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ORIGINAL RESEARCH

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Expression of interleukin 1, interleukin 27, and TNF α genes in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy: A case-control study

Mahdiyar Iravani Saadi[1] | Javad Salami[2] | Hanieh Abdi[3] | Nadiya Kheradmand[1] | Ehsan Nabi Bdolyousefi[1] | Mahmoud Torkamani[1] | Zahed Karimi[1] | Shahram Agah[1] | Zahra Rahimian[3] | Alireza Manafi[3]

[1]Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran

[2]Department of Nursing, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence

Alireza Manafi, Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.
Email: manafi8800@gmail.com

Ehsan Nabi Bdolyousefi, Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran.
Email: ehsan.nabi2015@gmail.com

Funding information

Shiraz University of Medical Sciences

Abstract

Background and Aims: Congestive heart failure is a complex multifactorial syndrome due to tissue hypoperfusion that is affected by some factors like inflammatory cytokines. In our study, we investigated the exact gene expression of three inflammatory cytokines in ischemic and idiopathic cardiomyopathy patients.

Methods: From 49 studied recipients in the ischemic group, 23 (46.9%) were male and from 40 studied recipients in the idiopathic dilated cardiomyopathy group, 19 (47.5%) were male. For the quantitative analysis of interleukin (IL)-1, IL-27, and tumor necrosis factor (TNF)-α messenger RNAs expression level, the SYBR Green real-time polymerase chain reaction method was performed using SYBRPremix Ex TaqTM II (Tli RNaseH Plus; Takara) and designed primers specific for each gene in an iQ5 thermocycler (BioRad Laboratories) according to the manufacturer's instructions.

Results: Our results showed that the expression level of IL-1 and TNF-α were significantly higher in the ischemic patients compared to healthy controls ($p < 0.001$, $p < 0.01$, respectively); also, we found higher levels of IL-1 and IL-27 gene expressions in idiopathic patients compared to healthy controls ($p < 0.001$, $p < 0.001$, respectively). There were not any significant differences in IL-1, IL-27, and TNF-α expression levels between ischemic patients and idiopathic ones.

Conclusion: Although we would introduce IL-1, IL-27, and TNF-α as effective inflammatory cytokines on myocardial functions in ischemic and idiopathic cardiomyopathy patients, there is not any difference between these two groups in gene expression of three main inflammatory cytokines.

KEYWORDS

congestive heart failure, idiopathic dilated cardiomyopathy, interleukin, ischemic cardiomyopathy

1 | INTRODUCTION

Congestive heart failure (CHF) is a complex multifactorial syndrome due to tissue hypoperfusion and body fluid retention that is presented by fatigue, cachexia, shortness of breath, and inability to do some ordinary daily activities.[1] The most common cause of CHF is ischemic insults to the myocardium (myocardial infarction), while other probable reasons such as hypertension, alcohol usage, viral infection, and muscle abnormalities occurred by genetic defects should not be forgotten.[2] Notwithstanding previous studies on this chronic syndrome, there is a major question that which pathogenesis is responsible for left ventricular failure and cardiomyopathy in the absence of ischemic events of the myocardium.[3] About one-third of CHF patients suffered from dilated cardiomyopathy (DCM). Cardiomyopathy is a condition of deterioration of myocardial function and structure that finally leads to heart failure (HF). In dilated one's, patients suffered from dilatation of one or both ventricle sizes with reduction of ejection fraction. If primary and secondary etiologies are excluded, DCM is considered idiopathic (IDCM). In another word, it is defined as nonischemic cardiomyopathy with depressed left ventricular function.[4] Cardiomyopathy also is the most common cause of heart transplantation in CHF patients.[5,6] Not only increasing in inflammatory cytokines but also overexpression of immunological antigens is seen in cardiomyopathy patients[3]; besides that, complex impaction of inflammatory and proinflammatory cytokines on CHF progression is not well understood.[7,8] Two major pathways of immune activation in these patients are explained in literature: the first one is direct antigenic stimulation, and the second one is immune activation secondary to cardiac injury. The last one exposes the heart to a bad immune response and triggers the patients` condition.[9] Tumor necrosis factor-α (TNF-α) is almost the most effective proinflammatory cytokine in HF patients that is not present in normal myocardium. Failed myocardium produces TNF-α in the bloodstream, but its` receptor is downregulated in the inflammatory process of HF.[10] In animal models, systemic administration of TNF α induces DCM phenotype in mouse's myocardium.[11] Also, blockade of the biological effect of TNF-α in humans has been shown to improve myocardial function and degree of disease severity in some surveys.[12,13]

