RESEARCH ARTICLE

# Evaluation of serum galactin-3 concentration in patients with heart failure

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**Heart failure (HF) is one of the world's most serious public health issues. The HF is a growing worry all around the world. Early detection of HF is significant because morbidity associated with the illness can be reduced. Galectin-3 (Gal-3), a soluble ß-galactoside binding lectin created by activated cardiac macrophages, has been shown in animal models to play an essential role in pathological ventricular remodeling. Galectin-3 has an important function in chronic inflammation and is a pathogenesis marker for inflammatory and/or fibrotic illnesses. This case control study was implemented to reveal the alliance of human Gal-3 with HF, which included 44 HF patients in the study group and 43 normal persons in the control group. The serum levels of human Gal-3 were determined by using sandwich ELISA technique. The results showed that the serum human Gal-3 level was significantly higher in the patient group than that in the control group. The study concluded that the human Gal-3 might be associated with HF.**

**Keywords: h**eart failure; galectin-3; myocardial fibrosis; chronic inflammation.

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## Introduction

Heart failure (HF) is a malfunction caused by a variety of factors. Rapid diagnosis is important since the condition has a high death and morbidity rate [1]. HF has been identified as a global health problem affecting roughly forty million individuals worldwide [2]. The incidence of HF in adults is believed to be around 2%, rising to 6-10% after the age of 65 [3]. The rate is more than 10% for people over the age of 75 [4]. Furthermore, the morbidity rate is predicted to rise due to risk factors such as diabetes, hypertension, obesity, and dyslipidemia [5]. Natriuretic peptides (NPs) are the only biomarkers that have been officially approved for use in the HF diagnosis. The functions of NPs include vasodilation, diuresis, natriuresis, and inhibition of cardiac remodeling. The NPs consists of atrial natriuretic peptide (ANP) which decreases blood pressure and cardiac hypertrophy and is secreted from atria, B-type natriuretic peptide (BNP) which acts locally to reduce ventricular fibrosis and is produced from ventricular muscle cells in response to volume and pressure overload, C-type natriuretic peptide (CNP) which controls local blood flow and systemic blood pressure and is secreted from cardiac fibroblasts and myocardium. However, the natriuretic peptides concentrations may be

affected by other characteristics or difficulties such as gender or age. On the other hand, galectin-3 (Gal-3) is unaffected by these difficulties and could be a possible accurate marker for HF diagnosis [1].

Gal-3 is a structurally distinct member of the ancient lectin family, which is expressed in different organs, cell types, and inside and outside of cells. The Gal-3's biological roles were previously linked to its carbohydrate-binding activity. However, many Gal-3 linked biological processes and new functions unconnected to lectin activity have been discovered over the last decade including cell-cell and cell-extracellular matrix (ECM) adhesion, cell proliferation and differentiation, signaling, the cell cycle, angiogenesis, apoptosis, and development regulation [6, 7]. Gal-3 is a 30 kDa protein produced by a variety of immune cells, comprising mast cells and macrophages, which are all involved in the mononuclear phagocytic system in different organs. Although Gal-3 is primarily found in the cytosol for cellular activity and in the nucleus for splicing, it is produced on surface of cell as well and released to the plasma by a diversity of cells [8]. Galectins are a protein family which has a unique carbohydrate recognition domain (CRD) of 130 amino acids [9]. Galectins can be presented in skeletal muscles, neurons, kidneys, placenta, active macrophages, mastocytes, gastrointestinal tract epithelial cells, and respiratory system. The position and intracellular action of galectins rely on the cell type and cell situation. Gal-3 expression has been observed in neutrophils, fibroblasts, mast cells, osteoclasts, and cancer cells. It is typically found in the spleen, lungs, adrenal glands, stomach, uterus, ovaries, colon, and can also be found in smaller concentrations in heart, brain, kidneys, liver, pancreas [10, 11]. Galectins are comprised a group of extensively expressed galactoside binding lectins and can influence rudimentary biological functions like tissue regeneration and immune cell activity regulation [12]. Galectins are categorized based on their CRD functions and numbers. The CRDs identify β-galactoside residues, particularly glycans that have N-acetyl galactosamine to create complexes to crosslink glycosylated ligands [9, 13]. Gal-3 has been found to play a vital role in a variety of physiological activities including antimicrobial activity, macrophage activation, and a mediator for regional inflammatory responses in multiple circumstances [14]. When Gal-3 is released into the extracellular environment, its interaction with cell surface receptor will initiate transmembrane signaling pathways for a variety of biological functions [15].

