Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Diyala- College of Medicine

Evaluation of Hormone BNP and Cytokines IL-6, IL-18 and TNF-α in Patients with Heart Failure

A thesis
Submitted to the council of the College of Medicine - University of Diyala in partial fulfillment for the requirements of the degree of Master of Science in Medical Microbiology

By

Ali Abdalhassan Ali

Clinical Laboratories

Supervised by

Prof.Dr. Ismail Ibrahim Latif
Ph. D. Immunology
Diploma in Internal Medicine - cardiology

Assistant Prof. Dr. Ali Mousa Jaafar
Board. D. Internal Medicine - cardiology

2020 A.D. **1441 A.H**

بِسْمِ اللَّهِ الرَّحْمَـٰنِ الرَّحِيمِ

(وَلَقَدْ آتَيْنَا دَاوُودَ وَ سُلَيْمَانَ عِلْمًا و قَالَا الْحَمْدُ لِلَّهِ الَّذِي فضَّلَنَا عَلَى كَثِيرٍ مِنْ عِبَادِهِ الْمُؤْمِنِينَ)

صَدَق اللَّهُ الْعَظِيْم

سورة النمل

الآية 15

Dedication

This thesis is wholeheartedly dedicated to my beloved mother, who has been my source of inspiration and gave me strength when I thought of giving up, who continually provide her moral, spiritual, emotional, and financial support.

To my beloved father, for earning an honest living for us and for supporting and encouraging me to believe in myself.

Ali Abd Alhassan

Acknowledgements

Praise be to Allah, the most merciful, the most compassionate, for the guidance, strength, power of mind, protection and skills, and for giving me a healthy life.

I express my sincere and whole hearted thanks, to my supervisor, Prof. Dr. Ismail I.latif for his regular advice, magnitude of dynamic and untiresome guidance, suggestion, immense help and encouragement throughout the course of this study. I am greatly indebted to his untiresome perseverance, which helped me present this work in the right perspective.

I express my deepest gratitude to my second supervisor Dr. Ali M. Jaafer for his encouragement, inspiring advice and moral support in carrying out this thesis work.

I would also like to take this opportunity to thank the deanship of Medical College / Diyala University; and the staff members of Microbiology Department.

I am sincerely indebted to all the internal medicine specialist in Baqubah Hospital, who helped me in identifying the suspected cases in this study.

I am thankful to the staff members in Baqubah hospital office and laboratory, and teaching laboratory in Baqubah Teaching Hospital for helping me in methodology.

As a final word, I would like to thank each and every individual who have been a source of support and encouragement and helped me to achieve my goal and complete my thesis work successfully.

Declaration

I hereby declare that this thesis is my original work except for quotation and citation which have been only duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at University of Diyala or other universities.

Ali Abd Alhassan Ali

Summary

Background: Heart failure (HF) is a condition in which the heart can no longer pump blood as efficiently as it used to**.** This is lead to a complex of clinical symptoms like (dyspnea, orthopnea, lower limb swelling). BNP is a neurohormone released from myocardium and increased when failure of heart is occure and used for diagnosing heart failure. TNFα, IL-6, and IL-18 is inflammatory cytokines, its concentration increasing in patients with heart failure, this caused by inflammation which is present in heart with failure.

Objectives: This study was designed for examining serum concentrations of TNFα, IL-6, and IL-18 in patients with HF, examining whether this cytokines was involved in the pathophysiology of the HF syndrome, and investigating the effectiveness of using BNP concentration as an indicator for heart failure.

Subjects and methods: The current study is a cross sectional study that was carried out in the center of Diyala province, Baquba Teaching Hospital, to determine the serum concentration of BNP, TNF-α, IL-6, and IL-18 in patients with heart failure. The samples were collected in 2 and a half months, from January the 15th to April the 1st 2019.

A total of 150 serum samples were collected . 100 patients with diagnosed heart failure, and the rest apparently healthy. The age range was 30-89 years, 50 of them were males, and 50 were females. BNP, TNFα, IL-6, and IL-18 concentrations were tested in the serum samples using the BNP, TNFα, IL-6, and IL-18 ELISA kit (from SunRed company - China). Human privacy was respected by taking the parents' verbal consent. Statistical analysis of data was carried out using the Statistical Packages for Social Sciences (SPSS), Version 25. Statistical

significance was considered whenever the P value was equal to or less than 0.05.

Results: The results showed that the BNP concentration range in HF group patients (50-1600) was wider than that in healthy control group (5-160) with a statistically significant difference between HF group and healthy control group (P = 0.0001). A statistically significant association was found between IL-6 concentration and heart failure (P = 0.0001), IL-18 concentration and heart failure (P = 0.0001), and TNFα and heart failure (P = 0.005). Also there is statistically association between grade of heart failure with BNP, TNFα, IL-6, and IL-18 with P value of 0.0001, 0.0001, 0.016, and 0.0001 respectively.

There are several factors and conditions that affect the concentration of these cytokines such as medication and clinical cardiac problems.

Conclusion: The concentrations of TNFα, IL-6, and IL-18 is elevated with increasing the severity of heart failure accompanied by BNP concentration elevation, where the increase the HF grade, the elevation the concentration of these cutokines.