Another cytokine that has a big role in the inflammatory pathogenesis of HF is interleukin-1 (IL-1).[14] Many studies emphasize on deleterious effects of IL-1 on infarction and remodeling of the heart.[15] This cytokine has an important impaction on modulating myocardial function and is increased in HF patients,[16] but according to some challengeable studies, concentrations of IL-1 in IDCM patients might not be elevated rather than in the control group.[17] In some other research, an effective role of IL-1 has been explained that could facilitate the immigration of macrophages and monocytes into tissues in inflammatory conditions.[18] Also, the administration of IL-1 receptor antagonists has been revealed to be a therapeutic strategy in treating inflammatory and autoimmune conditions.[19] Another survey showed elevated levels of IL-1β messenger RNA (mRNA) in IDCM patients in a comparative study.[20] As a matter of fact, autoimmunity is known as a pathogenic agent in IDCM patients.[21] On the other hand, raised inflammatory cytokinesis not only present in IDCM but also is seen in ischemic cardiomyopathy patients.[22] Serum levels of inflammatory cytokines and their correlation with disease severity and patients` prognosis in IDCM versus ischemic CMP patients is not still well understood. Therefore, we conducted this study to determine the exact expression of TNF-α, IL-1, and IL-27 (as a new probable effective cytokine in inflammatory processes) genes in these two groups and will compare them to each other and the control group.

2 | MATERIALS AND METHODS

The sample size was measured as a total of 89 nondiabetic patients, aged 35–75 years (49 patients with ischemic cardiomyopathy and 40 patients with IDCM) besides 49 age and sex-adjusted healthy nondiabetic controls based on previous studies. So in this case-control study, we enrolled a total number of 89 nondiabetic patients with known DCM with New York Heart Association (NYHA) Class II and III who were referred to the cardiology department affiliated to Namazee Hospital, Shiraz, Iran, between March 2016 and February 2019. The patients who participated in our study were DCM ones that were diagnosed more than three months before the study and received optimal medical therapy according to medical guidelines, and had no history of hospitalization. Of these patients, 49 were diagnosed as ischemic ones evidenced by coronary angiography consisting of advanced three-vessel coronary artery disease or thrombosis-induced transmural myocardial infarction, and 40 patients were included in the IDCM group after ruling out the possible causes by means of history, transthoracic echocardiography, and coronary angiography. Also, we enrolled 49 age and sex-adjusted healthy nondiabetic controls without any disease to compare with these two groups. We excluded patients with positive history of malignancy, alcohol or drug abuse, liver or renal dysfunction, chronic inflammatory disease, currently active or recent infection, and family history of DCM. Patients with a history of MI, recent cardiac surgery or a cardiac stent, or DCM due to genetic or muscular disorders were also excluded. All patients underwent two-dimensional echocardiography using a vivid E9 system (GE, Norway), and all measurements were performed according to the latest recommendations of the American Society of Echocardiography.[22] The left ventricular end-diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF) were calculated based on Simpson's biplane method. For homogenous sampling, the LVEDV index exceeding 100 ml/m^2 and LVEF between 20% and 35% were considered as inclusion criteria as previously described in similar performance.[15] The present methodology met all the rules that contributed to the Helsinki of Medical Sciences and won the approval of the Ethical Committee (IR.SUMS.MED.REC9045.39.01.93). All the experimental methods programed in the present study were in accordance with confirmed setups used in previous studies.