This study focused on the identification of the association between Gal-3 and HF through case control studies. The results of this study might provide valuable information for the development of a Gal-3 based HF diagnostic biomarker to improve the accuracy and effectiveness of HF diagnosis.

## Materials and methods

### Case selection

Two groups of people including 43 apparently healthy participants (24 male and 19 female) without additional medical health problems and 44 HF patients (22 male and 22 female) from Merjan Teaching Hospital (Babylon, Iraq) diagnosed by using echocardiography with cut off value of ejection fraction (EF) less than 54% in female and less than 52% in male were employed in this study, respectively. The basic information about all participants was shown in Table 1. All subjects included in this research were informed and consented to the procedures of this study. The research was approved by the ethics committees of the Ministry of Higher Education and Scientific Research and the Iraqi Ministry of Health (approval number: DSM-FO-1794).

### Determination of blood serum Gal-3 levels

Following an overnight fast, venous blood samples were obtained from all participants. The serum levels of human Gal-3 were then measured by using sandwich enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Jiaxing, Zhejiang, China)

**Table 1.** Basic information about all participants in both patient and control groups.

| Variables | | Groups | |
|---|---|---|---|
| | | Control | Patient |
| Gender | Male | 24 | 22 |
| | Female | 19 | 22 |
| Family history | Yes | 0 | 21 |
| | No | 43 | 23 |
| Smoking | Yes | 0 | 9 |
| | No | 43 | 35 |
| Alcohol consuming | Yes | 0 | 0 |
| | No | 43 | 44 |
| Total | | 43 | 44 |

**Table 2.** Baseline characteristics of patient and control groups.

| Variables | Groups | Mean ± SD | Range | P value |
|---|---|---|---|---|
| Age (y) | Control | 58.90 ± 14.16 | 39-78 | |
| | Patient | 59.18 ± 11.96 | 36-85 | > 0.05 |
| SBP (mmHg) | Control | 12.60 ± 2.03 | 12-14 | |
| | Patient | 15.59 ± 1.92 | 11-20 | < 0.001 |
| DBP (mmHg) | Control | 8.30 ± 1.36 | 8-10 | |
| | Patient | 10.06 ± 0.87 | 8.5-12 | < 0.001 |
| EF (%) | Control | 58.79 ± 10.16 | 52-68 | |
| | Patient | 41.40 ± 7.49 | 22-51 | < 0.001 |

**Notes:** SBP (systolic blood pressure), DBP (diastolic blood pressure), EF (ejection fraction).

following the manufacturer's instructions. The ELISA results were measured by using BioTek Epoch microplate reader (Agilent Technologies, Inc., Santa Clara, CA, USA) at wavelength of 450 mm.

### Statistical analysis

The SPSS (version 20) (IBM, Armonk, NY, USA) was employed in this study for statistical analysis. All the data were expressed as mean ± SD. The student's t-test was utilized for the comparison of data. A statistically significant level was considered once the *P* value was lower than 0.05.

## Results and discussion

### The baseline characteristics

The baseline characteristics of the control and patient groups were shown in Table 2. There were significant increases in patients' systolic blood pressure (SBP) and diastolic blood pressure (DBP), while a significant decrease in heart ejection fraction (EF%) compared to that in control group ($P < 0.001$). However, no significant difference in ages between patients and control groups was observed.

