Relation of Serum Leptin Levels and Acute Coronary Syndrome and Its Role in the Prediction of Future Cardiovascular Events.

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Abbreviations	Acronyms
%	Percentage
α-MSH	α-Melanocyte-Stimulating Hormone
ACS	Acute Coronary Syndrome
AgRP	Agoutirelated Peptide
ALT	Alanine Transferase
ANOVA	Analysis of Variance
apo B	Apolipoprotein B
BMI	Body Mass Index
BNP	Brain Natriuretic Peptid
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCK	Cholecystokinin
CCU	Coronary Care Unit
CHD	Coronary Heart Disease
CKMB	Creatine Kinase Myocardial Band
CRP	C – Reactive Protein
CSF	Cerebrospinal Fluid
CTA	Computed Tomographic Angiography
cTn	Cardiac Troponin T
CVEs	Cardiovascular Events
ECG	Electrocardiogram
EF	Ejection Fraction

ELISA	Enzyme-Linked Immunosorbent Assay
FMD	Flow Mediated Dilation
GP	Glycoprotein
GWASs	Genome-Wide Association Studies
HDL-C	High-Density Lipoprotein Cholesterol
HPA	Hypothalamic Pituitary Axis
HuGE	Human Genome Equivalent
IHD	Ischemic Heart Disease
IGF-I	Insulin-Like Growth Factor type I
IL	Interleukin
IVUS	Intravascular Ultrasound
JAK	Janus kinase
LBBB	Left Bundle Branch Block
LDL-C	Low-Density Lipoprotein Cholesterol
LEPR	Leptin Receptor
Lp(a)	Lipoprotein(a)
Lp-PLA2	Lipoprotein-Associated Phospholipase A2
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MTHFR	Methylene Tetrahydrofolate Reductase
n	Number
NPY	Neuropeptide Y
NSTE-ACS	Non ST segment Elevation Acute Coronary Syndrome
NSTEMI	Non ST-Elevation Myocardial Infarction
OCT	Optimal Coherence Tomography
PAI-1	Plasminogen Activator Inhibitor-1

PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein convertase, Subtilisin/kexin-9
PI3K	Phosphatidylinositide 3-kinases
POMC	Pro-opiomelanocortin
PPARG	Peroxisome Proliferator-Activated Receptor Gamma
PPY-36	Peptide YY-36
RWMA	Resting Wall Motion Abnormalities
SAP	Stable Angina Pectoris
SD	Standard Deviation
sICAM-1	Intercellular Adhesion Molecule
SIHD	Stable Ischemic Heart Disease
SNPs	Single-Nucleotide Polymorphisms
SST2	Somatostatin Receptor 2
STAT	Signal Transducer and Activator of Transcription
STEMI	ST-Elevation Myocardial Infarction
TCFA	Thin-Cap Fibroatheroma
THC	Tetrahydrocannabinol
t-PA	Tissue Plasminogen Activator
TTE	Transthoracic Echocardiography
UA	Unstable Angina
URL	Upper Reference Level
WMSI	Wall Motion Score Index

Abstract

Coronary artery disease is a major cause of death worldwide. Acute coronary syndrome includes unstable angina, non-ST segment elevation myocardial infarction and ST segment elevation myocardial infarction.

By activating immune cells or a direct action on the vascular wall, leptin may affect the initiation and progression of atherosclerosis. We investigated whether plasma leptin concentration is associated with coronary artery disease, with particular focus on the relationship between plasma leptin and the development of an acute coronary syndrome. Plasma leptin was measured in 50 patients with acute coronary syndrome. Their results were compared with those of 50 matched controls.