2.1 | Sample collection and ribonucleic acid isolation

Five-milliliter peripheral blood was collected in ethylenediaminetetraacetic acid-containing tubes from each patient at the time of diagnosis before

TABLE 1 The primers and thermocycling condition for the IL-1, IL-27, TNF-α, and GAPDH transcripts

Gene	Primer sequences (5'–>3')	PCR product length	Thermocycling condition
IL-1: F IL-1: R	CTTCAGCCAATCTTCATT CACTGTAATAAGCCATCAT	88 bp	95°C/2 min, 40 cycles of 95°C/30 s, 60°C/20 s, and 70°C/30 s
IL-27: F IL-27: R	CAGGCTCTACCCAGTAAC AATAAACCATCATCTCCCTAAAC	94 bp 80 bp	95°C/2 min, 40 cycles of 95°C/30 s, 57°C/20 s, and 70°C/30 s
TNF-α: F TNF-α: R	CAACCTCTTCTGGCTCAA TGGTGGTCTTGTTGCTTA		95°C/2 min, 40 cycles of 95°C/30 s, 58°C/20 s, and 70°C/30 s
GAPDH: F GAPDH: R	GGACTCATGACCACAGTCCA CCAGTAGAGGCAGGGATGAT	119 bp	95°C/2 min, 40 cycles of 95°C/30 s, 57.5°C/20 s, and 70°C/30 s

Abbreviations: F, forward; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IL-1, interleukin-1; R, reverse; TNF-α, tumor necrosis factor-α.

chemotherapy treatment and also healthy individuals. The peripheral blood mononuclear cells were isolated from each patient and controls using Ficoll-Hypaque density gradient centrifugation. Total RNA was extracted by TRIzol reagent (Invitrogen) according to the manufacturer's instructions and guidelines as previously described briefly.[23]

2.2 | SYBR Green real-time polymerase chain reaction

For the quantitative analysis of IL-1, IL-27, and TNF mRNAs expression level, the SYBR Green real-time polymerase chain reaction method was performed using SYBRPremix Ex TaqTM II (Tli RNaseH Plus; Takara) and designed primers specific for each gene in an iQ5 thermocycler (BioRad Laboratories) according to the manufacturer's instructions as previously described briefly.[24]

2.3 | Statistical analysis

Data were analyzed by Statistical Package for Social Sciences software, version 18. The demographic data was subjected to a descriptive analysis, and the results were presented as mean and standard deviation. Numbers and percentages were used to represent frequency. The differences in the mean expression level of IL-1, IL-27, and TNF-α before and after chemotherapy as well as patients according to the comparison of NYHA class, LVEF, and LVEDVI between patients with IDCM and ischemic DCM which were compared independent *t*-test. Also, the mean expression level of IL-1, IL-27, and TNF-α regarding laboratory data was analyzed by the χ^2 test. $p < 0.05$ was considered the limit for statistical significance.

3 | RESULTS

Of the 49 studied recipients in the ischemic group, 23 (46.9%) were male, and from the 40 studied patients in the IDCM group, 19 (47.5%) were male. The mean age of patients was 52 ± 1.6 ranged from 20 to 67 years, and the mean age of the control group was 48 ± 3.5 ranged from 19 to 84 years. Table 1 shows the primers and thermocycling conditions for the IL-1, IL-27, TNF-α, and glyceraldehyde 3-phosphate dehydrogenase transcripts.