### Blood serum Gal-3 levels

The serum Gal-3 concentration of patient group was significantly higher than that of control group ($P < 0.001$) (Figure 1). The results demonstrated that the blood serum Gal-3 concentration was related to age, sex, EF%, and smoking in patient group (Table 3). There was a significant increase in serum Gal-3 concentration in HF patients older than 55 years old compared to that in HF patients younger or equal to 55 years old. There were no significant differences in patients' serum Gal-3 concentrations in different gender, EF%, and smoking. The results of this study demonstrated that there was no significant

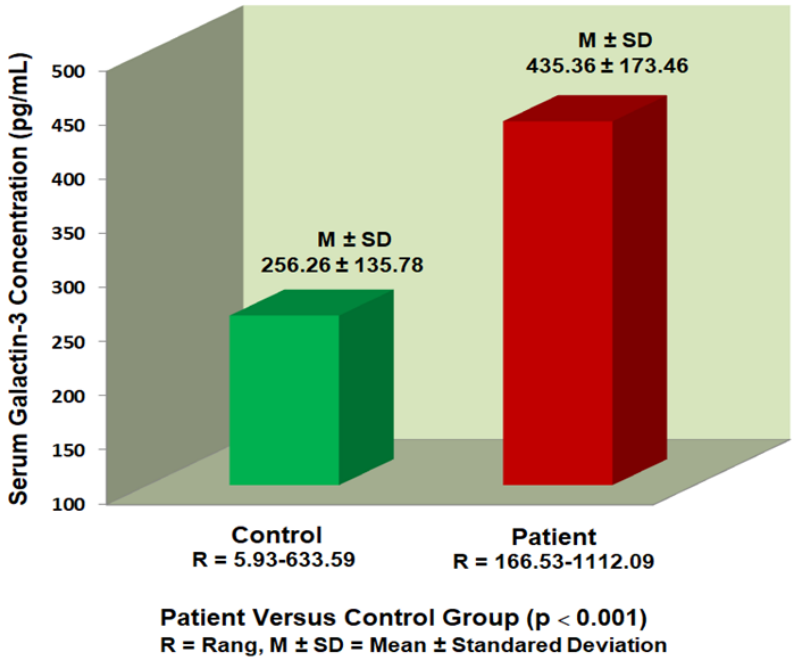


**Figure 1.** Serum Gal-3 concentration in patient and control groups.

difference in serum Gal-3 levels between male and female, which was accordance with the study performed by Neumann *et al*. [1]. However, the result was not compatible with the study that found higher serum Gal-3 concentrations in women than that in men [16].

Galectins can be present in a variety of cells [9]. Gal-3 expression was noticed in immune cells such as macrophages [8], fibroblasts [10], and different organs including heart [17]. Gal-3 works as a modulator of local inflammatory reactions and abnormalities that underpin an inflammatory state in numerous clinical circumstances [14]. The Gal-3's proinflammatory action is linked to activation of NF-kB transcription factor, stimulation of interleukin 6 (IL-6) and tumor necrosis factor (TNF), advancement of cell adhesion, encouragement of cell activation and chemotaxis, along with regulation of cell proliferation or apoptotic process [18]. Gal-3 secreted by activated cardiac macrophages has been demonstrated in animal models to have an essential role in pathological ventricular remodeling, and increased levels of circulating Gal-3 have been linked in the past to poor consequences in patients with nonspecific dyspnea as well as HF patients prior to their discharge from a HF hospitalization [18]. Furthermore, high blood Gal-3 concentrations are a foreboding of clinical failures linked with a greater risk of overall death or fatality resulting from cardiovascular causes and HF [20]. A greater relationship has been discovered between serum Gal-3 levels along with additional cardiovascular disease threat variables [16].

