Correlation Between Vascular Endothelial Growth Factor Level and The Severity of The Acute Thrombotic Events

Thesis Submitted by

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Correlation between Vascular Endothelial Growth Factor level and the severity of the acute coronary thrombotic events

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Abstract

Background: Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis. It is thought to be implicated in the pathogenesis of atherosclerosis and in atherosclerotic plaque neovascularization and thus promotes its infiltration by inflammatory cells which may trigger plaque destabilization.

Aim of the study: To investigate the level of VEGF in acute coronary syndrome patients and whether this level is higher than in control group and to determine whether this level is positively correlated with the severity of the disease and the short in-hospital prognosis or not.

Patients and methods: 78 patients (53 males & 25 females) their age ranged between 35 & 77 yrs with a mean age of 54.7±9 yrs were classified into***: Group 1***: 31 patients presented by unstable angina. ***Group 2***: 26 patients presented by non ST segment elevation infarction. Patients were furtherly divided according to the prior statin use into: ***1A***: statin treated patients in group 1 (16 patients***), 2A***: statin treated patients in group 2 (13 patients), ***1B***: non statin treated patients in group 1(15 patients) and ***2B***: non statin treated patients in group 2 (13 patients). ***Group 3***: 21 patients with no previous history of cardiac disease presented for chest pain evaluation & their results revealed normal coronary angiogram. All patients were subjected to 12-lead ECG, echocardiography, routine labs including cardiac biomarkers, Lipid profile, measurement of the serum VEGF by quantitative enzyme linked immunosorbant assay. Coronary angiograms were scored visually into: a severity score (0–3) defined the number of vessels with a luminal stenosis ≥50%. The severity and extent of CAD was graded using a modified Gensini score.

Results:

This study showed that the serum VEGF level was significantly higher in patients presented with either unstable angina or NSTEMI & were not previously treated with statin in comparison to control patients (357.5±142.8 & 257.0±146.7 vs 74.6±53.3 pg/L respectively, P < 0.001). And that the previously statin treated patients either in unstable angina or in NSTEMI groups had lower serum level of VEGF than controls (60.9±53.3 & 43.2±47.5 vs 74.6±53.3 pg/L respectively, P: 0.009). It also revealed that of the serum VEGF level did not differ between unstable angina patients and NSTEMI patients either in previously statin treated patients or in non previously statin treated patients (60.9±53.3 & 357.5±142.8 vs 43.2±47.5 & 257.0±146.7, pg/L, P value: 0.914 & 0.065) respectively.

When patients in both groups 1& 2 were stratified into 3 groups according to the serum level of VEGF , although there was a trend toward increase of number of coronary vessels affected in high VEGF level groups (1.92±0.76 vs 2.15±0.89 vs 2.21±1.03 in low, moderate and high VEGF groups respectively, there was no significant correlation between the serum level of VEGF and the coronary artery disease severity that assessed angiographicaly using modified Gensini score (9.16±4.81 vs 10.31±4.27 vs 9.79±5.02 in low, moderate and high VEGF groups respectively, P value: NS).

Recurrent ischemic attacks were significantly higher in patients with higher serum VEGF level compared with patients with low serum VEGF level (12.0 vs 38.5 vs 68.4% in patients with low, moderate and high VEGF respectively, p value: <0.001). Regarding development of heart failure, it occurred more in patients with higher serum VEGF level compared with patients with low serum VEGF level (12.0 vs 15.4 vs 36.8% in patients with low, moderate and high VEGF respectively, p value: 0.052).However was no significant correlation between arrhythmias or development of cardiogenic shock and the serum level of VEGF.

Conclusion: VEGF serum level is higher in non statin treated patients presenting with acute coronary syndrome and it may predict an adverse in-hospital prognosis but it was no correlation between VEGF serum level and angiographically defined disease severity.

Keywords: Vascular Endothelial Growth Factor level, acute coronary thrombotic events , NSTEMI

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Mohamed Hamdy

To
My Parents

Contents

List of Abbreviation

2D: 2 dimensions

ACC: American college of cardiology

ACS: Acute coronary syndrome

AHA: American heart association

ALT: Alanine transaminase

Ang.: Angiopoietin

APO B100: Apolipoprotein B100

APO E: Apolipoprotein E

AST: Aspartate transaminase

BBB: Bundle branch block

CABG: Coronary artery bypass graft

CAD: Coronary artery disease

CD: Clusters of differentiation

CD40L: Clusters of differentiation 40 ligand

Ck-MB: Creatine kinase MB isoform

CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines

CT: Computed tomography

CVD: Cardiovascular disease

DM: Diabetes mellitus

DNA: Deoxyribonucliec acid

ECG: Electrocardiogram

EF: Ejection fraction

ELISA: Enzyme linked immunosorbant assay

EPCs: Endothelial progenitor cells

FGF: Fibroblast growth factor

Flt. 1: fms-like tyrosine kinase

FS: Fractional shortening

G-CSF: Granulocyte colony stimulating factor

GP IIb/IIIa: Glycoprotein IIb/IIIa

Hb: Haemoglobin

HDL: High density lipoprotein

HIP: Hypoxia inducible protein complex

HIF: Hypoxia inducible factor

HS: Heparan sulphate

IHD: Ischemic hear disease

IL: Interleukin

iNOS: Inducible nitric oxide synthase

KDR: Kinase damain receptor

LDL: Low density lipoprotein

LV: Left ventricle

MI: Myocardial infarction.

