PROGNOSTIC VALUE OF HIGH SENSETIVE C-REACTIVE PROTEIN IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Thesis

Submitted for partial fulfillment of master degree in cardiology

By

Sherif Eid Zyada

M.B.B.CH

Supervisors

Prof. Dr. Ali Ahmed El.Abd

Professor of cardiology Faculty
Of Medicine Ain-Shams University

Dr. Mohamed Ismael Ahmed

Assistant Prof. of cardiology Faculty
Of Medicine Ain-Shams University

Faculty of Medicine
Ain-Shams University
2011

ACKNOWLEDGMENT

I would like to start by thanking ***GOD*** *for help during all the stages of this work, as a little part of this generous help through out our life.*

I would like to express my deepest appreciation and thanks to ***Dr. Ali Ahmed El.Abd*** *Professor of cardiology, Faculty of medicine, Ain-shams University, for his valuable cooperation, sincere guidance, devoting much of his time, and supports to accomplish this work.*

I want to thank ***Dr. Mohamed Ismael Ahmed****, Assistant Professor of cardiology, Faculty of medicine, Ain-Shams University for his advice and cooperation throughout this work.*

I would like to thank every one who helped me to complete this study.

I would like to express my thanks to my ***Father*** *and my* ***Wife*** *who continued supporting me in all the stages of this work.*

Last but not least, to the soul of my ***Mother*** *who has always been an inspiration and to my young child* ***Omnia*** *who has always been* a *push to a better future*.

Contents

Title	Page
***Introduction and Aim of the study** ***Review of Literature**	**1**
Chapter (1): Inflammation, Atherosclerosis, and Coronary Artery Disease	**3**
Chapter (2): C-reactive protein	**24**
Chapter (3): Acute Myocardial Infarction	**48**
***Patients and Methods**	**78**
*** Results**	**89**
***Discussion**	**106**
***Summary in English**	**115**
*** conclusion**	**117**
*** Limitations**	**118**
***Recommendations**	**119**
***References**	**153**
***Summary in Arabic**	

List of Figures

No	Description	Page
Fig 1	Initiation of atherosclerosis.	**8**
Fig 2	Progression of atherosclerosis	**9**
Fig 3	Thrombotic complication of atherosclerosis	**16**
Fig 4	Sources of inflammatory markers and cytokines	**21**
Fig 5	Risk factors for CAD among all the studied patients	**90**
Fig 6	Hospital course of the studied patients with adverse cardiac events.	**93**
Fig 7	Hospital cardiovascular events among all the studied patients.	**93**
Fig 8	Cardiovascular events after 6 months.	**94**
Fig 9	Cardiovascular events among all the studied patients after 6 months	**95**
Fig 10	Relation between CRP and risk factors for coronary artery.	**96**
Fig 11	Correlation between CRP and CPK-MB	**98**
Fig 12	Correlation between CRP and EF%.	**99**
Fig 13	Correlation between CRP and wall motion score index.	**99**

LIST OF Tables

Table No	Title	Page
Table 1	Aspects of Diagnosis of Myocardial Infarction by Different Techniques	**48**
Table 2	Interpretation of ST segment elevation in diagnosis of MI	**65**
Table 3	Cardiac Arrhythmias and Their Management During Acute Myocardial Infarction	**69**
Table 4	Baseline general characteristics of the studied patients	**90**
Table 5	Results of laboratory investigations among all the studied patients.	**91**
Table 6	Relation between mean level of hs-CRP among patients with in-hospital complications and those without in-hospital complications	**91**
Table 7	Hospital course of the studied patients with adverse cardiac events.	**92**
Table 8	Cardiovascular event after 6 months	**94**
Table 9	CRP among patients with and without cardiovascular events during follow up.	**95**
Table 10	Comparison between patients with CRP<10mg/dl and CRP>10mg/dl	**96**
Table 11	Shows the degree of stenosis according to coronary angiography among the studied patients.	**97**
Table 12	TIMI flow in the culprit vessel before PCI	**97**
Table13	Correlation between CRP and some of the significant parameters.	**98**
Table 14	Relation between peak CPK and hs-CRP<10mg/dl and hs-CRP>10mg/dl.	**100**
Table 15	Relation between Mean CPK-MB and hs-CRP<10mg/dl and hs-CRP>10mg/dl.	**100**
Table 16	Relation between EF and hs-CRP<10mg/dl and hs-CRP>10mg/dl.	**101**
Table 17	Relation between SWMA and hs-CRP<10mg/dl and hs-CRP>10mg/dl.	**101**
Table 18	Multivariate analysis of the predictors of adverse cardiovascular events after 6 months showed that CRP > 10 mg was the most significant predictor of adverse cardiovascular events.	**102**
Table 19	Univariate analysis for the determination of the effect of CRP in the prediction of cardiovascular events.	**102**
Table 20	Relation between serum levels of CRP and Complication in patients treated with invasive vs. conservative therapy	**103**