Gal-3 doesn't serve as an organ-specific marker, but rather a pathogenesis marker for inflammatory and/or fibrotic illnesses. Because the main origins of circulating Gal-3 may not be frequently recognizable and an individual with cardiac disease may experience various levels of inflammation and fibrotic process advancement, serum Gal-3 concentrations may represent various stages of the pathophysiological situation and hard to distinguish fibrosis and myocarditis, and hence does not precisely reflect these disorders [11, 20]. However, Galectins' assorted clinical involvement in various disorders suggests a role as a regulator of inflammation, coupling inflammation-linked macrophages to fibrosis

**Table 3.** The relationship between serum Gal-3 concentration and age, gender, EF%, and smoking in patient group.

| Variables | | Number | Serum Gal-3 concentration (pg/mL) | | |
|---|---|---|---|---|---|
| | | | Mean ± SD | Range | *P* value |
| **Age (y)** | ≤ 55 | 20 | 355.64 ± 87.13 | 166.53-496.49 | < 0.01 |
| | > 55 | 24 | 501.80 ± 199.63 | 205.03-1112.09 | |
| **Gender** | Male | 22 | 390.72 ± 119.94 | 166.53-705.39 | > 0.05 |
| | Female | 22 | 480.00 ± 207.49 | 187.83-1112.09 | |
| **Smoking** | Yes | 9 | 480.86 ± 149.35 | 371.05-749.42 | > 0.05 |
| | No | 35 | 423.66 ± 179.21 | 166.53-1112.09 | |
| **EF (%)** | ≤ 40 | 19 | 407.87 ± 107.52 | 166.53-705.39 | > 0.05 |
| | > 40 | 25 | 456.26 ± 210.21 | 187.83-1112.09 | |

progression [21, 22]. Galectins perform a significant role in fibrotic events in addition to influencing inflammatory pathways. The progression of myocardial fibrosis is an essential pathophysiological factor in HF. The degree of Gal-3 expression in the heart is nearly unnoticeable in cardiomyocytes, but it approaches a substantially larger concentration in heart fibroblasts [8].

Gal-3 is a biomarker for ventricular remodeling and myocardial fibrosis, and an essential controller for both long-term and acute inflammatory situations along with inflammation that leads to fibrosis within numerous tissues [21, 23]. Gal-3 is thought to be implicated in the beginning and advancement of myocardial fibrosis, while its expression tends to be low in a healthy heart but increases in fibrotic illnesses such as HF and atrial fibrillation [24]. Elevated Gal-3 production stimulates the secretion of inflammatory mediators comprising transforming growth factor (TGF) or interleukin 1 and 2 (IL-1, IL-2) along with the proliferation of cardiac fibroblasts [25]. Irrespective of the cause, cardiac inflammation and fibrosis are strongly embroiled to the pathophysiological pathways of myocardial tissue remodeling in HF [21]. Several cardiac disorders such as acute ischemic stroke, atherosclerosis, acute coronary syndrome, HF, cardiomyopathies, arterial hypertension, and atrial fibrillation have all been linked to increased Gal-3 expression [26]. A connection has been presented between cardiac remodeling and the HF development [27]. The cardiac remodeling process can be activated by myocardial infarction, hemodynamic overload, myocarditis, and neurohormonal activation [28-30]. Several studies showed a positive correlation between serum Gal-3 concentration and degree of heart failure while there was a negative correlation between serum Gal-3 concentration and left ventricular ejection fraction. A relationship had additionally been discovered between Gal-3 levels and alterations in left ventricular function and structure, which Gal-3 could participate in the left ventricular remodeling process in HF patients [31, 32]. The impact of Gal-3 is tightly linked to the clinically important HF markers, especially natriuretic peptides (NPs). Felker *et al*. validated the link between increasing Gal-3 serum level and the severity of HF as monitored by the concentration of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) [18]. Furthermore, the investigations proved that Gal-3 had a greater specificity in predicting the occurrence as well as progression of HF than NT-proBNP concentration solely [32].

## Conclusion

The results of this study showed that Gal-3 was positively associated with HF, which created wide-ranging possibilities of Gal-3 usage in the diagnosis of cardiovascular diseases. The measurement of blood serum Gal-3 level may be beneficial in terms of prognosis and risk classification for HF.

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