TABLE 2 Baseline characteristics of ischemic and idiopathic cardiomyopathy patients

Characteristics	Ischemic DCM (*n* = 49)	Idiopathic DCM (*n* = 40)	*p*
Age (y)	53.21 ± 6.2	51.3 ± 9.5	0.22
BMI (kg/m^2)	26.7 ± 3.2	24.3 ± 1.4	0.431
Gender (male/n, %)	23 (46.9%)	19 (47.5%)	0.758
Risk factors			
Smoking	11 (22.4%)	8 (20.0%)	0.651
LDL-C > 130 mg/dl (*n*, %)	7 (14.2%)	5 (12.5%)	0.901
TG > 150 mg/dl (*n*, %)	10 (20.4%)	7 (17.5%)	0.574
HDL-C < 40 in men or <50 in women (*n*, %)	4 (8.1)	3 (7.5%)	0.105
Hypertension	9 (18.3%)	8 (20.0%)	0.13

Abbreviations: BMI, body mass density; DCM, dilated cardiomyopathy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Table 2 displays the baseline characteristics of ischemic and IDCM patients and there were not any significant differences in demographic data of the two groups. The functional status and echocardiographic findings of patients with DCM are also summarized in Table 3. We found that LVEF and LVEDVI were higher in ischemic DCM patients compared to IDCM individuals, but it was not significant ($p = 0.07$ and 0.11, respectively). Indeed, there was no difference between stages of NYHA class in the two groups.

3.1 | IL-1, IL-27, and TNF-α gene expression in ischemic patients and controls

The mRNA expression analysis of IL-1, IL-27, and TNF-α gene measured as cycle threshold (C_t) and ΔC_t values. Our results showed that the expression level of IL-1 and TNF-α were significantly higher

Variable	Idiopathic DCM, n = 49	Ischemic DCM, *n* = 40	*p*
NYHA class (*n*, %)	16 (32.6%)	16 (40.0%)	0.50
LVEF (%)	26.8 ± 4.07	31.57 ± 6.21	0.07
LVEDVI (ml/m^2)	143.29 ± 29.1	135.25 ± 39.4	0.11

Note: Data was expressed as mean ± SD or numbers.

Abbreviations: DCM, dilated cardiomyopathy; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

TABLE 3 The comparison of NYHA class, LVEF, and LVEDVI between patients with idiopathic and ischemic dilated cardiomyopathy

in the ischemic patients compared to healthy controls ($p < 0.001$, $p < 0.01$, respectively). However, no significant difference was observed between IL-27 in the Ischemic patients compared to healthy controls (Figure 1).

3.2 | IL-1, IL-27 and TNF-α gene expression in idiopathic patients and controls

After the statistical analysis, our results revealed that the expression level of IL-1 and IL-27 were significantly higher in the idiopathic patients compared to healthy controls ($p < 0.001$, $p < 0.001$, respectively). However, no significant difference was observed between TNF-α in the idiopathic patients compared to healthy controls (Figure 2).

3.3 | IL-1, IL-27, and TNF-α gene expression in ischemic patients and idiopathic (left) patients

Our results demonstrated that the expression level of IL-1, IL-27, and TNF-α were not significantly higher in the idiopathic patients compared to ischemic ones (Figure 3).

4 | DISCUSSION

Our study investigated the exact gene expression of three inflammatory cytokines in CHF patients. So, we found that IL-1 and TNF-α were higher in ischemic DCM patients than controls, and gene expression of IL-1 and IL-27 also were higher in IDCM than in the control group, while there were not any significant differences of TNF α between these two groups.

TNF-α and IL-1 are two cytokines with negative inotropic effects on the myocardium by uncoupling β-adrenergic signaling;[25] they have a big role in myocardial remodeling and hypertrophy after myocardial infarction.[26] Notwithstanding many previous pieces of research on CHF, the fact that myocardial insults provoke inflammatory cytokines activity or inflammatory system deteriorate the condition of patients by activating direct antigenic pathways and the immune system has remained as a puzzle.[9] Van Tassell et al. in an experimental study showed that overexpression of the IL-1 gene in systolic HF patients can lead to poor exercise tolerance. They did their study to discover any new approach to the treatment of HF patients and finally proposed IL-1β blockade as a novel treatment for future success approaches in the treatment of these patients.[27] Also, in another study, anakinra as an IL-1 blockade agent was used to reduce the systemic inflammatory response in acute decompensated HF patients, and finally, their results supported their hypothesis.[28] Inconsistent with these, Kang et al.[29] observed a significant increase in brain proinflammatory cytokines (IL-1) in ischemic induced HF rats. On the other hand, researchers examined whether the blockade of TNF α as a new neurohormonal pathway could be effective in the treatment of HF patients or not. Finally,

