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## Evaluation of Serum Osteopontin and Growth Differential Factor-15 in Patients with Heart Failure

### ABSTRACT

**Background:** Heart failure (H.F) is a condition in which the heart cannot supply the body's tissues with enough amount of blood. Certain conditions such as narrowing arteries in heart (coronary heart disease) or hypertension gradually make heart weak or stiff to fill and pump efficiently. Osteopontin (OPN) is a glycoprotein expressed in many types of cells including bone, immune, endothelial cells, and others. OPN has an important role in mineralization and bone resorption. Growth differential factor-15 (GDF-15) is a member of transforming growth factor  $\beta$  (TGF $\beta$ ) cytokine superfamily, GDF-15 is highly expressed in cardiomyocyte, adipocyte, macrophage, and other cells.

**Aim:** to evaluate levels of OPN and GDF-15 in patients with heart failure

**Patients and methods:** This study was achieved from August 2020 to October 2020, it was conducted on 22 patients with CVD who attended to cardio care unit (CCU) in Al-Ramadi teaching hospital in period from August to October 2020. The results were compared with 30 healthy control subjects. About four milliliters of venous blood were collecting in gel tube from patients and controls to estimate OPN and GDF-15 by ELISA method. Furthermore, fasting blood sugar (FBS) and total cholesterol (CHO) were measured for patients and control groups.

**Results:** the level of OPN was significantly high in H.F patients ( $51.18 \pm 23.57$  ng/ml) compared to control group ( $1.07 \pm 0.41$  ng/ml) furthermore FBS and CHO mean concentrations were significantly high in H.F. patients ( $195.46 \pm 89.16$  mg/dl), ( $153.38 \pm 45.14$  mg/dl) respectively, compared with control group (FBS  $97.08 \pm 13.84$  mg/dl), (CHO  $112.18 \pm 10.64$  mg/dl).

**Conclusion:** the study's results showed that a significant increase in level of OPN and GDF-15 as a biomarker for heart failure patients and there was a correlation between both OPN and GDF-15 with blood glucose concentration, also hyperlipidemia was present in H.F. patients.

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## Introduction:

Heart failure (H.F) is a condition in which the heart cannot supply the body's tissues with enough amount of blood (1). Certain conditions such as narrowing arteries in heart (coronary heart disease) or hypertension gradually make heart weak or stiff to fill and pump efficiently (2). H.F is a common end-stage of numerous different diseases. process that impairs cardiac functions (3). Hypertension and coronary artery disease (singly or together) are major causes of heart failure in world, valvular heart diseases are less frequent etiology of H.F (4). Nutritional cardiac diseases are much more common in developing countries (5). There are two types of H.F, Acute heart failure (AHF) is defined as a rapid onset of signs and symptoms of H.F (6). It happens when there is a sudden increase in intracardiac filling pressure and acute myocardial dysfunction which can lead to peripheral perfusion and pulmonary edema (7). Second type is Chronic heart failure (CHF) which defined as a long term condition that gradually become worse overtime, it

cannot be cured, but symptoms can be managed (8). There are different types of CHF, classified according to how the heart reacts when it pumps blood. The two types are:

- heart failure with reduce ejection fraction (HFrEF) also called systolic heart failure (9). This type occurs when the heart is too weak and does not squeeze normally (10). the second type of CHF is heart failure with preserved ejection fraction (HFpEF), also named diastolic heart failure, this occurs when heart is do not fill with blood normally (11).

Osteopontin (OPN) is one of noncollagenous protein in bone matrix and various organs including those without matrix, also present in plasma (12).

OPN is highly negatively charged glycoprotein, identified in Osteoblast at first time (13), it also Known as early T-Lymphocyte Activator 1 (ETA1) protein, and bone sialoprotein 1 (BSP1) (14).

Its name forms by two parts, the prefix "Osteo" indicates to bone, and the

suffix "Pontin" derived from "Pons" the Latin word for bridge, this name signifies.

osteopontin role as a linking protein (15). Human OPN is an extracellular structural protein composed of about 314 amino acid residues (16) and has about 30 carbohydrate residues attached including 10 sialic acid residues (14), its molecular weight approximately 32 KDa protein, but due to extensive post-translational modification its molecular mass ranges from 45 to 75 KDa (17). OPN is aspartic acid rich, N-linked glycoprotein that may be highly phosphorylated on serine and threonine depending on cell type (18).