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BNP	Brain natriuretic peptide
C	cholesterol
CABG	Coronary bypass graft surgery
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CK	Creatine kinase
CK-MB	Creatine kinase myocardial band
CMR	cardiac MRI
COX	Cyclo-oxygenase
CRP	C-reactive protein
cTnT or cTnI	Cardiac troponin T or cardiac troponin I
dL	Deciliter
ECG	Electrocardiogram
EDTA	Ethylenediamine triacetic acid
EF	Ejection fraction
ESC	European Society of Cardiology
GPIIb/IIIa inhibitors	Glypoprotein IIb/IIIa inhibitors
HDL	High-density lipoprotein
HR	Hazard ratio
hs	high-sensitivity
hsCRP	High-sensitive C-reactive protein
ICAM-1	Intercellular adhesion molecule-1
IL	interleukin
INF	Interferon
IU	International units
kDa	(Kilo Daltons) represent molecular weight
LAD	left anterior descending
LBBB	Left-bundle branch block

Continue to List of Abbreviation

LCX	left circumflex
LD	lactate dehydrogenase
LDL	Low-density lipoprotein
LMWH	Low molecular weight heparin
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAC	membrane attack complex
MACE	Major Adverse Cardiovascular Events
MCP-1	Monocyte chemo attractant protein-1
mg	Milligram
MI	Myocardial infarction
mL	Milli liter
MMP-9	Matrix Metaloproteinase-9
MRP	Myeloidrelated protein
mv	Milli volt
n-PA	lanoteplase
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
PAI-1	plasminogen activator inhibitor 1;
PCI	Percutaneous coronary intervention
PPAR	peroxisome proliferator-activated receptor
RAAS	renin-angiotensin-aldosterone system
r-PA	reteplase
RR	Risk ratio
SAA	Serum amyloid A protein
SMC	smooth muscle cell
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TNF-α	Tumor necrosis factor
TnI	troponin I
TNK	tenecteplase
TnT	troponin T
t-PA	tissue plasminogen activator
UFH	Unfractionated heparin
VCAM-1	Vascular adhesion molecule 1
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

Inflammation is established as an important contributor to atherogenesis and acute atherothrombosis **(Libby P et al 2002)** .

Researchers and clinicians have thus turned to biochemical markers of inflammation as possible non-invasive indicators of underlying atherosclerosis, the risk of first or recurrent cardiovascular events and the success of therapeutic and preventive interventions **(Morrow DA and Braunwald E 2003).**

High-sensitivity C-reactive protein (hs-CRP) measurement is the most extensively studied of these markers and is associated with the risk of adverse cardiovascular outcomes in apparently healthy individuals and in patients with established coronary artery disease **(Pearson TA et al 2003).**

hsCRP also remains predictive of cardiovascular events after accounting for the presence and severity of angiographically determined stenosis among symptomatic patients treated conservatively **(Zebrack JS et al 2002)**.

Aim of the work

The aim of our study will be to assess prognostic value of high sensitive C-reactive protein in patients with acute ST-segment elevation myocardial infarction.

CHAPTER : (2)
C-reactive protein

Introduction :

Increasing evidence of atherosclerosis suggests a prominent role for inflammatory processes in its pathogenesis **(Hansson and Libby et al 2006)**. Inflammatory cells and soluble mediators are key components of the atherosclerotic plaques in the different steps of lesion evolution **(Carter et al 2005).**

Several inflammatory markers have been associated with a greater likelihood of cardiovascular diseases. Of those C-reactive protein (CRP) and myeloperoxidase (MPO) are the most well known. Therefore, It has been proposed that increased use of the monitoring of inflammatory and other diagnostic markers could be of use in the screening and prediction of the risk of infarction**. (Niskanen et al 2006)**

CRP is an acute phase protein that has been shown to be a marker of systemic inflammation, elevated in response to injury, infection and other inflammatory stimuli. It is directly related to IL-6 stimulation and, unlike other acute phase reactants, its levels remain stable over long periods in the absence of new stimuli. However, CRP is not only a powerful inflammatory marker, but increasing evidence suggests that CRP may also

directly participate in the inflammatory process of atherogenesis. **(Inoue T et al 2005)**

Recent studies have also shown that CRP originates not only in the liver, but also from other tissues, including SMCs from normal coronary arteries and diseased coronary artery bypass grafts as well as coronary artery endothelial cells which may provide an explanation for potential local actions of CRP **(Singh Pet al 2007).**

