Contributions of Depression and C-Reactive protein level to Coronary Heart Disease

Thesis For Partial
Fulfillment Of Master Degree In
Cardiology
by

Dr. Mohamed Hussien Hanouda MB.Bch

Supervised by

Doctor . Yasser Gomaa Mohamed
Assistant Professor of Cardiology
Ain shams university

Doctor. Hisham Ahmed Ramy
Assistant Professor of Psychiatry
Ain shams university

Doctor . Hebatalla Mohamed Attia
Lecturer of Cardiology
Ain Shams university

Ain Shams university
٢٠٠٦

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LIST OF ABBREVIATIONS

ACS	**Acute Coronary Syndrom**
CABG	**Coronary artery bypass graft operation**
CHD	**Coronary heart disease**
CHS	**Cardiovascular Health Study**
CRP	**C-reactive protein**
IL-٦	**Interleukin-٦**
LPS	**Lipopolysaccharide**
MI	**Myocardial infarction**
MCP-١	**Monocyte chemoattractant protein**
MIP-١a	**Monocyte inflammatory protein**
NO	**Nitric oxide**
PHS	**Physician's Health Study**
SSRIs	**Selective serotonin reuptake inhibitors**
TNF	**Tumor necrosis factor**
VCAM-١	**Vascular cell adhesion molecule-١**
VSMC	**Vascular smooth muscle cells**

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INTRODUCTON

"For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."

William Harvey

In ١٦٢٨, William Harvey defined the circulatory system as we know it and proposed a link between the mind and the heart. This potential association received little attention for >٣٠٠ years, until Frasure-Smith and colleagues(١) published a study demonstrating that patients who are depressed at the time of an acute myocardial infarction (MI) have markedly elevated mortality as compared with patients who are not depressed. Since then, >١٠٠ studies have investigated this relationship, providing evidence that depression is prevalent (≈٢٠% to ٣٥%) in populations with cardiovascular disease, is predictive of developing cardiovascular disease, and is predictive of adverse outcomes among patients with existing cardiac disease.(٢,٣) Depression, however, remains largely off the radar screen of cardiac care, in large part because of confusion about the nature of the association between depression and cardiovascular disease and the role of cardiovascular clinicians with regard to depressed patients.

Depressive symptomatology, especially excess fatigue, feelings of general malaise, and increased irritability, have been found by many researchers to belong to the precursors of first and recurrent ACSs (٤-٦). The origin of these feelings is still poorly understood. Detailed investigations showed that the feelings of exhaustion and malaise are not or are only modestly associated with left ventricular ejection fraction and the amount of vessel disease (٧,٨). Significant associations have been observed between this state and "prolonged overtime work," "financial problems," and other life stressors, suggesting that the depressive symptomatology may reflect a breakdown in adaptation to prolonged stress (٩). However, this state has also been observed in otherwise healthy and happy subjects. The strength of the association between these feelings and the occurrence of an ACS seems to be inversely related to the duration of the symptoms (١٠). This raises the question of whether the depressive symptomatology is associated with

functional processes in a coronary artery leading to an acute occlusion, especially with inflammation. Atherogenesis has been proposed to represent a sequence of events triggered by the response to vascular injury. The main forms of injury to the vessel wall are oxidized low-density lipoproteins, blood flow shear, oxygen-derived free radicals, vasoactive amines, and cigarette smoking. Recent investigations indicate that infections by CMV or *Chlamydia pneumoniae* also might belong to these factors (١١-١٣). The presence of numerous macrophages and T-lymphocytes in the coronary lesion indicates that not only is there an inflammatory reaction secondary to tissue damage but also a true, primary immunological reaction. The activated macrophages play a role in the fibroproliferative process by their capacity to form PDGFs. They also secrete cytokines, including IL-١ß, IL-٦, and TNF-α. These cytokines can induce proliferation and migration of smooth muscle cells by stimulating other growth factors. When the response becomes excessive, high doses of IL-١ and TNF-α can inhibit the proliferative effect of growth factors by downregulating PDGF receptors (١٤-١٦).

The cytokines are tailored to function as an "SOS signal" for tissue damage. This information is relayed to other parts of the body, including the brain, where they evoke feelings of lack of well-being, general malaise, sickness, and tiredness (١٧-١٩). Therefore, the feelings of exhaustion that occur before an acute coronary event may form part of the reaction to inflammation. This chain of events is still rather speculative. However, testable hypotheses may be derived from this model.

