usual inflammatory cytokine IL-1β reduces heart contractility after being administered quickly. It results in reduced b1-adrenergic response, reversible acute and chronic contractile dysfunction, and may have an effect on the pathophysiology of acute decompensated HF as well as the pathogenesis of inflammatory
cardiomyopathies (10). Recently, it has also been proposed that IL-1β causes systolic dysfunction and exercise intolerance in HF patients, reinforcing the idea that this cytokine has a cardio-depressant effect on CM and chronic heart disease. (11).

Both pro- and anti-inflammatory effects can be shown in IL-6. It is generated by cardiovascular cells such as endothelial cells, vascular smooth muscle cells, and ischemic myocytes in addition to immune cells and immune accessory cells like monocytes and macrophages, what makes IL-6 particularly interesting to physicians is its involvement not only with inflammation but also with the regulation of cardiac metabolism. In cardiomyocytes and cardiomyopathy patients IL-6 exerts a negative inotropic effect and promotes a hypertrophic response (12).

TNF-α is a pleiotropic cytokine, which is a primary regulator of inflammatory responses and is implicated in the pathophysiology of several inflammatory and autoimmune diseases (13). The most frequent causes of inflammatory DCM are infections and autoimmune diseases. No matter the cause of the myocardial injury, whether hereditary or environmental, causes inflammation and draws immune cells to the heart to repair the myocardium (14).

MATERIAL AND METHODS

Sixty patients (men and women) with CM after being diagnosed by the physician and thirty healthy subjects with the same age range (40-70) years participated in the study who were attending to the Iraqi Center for Heart Diseases, Ghazy Al-hariri Hospital for surgical specialties in the Medical City in Baghdad. An experienced cardiologist has diagnosed the patients based on alterations in the ECG, an Echocardiogram, and a chest x-ray. The study was conducted from November 2021 to April 2022. Blood samples were collected from all of the study participants, and the serum was separated for determination of the level of IL-1β, IL-6, and TNF-α by sandwich Enzyme-Linked Immunosorbent Assay (ELISA). The kits were products of BOSTER Biological Technology (USA) (15-16).

Ethical approval

Approval of this study was obtained from the University of Baghdad Academic and Ethical Committee. Informed consents from all the patients were taken. This study was carried out in accordance with the World Medical Association Code of Ethics (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The statistical analysis system- SAS (2012) program was used to detect the effect of different factors on study parameters. A T-test was used to significantly compare between means. All results were expressed as mean ± standard error (SE) (17).

RESULTS

Table (1) revealed an elevation in the concentration of IL-1β (15.71 ± 0.33 pg/ml) in CM patients in comparison with control (4.59 ± 0.17 pg/ml). Also, the finding revealed a highly significant (P≤0.01) increase in the concentration of Interleukin-6 (65.84 ± 0.73 Pg/ml) in CM patients in comparison with the control group (7.60 ± 0.18 Pg/ml). The same table demonstrated a highly significant (P≤0.01) elevation in the concentration of TNF-α (17.81 ± 0.58 Pg/ml) in CM patients in comparison with the control group (6.26 ± 0.34 Pg/ml).

Table (1): Level of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in Cardiomyopathy patients and control

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SE</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>IL-1β pg/ml</td>
<td>IL-6 pg/ml</td>
<td>TNF-α pg/ml</td>
<td></td>
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<tr>
<td>Cardiomyopathy patients</td>
<td>15.71 ± 0.33</td>
<td>65.84 ± 0.73</td>
<td>17.81 ± 0.58</td>
<td></td>
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<tr>
<td>Control</td>
<td>4.59 ± 0.17</td>
<td>7.60 ± 0.18</td>
<td>6.26 ± 0.34</td>
<td></td>
</tr>
<tr>
<td>T-test</td>
<td>0.971 **</td>
<td>2.092 **</td>
<td>1.729 **</td>
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</tbody>
</table>
| P-value                | 0.0001      | 0.0001     | 0.0001     ** (P≤0.01).

DISCUSSION

The enormously significant increase in the level of Interleukin1β in CM patients agrees with the study of Bujak and Frangogiannis (18) where they noticed a highly increased level of IL-1β in the selected group of cardiomyopathy patients compared to the control group. IL-1β is largely produced by macrophages, although it is also produced by epithelial, lymphoid, epidermal, and vascular tissue. Some cell types, including endothelial, tubular, mesangial, and epithelial cells, are also involved in the synthesis of IL-1β. This may be related to different cytokines, which may affect cardiomyocytes in an autocrine or paracrine manner (19).