Growth differential factor-15 (GDF-15) is a member of the transforming growth factor- $\beta$  (TGF- $\beta$ ) cytokine super family (19), it also known as macrophage inhibition cytokine-1 (MIC-1) (20). It considered as stress responsive cytokine. It is highly expressed in cardiomyocytes, adipocyte, macrophage, vascular smooth muscle cells, and endothelial cells in normal and pathological status with different levels (19).

The functions of GDF-15 are not fully cleared, but it seems to have a role in inflammatory regulation pathways and involved in apoptosis regulation, cell growth, and cell repair which are biological processes involved in cardiovascular and neoplastic disorders (21,22,23).

#### **patients and methods:**

This study was achieved in AL-Ramadi teaching hospital from August 2020 to October 2020. It was conducted on twenty two individuals who had heart failure, and thirty healthy control subjects. The information about patients in this study was performed from patient's hospital records. The samples were collected from AL-Ramadi teaching hospital- Cardio care Unit (CCU) on patients with H.F and hypertension. Thirty apparently healthy sex age matched controls were included in this study. Patients who had cancer, liver diseases, autoimmune diseases, renal diseases, covid-19, bone disorders and any inflammatory diseases were excluded in all cases.

#### **Results:**

OPN level was significantly high in H.F

patients (51.18±23.57 ng/ml) compared with control group (1.07±0.41 ng/ml). and there was a highly increasing in the level of GDF-15 in H.F patients' group (686.63±198.14 ng/ml) compared with healthy control group (85.89±14.64 ng/ml) the study found 81.8% of H.F patients was smoking and 18.2% of them was not. the level of FBS was significantly increased in patients' group (195.46±89.16 mg/dl) compared

with healthy control group (97.08±13.84 mg/dl). The level of CHO was significantly high in H.F patients' group (153.38±45.14 mg/dl) comparing with healthy control group (112.18±10.64 mg/dl). Table 1.

| PARAMETER | H.F PATIENTS' GROUP | CONTROL GROUP |
|-----------|---------------------|---------------|
| OPN       | 51.18±23.57         | 1.07±0.41     |
| GDF-15    | 686.63±198.14       | 85.89±14.64   |
| FBS       | 195.46±89.16        | 97.08±13.84   |
| CHO       | 153.38±45.14        | 112.18±10.64  |