Several observational studies have reported that negative emotions such as major or clinical depression and depressive symptoms are risk factors for coronary heart disease (CHD) in the general population.(٢٠-٢٥) However, the mechanisms underlying this association are mostly unknown. The contribution of inflammation to the origin of CHD has been investigated, and prospective studies have shown that levels of interleukin-٦ (IL-٦), C-reactive protein (CRP), fibrinogen, and adhesion cellular molecule (ICAM-١) are predictive of CHD in healthy populations.(٢٦-٣١) Additionally, some cross-sectional studies have shown that subjects with clinical or major depression, and possibly

depressive symptoms, have higher levels of circulating inflammatory markers, including IL-٦, CRP, and fibrinogen.(٣٢-٣٦) Thus, the hypothesis was raised that inflammation might partially mediate the relationship between depressive disorders and CHD. Nonetheless, evidence supporting the association of depressive disorders with inflammatory markers is weak. Although ٣ studies on major and clinical depression have reported consistent results,(٣٢-٣٤) ٣ studies on depressive symptoms have provided mixed results.(٣٧-٣٩)

In our study, we sought to explore whether depressive mood assessed by questionnaire is associated with a wide range of circulating inflammatory markers. Then, we estimated the contribution of depressive mood and circulating inflammatory markers to the risk of CHD.

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The aim of the present study to evaluate the impact of depression on ischemic heart disease to determine if clinical depression is an independent risk factor for incident coronary artery disease and to investigate the association between history of major depressive episode and presence of low-grade systemic inflammation as measured by serum C-reactive protein (CRP).

REVIEW OF LITERATURE

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ATHEROSCLEROSIS

AN INFLAMMATORY DISEASE

Since the "incrustation" hypothesis of von Rokitansky(٤٠) in ١٨٥٢ and "lipid" hypothesis of Virchow(٤١) in ١٨٥٦ there has been great interest in the pathogenesis of atherosclerosis. Increasingly, the atherosclerotic process is seen as the response of the vessel wall to chronic, low grade injury.(٤٢-٤٣) Initially there is dysfunction of the endothelium with accumulation of macrophages and lymphocytes subendothelially.(٤٤)

The earliest discernible lesion of atherosclerosis is the "fatty streak" which histologically is an aggregation of lipid laden macrophages and T cells within the intima.(٤٤) The presence of fatty streaks are almost universal in adults and are found in the coronary arteries of ٥٠% of children between ١٠ and ١٤ years of age.(٤٥-٤٦) These fatty streaks precede the development of more complex lesions composed of a fibrous tissue cap containing smooth muscle cells overlying a core of lipid and necrotic material. As the volume of the plaque increases, there is initially xidized g of the arterial wall, increasing the external vessel diameter and reducing the degree of luminal narrowing.(٤٧)Plaques within the coronary circulation remain clinically "silent" until either:

(١) The process of vessel wall xidized g is overwhelmed and there is sufficient plaque encroachment into the vessel lumen to cause symptoms, or

(٢) Rupture of the fibrous cap of the plaque occurs with subsequent thrombosis within the coronary artery sufficient to result in an acute coronary syndrome.

Within normal coronary arteries the circumferential wall stresses applied during the cardiac cycle are distributed evenly. In atherosclerotic segments of the vessel, due to the inelasticity of the fibrous cap of the plaque, considerable stress during systole is applied to relatively small focal areas of the cap.(٤٨)This increase in focal wall stress is increased where the cap is thin or uneven in thickness and in the absence of a high grade stenosis.

An in vitro study on human aortas has shown that fibrous caps which become infiltrated with macrophages lose mechanical strength and elasticity.(٤٩) Within the coronary vasculature, the immediate site of plaque

rupture or erosion has been found to be consistently marked by an inflammatory process at postmortem examination.(٥٠-٥١) Further postmortem data have demonstrated the presence of focal inflammatory cell infiltration within the fibrous caps of unruptured atherosclerotic plaques both within the coronary circulation and in peripheral vessels.(٥٢-٥٤)This infiltration is most commonly seen at the edge of the plaque ("shoulder region") which computer oxidized has shown to be the site of greatest systolic stress in eccentric plaques.(٥٤-٥٥) In an elderly population with a mean age of ٧٨ years, between ٣٠% and ٤٠% of the coronary plaques studied postmortem were found to have inflammatory cells within the fibrous cap and were considered to be at risk of rupture.(٥٣)

Coronary atherectomy specimens taken from patients with acute coronary syndromes have shown evidence of recent immune activation with increases in the proportion of active T lymphocytes present. (٥٦) Among patients with acute coronary syndromes, inflammatory markers have been found to have prognostic importance. Evidence for this was initially found among ٢٠ patients admitted to hospital with unstable angina. In those with an initial C reactive protein concentration greater than ٣.٠ mg/l (exceeding the ٩٠th centile of the normal distribution) there were more ischemic episodes and major adverse cardiac events on short term follow up than in those whose C reactive protein was below this level. (٥٧) The prognostic value of both C reactive protein and fibrinogen concentrations has since been confirmed in larger studies among patients with unstable angina and non-Q wave MI. (٥٨-٥٩)

These results suggest the possibility of risk stratification of patients admitted to hospital with acute coronary syndromes based on their inflammatory markers. A small study, which attempted to do this, followed up ٧٢ patients who were admitted to hospital with chest pain refractory to medical treatment. (٦٠) Because of the small number of patients, the end points taken in this study were evidence of transient myocardial ischemia and the presence of multivessel coronary disease or intra-coronary thrombus on angiography. No correlation was found between C reactive protein and these end point