The mechanism harms the cardiomyocytes because IL-1 is released through cell lysis, macrovesicle shedding, and from secretory lysosomes (20). IL-1 binds to its receptors, called interleukin-1 receptor 1 (IL-1R1), then attaches to the co-receptor chain, named the accessory protein (IL-1RAcP). After securing this structure, another protein, MyD88, binds to the Toll-IL-1 receptor (TIR). Most kinase proteins have a phosphor group, nuclear factor-κB (NF-κB), and a different assortment of inflammatory genes like IL-6 (21). The
results of the present study are supported by the results of the study done by Luo et al. (22) who has been hypothesized that IL-1, as well as other cardiomyopathies such as myocarditis and HF, may have a role in the development of other heart conditions. The decrease of cardiac function in DCM of many causes is thought to be a result of cytokine activation, especially IL-1. Van Tassell et al. (23) mentioned in their study that IL-1 β is involved in the progression and development of HF. Also, Segiet et al. (24) reported that IL-1 β, a pro-inflammatory cytokine, has been linked to cardiac remodeling and changes in the contractility and relaxation of the ventricles; IL-1β overexpression has also been linked to changes in the myocardium. Cardiac-derived IL-1β reduces contractility within the cardiovascular system by causing calcium leakage from the sarcoplasmic reticulum, which eventually encourages cell death and tissue remodeling through a nitric oxide-dependent mechanism (25).

The extremely large increase in IL-6 levels in the cardiomyopathy in the current study is in agreement with the study of Høgye et al. (26) who observed an increased rise in serum concentration of IL-6 in the selected group of dilated and hypertrophic cardiomyopathy patients in comparison with the control group. The IL-6 levels varied according to the cause of HF. It was much higher in people with HF brought on by cardiomyopathy and ischemic heart disease than in those with valvular heart disease or hypertensive heart disease (27). In recent years, it has been revealed that individuals with HF, as well as those with HCM and DCM, had higher levels of circulating IL-6 and soluble IL-6 receptor (IL-6R).

Furthermore, systemic IL-6 levels are powerful independent predictors of eventual clinical outcomes in patients with HF and correspond with the degree of left ventricular dysfunction. Based on these findings, the present study supports them by showing that IL-6 levels were greater in DCM patients which explains the effect of this cytokine in the progression of the disease (28). Gullestad et al. (29) stated in their study that IL-1β, IL-6, and TNF-α are the most important cytokines involved in the progression and development of CM and HF.

With regard of TNF-α the results showed a highly significant increase in patients with CM and this is in agreement with Lecour and Richard (30) whose results proved the involvement of TNF-α in the development and progression of cardiomyopathy. A previous study by Zhang et al. (31) indicated a significant increase in the concentration of TNF-α in both DCM and HF patients. These findings may suggest that TNF-α concentration may reflect intrarenal activity. Thus, the concentration of TNF-α is directly related to the development of progression of HF. It is possible that the effects of TNF-α on cardiomyocytes, macrophages, and the extracellular matrix contribute to the progression of heart HF through mediated unfavorable remodeling. And TNF-α causes harmful inotropic activities in cardiomyocytes by interfering with calcium homeostasis. It also has the potential to produce an apoptotic response in cardiomyocytes by activating the intrinsic cell death pathways (32). Studies on transgenic mice overexpressing TNF-α specifically in the heart have shown that these mice exhibit increasing LV dilatation and cardiac energy abnormalities and that TNF-α activates matrix metalloproteinases that break down the extracellular collagen matrix, causing LV dilatation (33).

CONCLUSION

It can be concluded from the current results that the pro-inflammatory cytokines play a major role in the development and severity of cardiomyopathy in Iraqi patients. Due to its relationship to the development and progression of CM and HF, the inhibition of pro-inflammatory cytokines may be able to slow the advancement of CM. However, more studies about pro-inflammatory cytokines are needed.

Conflict of interest

There are no conflicts of interest according to the author.

Availability of data

The paper itself contains the data sets that are used to support the finding.

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