**Table 1: Mean (±SD) Values of OPN and Biochemical Marker (FBS and CHO) in patients and control groups.**

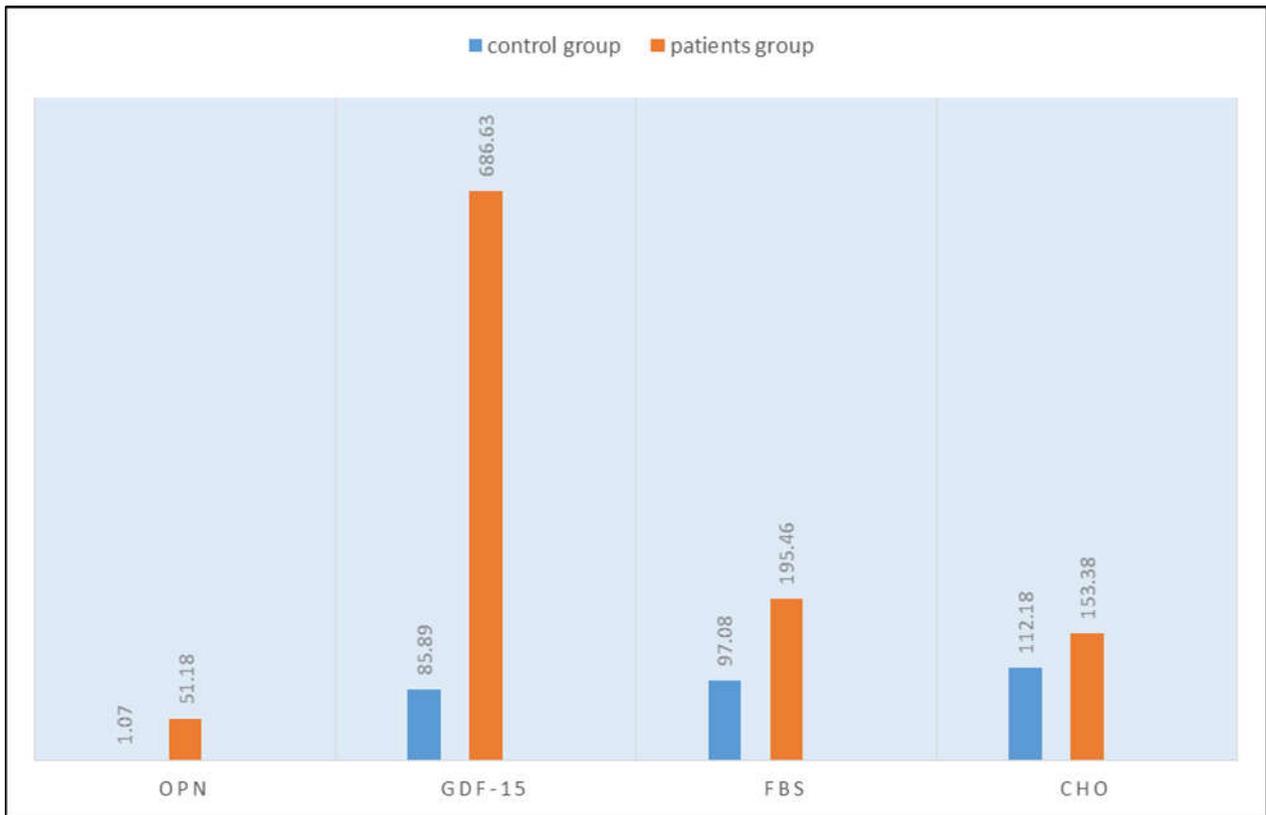


Figure 1: OPN, GDF-15 and biochemical parameter in patients and control group.

### Discussion:

The measurement of OPN level in patients' group with heart failure was significantly higher than that of healthy control group ( $P=0.007$ ). and this finding may be due to Angiotensin II which induce wound healing and cardiac remodeling by promoting OPN expression in the injured myocardium (24), So OPN considered as a marker of fibroblast and myofibroblast maturation and differentiation after cardiac injury (25). Increased OPN level in patients may be because hypoxia that affects

them because prolonged reduce blood supply to body due to HFrEF (26). And these results agree with (Lok et al.,2019) (27), they found that OPN level was highly increased in M.I and H.F cases. GDF-15 concentration in patients' group was too high by comparing with the control healthy group ( $P<0.005$ ) And this may be due to response to stress on cardiovascular system, hypertension, Angiotensin II, and vascular endothelial growth factor (VEGF), these factors induce secretion of GDF-15 from cardiac myocytes and

other cell types like endothelial cells, cardiac fibroblast, and vascular smooth muscle cells in autocrine way (28).

and this result was agreed with (Xu et al., 2014) (29) and (Kempf et al., 2009) (30), these studies found that GDF-15 level is increased in several form of CVDs and this indicates that GDF-15 can considered as a biomarker in diagnosis and follow up of CVD.

OPN was significant correlated to GDF-15  $R=0.350$ ,  $P=0.006$  because they were directly proportional to cardiovascular disorders.

The present study found that the concentration of blood glucose was significantly high in patients group compared with healthy control group ( $P<0.05$ ). and there Was positive Correlation between GDF-15 and FBS ( $R=0.369$ ,  $p=0.004$ ) and this finding is in agreement with (Bao et al., 2013) (31), So it suggest that high blood glucose promotes GDF-15 expression which may modulates cellular apoptosis in negative feedback manner, Hyperglycemia is the main chronic symptom of diabetes, it increased reactive oxygen species (ROS)

formation, which leads to cellular injury and death (32), ROS increasing can cause cells apoptosis, (Ho et al.,2006)(33) provides that GDF-15 protects endothelial cells against high glucose induced cellular injury by activation PI3,AKT, and eNOs signaling pathway.

there was positive correlation between OPN and FBS ( $R=0.210$ ,  $P=0.03$ ) and this study agreed with (Daniele et al.,2018) (34). This result suggests that diabetes mellitus type 2 (DMT2) has a role in OPN expression and its relationship with CVD, so increased level of OPN can considers a biomarker for CVD in DMT2 patients.

high cholesterol level in patients group promotes the atherosclerosis process leading to deposition of cholesterol and fatty acids in the tunica intima of artery wall (35) Eventually these deposits may build up making it difficult for enough blood to flow through arteries and can blocked suddenly and forming a clot that cause Myocardial infraction which may become to be H.F with time.

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