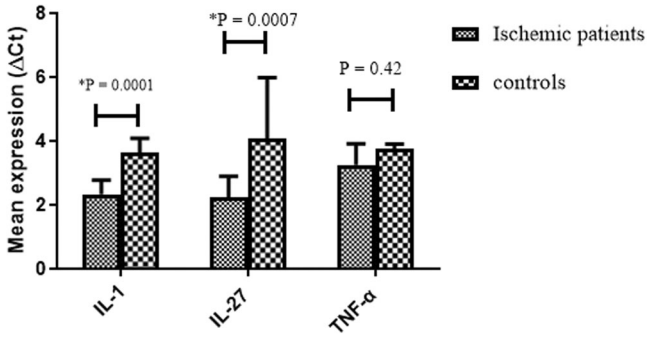

FIGURE 1 The boxplot of mean IL-1, IL-27, and TNF-α ΔC_t in ischemic patients (left) and control (right) group. C_t, cycle threshold; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α.

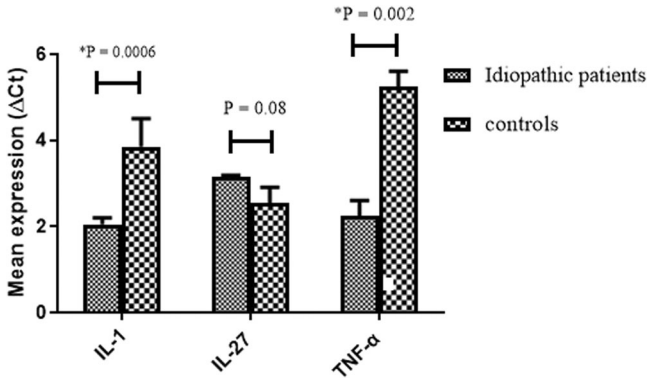

FIGURE 2 The boxplot of mean IL-1, IL-27, and TNF-α ΔC_t in patients with idiopathic DCM (left) and control (right) groups. C_t, cycle threshold; DCM, dilated cardiomyopathy; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α.

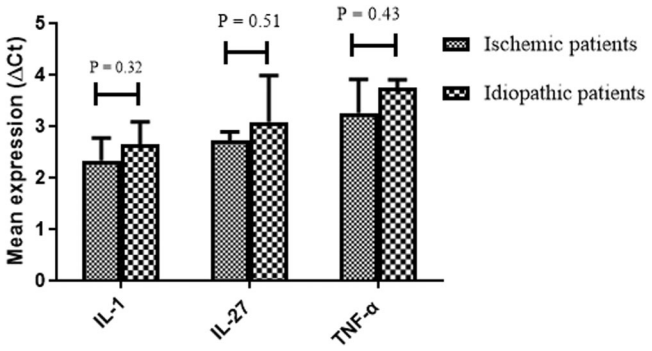

FIGURE 3 The boxplot of mean IL-1, IL-27, and TNF-α ΔC_t in ischemic patients (left) and idiopathic DCM (right). C_t, cycle threshold; DCM, dilated cardiomyopathy; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α.

they found out that this blockade is a well-established way to improve functional status and myocardial functions.[12] IL-27 as a novel member of IL-12 group cytokines is high in patients with coronary artery disease,[30,31] but its exact function in ischemic insults to the myocardium is unclear. Ma et al.[31] in an experimental study, showed its cardioprotective effects in ischemic events of rat` hearts. Unlike this finding, Hirase et al.[32] investigated the immunoregulation of macrophages in mice by lacking IL-27 and its receptor, so finally concluded that IL-27 plays an inhibitory role in atherosclerosis with adjustment the activation of macrophages in mice. Our study found that IL-27 is significantly higher in IDCM patients than the control group while this correlation was not significant between ischemic DCM ones and controls.