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List of abbreviations

Abbreviation	Meaning
A.M.I	Acute myocardial infarction
A.S	Angina stable
A.U	Angina unstable
ADHF	Acute decompensated heart failure
AHF	Acute heart failure
BNP	Brain natriuretic peptide
CHF	Chronic heart failure
E.F	Ejection fraction
ELISA	Enzyme-linked immunosorbent assay
HF	Heart failure
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
I.H.D	Ischemic heart disease
I.S	Ischemia
IL-18	Interleukine-18
IL-18 BP	Interleukine-18 binding protein
IL-6	Interleukine-6
L.B.B.B	Left bundle branch block
L.V.H	Left ventricular hypertrophy
M.I	Myocardial infarction
PCI	Percutaneous coronary intervention
STAT3	Signal transducer and activator of transcription 3
TNFα	Tumor necrosis factor alpha

Chapter one

Introduction

Chapter one

Introduction

1.1. Background

Heart failure (HF) is a condition which is the complex of clinical symptoms like (dyspnea, orthopnea, lower limb swelling) Accompanied by pulmonary congestion, elevated jugular venous pressure that are indicated to clinical syndrome of heart failure due to abnormalities of structure or function of heart which cause reducing of cardiac output or elevated intracardiac pressures (Ponikowski *et al*., 2016).

Heart failure is a condition in which the heart can no longer pump blood as efficiently as it used to. This causes blood and other fluids to retaind in the body – particularly in the liver, lungs, hands, and feet (Ponikowski *et al*., 2016). Heart failure effects are extensive, whereas the study of heart failure implications does not only in terms of mortality and morbidity of individual impacts, it is also for the infrastructure desired to supplying care for these patients (NICE, 2010). For instance, inside the UK, £980 million per year is spending to managing of HF, in addition, the World Bank has been estimated the global of economic cost approximately $108 billion per year (Cook *et al*., 2014). According to New York Heart Association (NYHA) functional classification, the term of HF can be used for the patients whose established chronic heart failure (CHF), since 20-30 years ago the understanding of pathophysiological and provision of disease-modifying therapies have been significantly improved (Bleumink *et al*., 2004).

Recent study have been proved that the concentration of cytokines are significantly increased in the case of heart failure; although, the clinical and pathophysiological importance role remain still unclear (Ahluwalia *et al.*, 2013).

The pathophysiological role of cytokines and clinical significance remain still unclear, cytokines are active proteins, low molecular weight which act in an autocrine to modulate cell function. The most remarkable pro-inflammatory cytokines implicated in HF are interleukin 1 (IL-1), interleukine 6 (IL-6), and tumor necrosis factor α (TNFα) which are secreted from the mononuclear cells and myocardium (Ahluwalia *et al.*, 2013).

Tumor necrosis factor α has not completely understood the physiological function in the heart. It participates in the cardiac dysfunction developments, also it has been known for its cardio protective effects (Rathi and Dhalla, 2002).

In congestive heart failure the circulating levels of IL-6 are increased as well correlate with its progression and functional class. Numerous studies found that IL-6 related to cytokines are able to stimulate cardiomyocyte hypertrophy in various cell signaling pathways, involving Signal transducer and activator of transcription 3 (STAT3).

Interleukin-18 (IL-18) is a proinflammatory cytokine which is able to stimulate interferon γ (IFN-γ) production (Nakamura *et al.*, 1989).

Interleukin-18 play important role in human myocardial infarction and HF. The expression of IL-18 increasing in human atherosclerotic plaques collected during carotid endarterectomy and its gathering is correlated with plaque destabilization (Mallat *et al*., 2001).

High serum levels of IL-18 were correlated with a rise risk of developing cardiovascular disease (CVD) in population, lead to increasing of mortality in HF patients and development of congestive HF and AMI in patients with acute coronary syndromes (Blankenberg, 2002; Kaptoge *et al*., 2013).

During the response to atrial/ventricular dilation or volume overload, Atrial and brain natriuretic peptide began to be secreted from cardiomyocytes.

Although brain natriuretic peptide (BNP) synthesized in ventricles and Atrial natriuretic peptide (ANP) in atrium, they can make them in every chamber in pathological conditions. Pro-BNP is released as a response to volume expantion or stress. Then, it is cleave to biologically effective BNP and inefficent N-terminal segment (NT-proBNP) (Daniels and Maisel, 2007; Hall, 2004). BNP consider specific marker for heart failure and the circulating levels of NT-proBNP and BNP have been utilized in prediction assessment and diagnosis for heart failure (Lainchbury *et al*., 2009).

Brain natriuretic peptide (BNP) released from cardiac ventricular myocytes in response to volume or pressure overload (Loncar *et al*., 2012).

1.2. Aims of the study : The study aims at :

1- Examining serum concentrations of IL-6, IL-18, and TNFα in patients with CHF.

2- Examining whether these cytokines were involved in the pathophysiology of the HF syndrome.

3- Investigating the effectiveness of using BNP concentration as an indicator for heart failure.