MMPs: Matrix metalloporteinases

MRI: Magnetic resonant image

mRNA: Messenger ribonucliec acid

NAD(P)H: Nicotinamide adenine dinucleotide phosphate

Neu: Neuropilin

NFkB: Nuclear factor kappa B

NO: Nitric oxide

NOS: Nitric oxide synthase

NSTEMI: Non ST elevation myocardial infarction

PC: Prothrombin concentration

PCI: Percutaneous coronary intervention

PDGF: Platelet derived growth factor

PG: Proteoglycan

PIT: Pathologic intimal thickening

PLGF: Placental growth factor

Plt: Platelet

PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy

RBCs: Red blood cells

RTK: Receptor tyrosine kinase

SMC: Smooth muscle cell

STARS: STent Anti thrombotic Regimen Study

STEMI: ST elevation myocardial infarction

TGFβ: Transforming growth factor β

TGs: Triglyerides

TIMI: Thrombolysis in myocardial infarction

TLC: Total leucocytic count

TLRs: Toll like receptors

TNFα: Tumor necrosis factor-α

Tn: Troponin

UA: Unstable angina

VEGF: Vascular endothelial growth factor

VEGFR: Vascular endothelial growth factor receptor

VPF: Vascular permeability factor

VSMCs: Vascular smooth muscle cells

WHO: World health organization

WMSI: Wall motion score index

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Introduction

In coronary atherosclerosis, angiogenesis within the adventitia of arterial walls is seen in the development of plaques, and extends into the media and intima as the lesions progress. Furthermore, the expression of vascular endothelial growth factor (VEGF), an essential component in angiogenesis, has been positively correlated with the number of intimal blood vessels found within coronary atherosclerotic plaques. ***[Moulton KS 2001]***

Myocardial necrosis or ischemia can trigger a response to improve myocardial perfusion by the formation of new capillaries (angiogenesis) and by the enlargement of preexisting collateral vessels (arteriogenesis). Both angiogenesis and arteriogenesis are highly regulated processes that require the orchestrated interaction of endothelial cells, extracellular matrix, and surrounding cells mediated by a cascade of growth factors, their receptors, and intracellular signals. ***[Helisch A, et al, 2003 & Yancopoulos GD, et al, 2000]***

Vascular endothelial growth factor (VEGF), a highly specific mitogen for endothelial cells, is a key regulator of angiogenesis. An ever growing interest has been focused to this growth factor because it is thought to be implicated in the pathogenesis of atherosclerotic plaque progression as it was suggested that VEGF mediates atherosclerotic plaque neovascularisation and thus promotes its infilteration by inflammatory cells. These events, through a complex mechanism trigger plaque destabilization. ***[Mofidi R, et al, 2001]***

VEGF acts via two tyrosine kinase receptors, VEGF receptor -1 and VEGF receptor -2, Biological response mediated by the activation of these two receptors are somewhat different, the activation of VEGFR-2 induce cell proliferation, while activation of VEGFR-1 does not. ***[Neufeld G, et al, 1999]***

Thus VEGF plays a key role in the cascade of angiogenesis, which is considered to promote plaque progression and destabilization. ***[Gille H, et al, 2001 & Carmeliet P, et al, 2000]*** Nonetheless VEGF mRNA, protein, and its receptors' expression can be rapidly upregulated in the myocardium within minutes of ischemia (or hypoxia) ***[Hashimoto E, et al, 1994]***

Plasma concentrations of VEGF and a soluble form of its receptor are quantifiable by an enzyme linked immunosorbent assay (ELISA). Plasma concentrations of both VEGF and a soluble form of its receptor may be abnormal in patients with coronary artery disease and peripheral vascular disease. Raised concentrations of VEGF have also been found in patients with risk factors for coronary artery disease, such as hypertension and hyperlipidaemia, but with no clinically overt disease. ***[Chung NA, et al, 2003, Belgore FM, et al, 2001, Roller RE, et al, 2001 & Ogawa H, et al, 2000]***

On the basis of the reported data it may be expected that it maybe positive correlation between the level of VEGF level and manifestations of complicated destabilized coronary atherosclerotic plaque.

Aim of work

- To investigate the level of the vascular endothelial growth factor in patients presented with non ST elevation acute coronary syndrome and to determine whether this level is higher than in the control group.

- To determine whether this level is positively correlated to the severity of the disease and the short in-hospital prognosis or not.

Chapter I

Acute Coronary Thrombotic Events

Introduction:

Heart disease is the major cause of death in the United States and many of other countries. Many patients with heart disease present at the hospital with an acute coronary syndrome (ACS) and many of them face a significant risk of morbidity and death. Although timely and appropriate treatment reduces the risk of an immediate or subsequent poor outcome, the high prevalence of risk factors for coronary artery disease (CAD) ensures that the prevalence of future ACS will also remain high. ***[Rogers WJ, et al, 2000]***

Theories of atherosclerotic plaque formation have changed, such that cholesterol is no longer the lone culprit in CAD. Cellular signaling associated with inflammation is increasingly implicated in the initiation and progression of atherosclerotic plaques. Atherosclerotic plaques have been shown to develop early in life and remain subclinical for years or decades, depending on the accelerating effects that risk factors and genetic predisposition to CAD will have on disease progression. ***[Rogers WJ, et al, 2000]***

This chapter reviews the epidemiology, pathophysiology, and different clinical presentation and classification of ACS and identifies areas of need that, if addressed, may help to reduce the high rate of morbidity and mortality in patients presenting acute coronary syndrome.