Ishikawa found that CRP plays an important role on plaque vulnerability and in the pathogenesis of unstable angina, as well as restenosis after coronary intervention **(Ishikawa T et al 2003).** It is produced at the site of the culprit plaque, via the existence of CRP gradient in coronary arterial blood, sampled just distal and proximal to the culprit lesions **(Inoue T et al 2005)**

The transcardiac CRP gradient (coronary sinus minus peripheral blood), and activated Mac-1, increased gradually after stenting, reaching a maximum at 48 h. Further, there was a positive correlation between the transcardiac CRP gradient and activated Mac-1 at 48 h. These findings suggest CRP is produced at the site of the vulnerable plaque or the vessel wall injured by PCI and this locally released CRP may play a role in Mac-1 activation and restenosis **(Inoue T et al 2005).**

In contrast to many other inflammatory markers, assay techniques for high sensitive (hs)-CRP are reliable, fully automated, and sensitive, providing a simple clinical tool for the careful assessment of systemic inflammation **(Wilkins J et al 1998)**

Therefore, a statement from the US Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) recommended that CRP has the assay characteristics most conducive to use in clinical practice compared with other inflammatory markers **(Pearson TA et al 2003).** Circulating levels of CRP have been found to be related to a number of well known cardiovascular risk factors, such as obesity, smoking, blood pressure, serum triglycerides, apolipoprotein B, fasting blood glucose, heart rate, serum fibrinogen and inversely to HDL-cholesterol levels, both in children and in adults **(Cook DG et al 2000).** Healthy individuals with at least one of their parents with myocardial infarction (MI) had elevated CRP levels compared with those without heredity for myocardial infarction **(Margaglione M et al 2000**). In a recent study, conducted on patients with various cardiovascular risk factors but no CAD (diabetic, hypertensive, smokers, and obese), in addition to healthy controls, the CRP levels, age, waist circumference, homocysteine, and triglycerides were predictors of intima-media thickness of the carotid artery assessed by Doppler, while CRP, age, and triglycerides were predictors of plaque formation **(El-Gendi SS et al 2008).**

Biological properties of CRP :

CRP belongs to the pentraxin family of proteins; consisting of five identical subunits which associate to form a stable disc-like pentameric structure. The gene for CRP is on chromosome 1, and about 35 to 40% of the variability of baseline CRP concentrations between different healthy individuals is controlled by genetic polymorphisms in the CRP gene **(Lange LA, et al 2006)**. Plasma CRP is predominantly produced by the hepatocytes and regulated by cytokine interleukin- 6 (IL-6), and to a much lesser extent also by IL-1and tumor necrosis factor (TNF)- **(Black S,et al 2004)**. although extrahepatic synthesis of CRP has also been reported in neurons, atherosclerosis plaques, monocytes, lymphocytes, and some tumors **(Jialal I, et al 2004)**. The liver is also the only significant site through which CRP is cleared at a constant rate from the plasma. As such, the plasma CRP concentrations are almost solely determined by the synthetic rate of its production in the liver **(Pepys MB and Hirschfield GM 2003).**

Furthermore, the half-life of CRP is about 19 hours and this does not change in healthy conditions or disease. For these reasons, elevated circulating levels of CRP in inflammatory states are secondary to an increase of CRP production **(Jialal et al 2004).**

In healthy subjects, the CRP baseline concentration in the plasma is about 0.8 mg/l, and is in part genetically regulated **(Tall 2004).** Single nucleotide polymorphisms (SNPs) in both CRP gene and in a number of other genes regulating CRP secretion have been found associated with CRP baseline levels in humans **(Zhang YY et al 2007).** Although still controversial, the modulation of CRP levels by other gene products might be considered as a very promising field for future investigations. Further studies of larger samples are warranted to assess the determination of CRP levels by polymorphisms in other genes. In humans, the gene encoding CRP is mapped to chromosome 1 (1q23-24) and consists of 2 exons. SNPs in the CRP gene promoter have been found associated to differences in baseline serum CRP levels **(Kovacs et al 2005).**

In addition, also polymorphic sequences in other portions of CRP gene have been identified and associated with immune-mediated diseases or inter individual variations of baseline CRP production **(Kathiresan S et al 2006)**. Another study showing that the most common causes of CRP deficiency are represented by liver failure or therapies affecting the acute-phase stimulus **(Vermeire S et al 2004).** Therefore, SNPs in other genes and clinical conditions appear as implicated in the regulation of CRP baseline levels rather than SNPs in CRP gene. On the other hand, CRP secretion is increased by infections (bacterial, fungal,