It is believed that myocardial ischemic insults enforce myocardium to produce TNF α, and the inflammatory process is known to have a significant correlation with coronary atherosclerotic events in CHF patients. In a big database trial, Vesnarinone trial, Deswal et al.[33] concluded that the most important inflammatory cytokines such as TNF-α and IL-6 have more gene expression in ischemic DCM than IDCM patients. Another study that supports the lower expression of TNF-α and IL-1 genes in IDCM patients is the Bironaite study.[17] But we did not find any significant differences of any cytokine between ischemic DCM patients and IDCM ones. In a similar study that was carried out by Iravani Saadi et al.,[15] they compared IL-6 and IL-18 as two effective inflammatory cytokines between ischemic DCM and IDCM. They found that these two cytokines have higher expression in IDCM and ischemic ones than the control group, but in the same line of our study, they did not find any significant difference between IDCM and ischemic DCM patients compared to each other. According to these findings, we can produce IL-27 as a novel inflammatory cytokine in HF patients, particularly in ischemic DCM ones. Moreover, it is hopeful of describing new pathways of therapy guidelines in HF patients as a complex syndrome with complex treatments.

5 | LIMITATIONS

HF patients due to ischemic insults after myocardial infarctions were more frequent than idiopathic ones. Our small sample size due to the exclusion of decompensated patients was one of the shortages and limitations of this study. Also, we suggest enrollment of all stages of HF patients and evaluation of any stages correlations with the expression of different cytokines for future studies.

6 | CONCLUSION

In our study, we found that there were not any significant differences in inflammatory cytokines (TNF-α, IL-1, and IL-27) between ischemic DCM and IDCM patients. IL-27 as a newly introduced cytokine was higher in IDCM patients than controls. TNF-α was not significantly higher in IDCM than controls. Additionally, IL-27 did not have higher expression in ischemic DCM patients than controls, but some surveys have been introduced it as an effective factor on myocardial functions in ischemic/reperfusion events. According to these antitheses in our results and other research and the importance of the matter, further studies are recommended in the future.

AUTHOR CONTRIBUTIONS

Mahdiyar Iravani Saadi, Javad Salami, Hanieh Abdi, and Alireza Manafi: Conceptualization. **Zahed Karimi and Alireza Manafi**: Formal analysis. **Nadiya Kheradmand, Ehsan Nabi Bdolyousefi, Mahmoud Torkamani, Zahed Karimi, and Shahram Agah**: Investigation. **Mahdiyar Iravani Saadi and Alireza Manafi**: Methodology. **Mahdiyar Iravani Saadi**: Project Administration. **Alireza Manafi**: Supervision. **Mahdiyar Iravani Saadi, Shahram Agah, and Zahra Rahimian**: Writing – original draft preparation. **Zahra Rahimian and Ehsan Nabi Bdolyousefi**: Writing – review and editing. Alireza Manafi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available on request from the authors. SPSS data of the

participant can be requested from the authors. Please write to the corresponding author if you are interested in such data.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences and all patients signed a predefined written informed consent before entering the trial. All protocols conformed to the 1975 Helsinki Declaration ethical guidelines.

TRANSPARENCY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to internal ethical policies (sample bank of cardiomyopathy patients available in "Muhammad Rasoololah Research Tower affiliated with Shiraz University Of Medical Sciences") and privacy maintenance of patients` data but are available from the corresponding author on reasonable request.

ORCID

Zahra Rahimian http://orcid.org/0000-0002-8731-8403

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