Plasma leptin levels were significantly higher in the acute coronary syndrome group compared to the controls (4.8 vs. 4.5 ng/mL, $P = 0.001$). These findings suggest that plasma leptin levels may be a useful marker of systemic inflammation, and measurement of plasma leptin may be helpful in assessing the risk of developing coronary heart disease. In patients with acute coronary syndrome, significant elevation of discharge leptin levels compared to admission levels was invariably associated with adverse in-hospital outcome compared to patients who did not experience this outcome (5.93 from 5.88 vs. 4.47 from 5.63 ng/dL, $P = 0.032$). Elevation of the follow up leptin levels compared to the discharge levels in patients who had short-term cardiovascular events, although was not statistically significant, could also be a risk for having short-term CVEs (4.9 from 4.4 vs. 4.5 from 5.9, $P = 0.61$). So leptin connotes a poor prognosis with excess morbidity and mortality.

Key Words:

Acute coronary syndrome, Leptin, Coronary artery disease.

Introduction

Discovered in 1994, leptin is the product of the obesity (ob) gene and is a 16-kDa hormone with pleiotropic actions in multiple organ systems. There is increasing interest in the potential role of leptin in the cardiovascular system, as accumulating evidence suggests that leptin is involved in insulin sensitivity, angiogenesis, vascular and endothelial function, and myocyte proliferation [1]. Thus, examination of leptin signaling may provide insight into the complex relationship to cardiovascular disease.

Consistent with this idea are the results of two nested case-referent studies indicating that leptin might be a risk factor for myocardial infarction (MI) and stroke [2, 3]. In a large prospective study of leptin and cardiovascular risk, which utilized the West of Scotland Coronary Prevention Study (WOSCOPS) population, leptin was found to be a modest independent predictor of coronary events during a five-year follow-up period [4].

In another large prospective study, plasma leptin level was an independent predictor of cardiovascular events among patients with coronary atherosclerosis confirmed by angiography. The only variables positively correlated with the combined end point were leptin and number of coronary vessels with significant stenoses. The prognostic association of increased serum leptin level was likely due to factors such as increased sympathetic activity, enhanced platelet aggregation, or increased oxidative stress [5].

Hence, the correlation of serum leptin level with the advent of acute coronary syndromes and the predictive ability of leptin level for the occurrence of future coronary events needs further studying……

Aim of the work

This study is conducted to estimate serum leptin levels in patients admitted with acute coronary syndrome compared to healthy matched controls, to correlate this level and the in-hospital outcome regarding morbidity and mortality, and also to evaluate the predictive power of serum leptin for the short-term cardiovascular events (CVEs).

Chapter 1:

Review of Literature

Acute Coronary Syndrome

BACKGROUND

Definitions

Coronary artery disease (CAD) is the single most common cause of death in the developed world, responsible for about one in every six deaths. In 2010, out of 52.7 million deaths worldwide, approximately 15.6 million were due to cardiovascular disease [6].

CAD has been classified as stable ischemic heart disease (SIHD), acute coronary syndromes, and sudden death. CAD may present clinically in many ways, extending from an asymptomatic finding to unexpected cardiac collapse. SIHD is always secondary to coronary atherosclerosis, leading to mismatch of coronary blood flow and adenosine triphosphate homeostasis (imbalance of supply and demand) and a stable pattern of coronary ischemia. The clinical pattern includes stable angina pectoris and myocardial hibernation [7].

ACUTE CORONARY SYNDROMES

Acute coronary syndrome (ACS) is a unifying term representing a common end result, acute myocardial ischemia. Acute ischemia is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis and is associated with an increased risk of cardiac death and myonecrosis [8]. It encompasses acute MI (resulting in ST-segment elevation or non–ST-segment elevation) and unstable angina. Recognizing a patient with ACS is important because the diagnosis triggers both immediate triage and management [9].

Because NSTEMI and UA are indistinguishable at initial evaluation and the entity of UA is receding as the sensitivity of biomarkers of myocardial injury increases, they are often described together as NSTE-ACS. Features that help

differentiate ACS from stable angina are (1) onset of symptoms at rest (or with minimal exertion) and lasting longer than 10 minutes unless treated promptly; (2) severe, oppressive pressure or chest discomfort; and (3) an accelerating pattern of symptoms that develop more frequently, occur with greater severity, or awaken the patient from sleep. Symptoms alone do not suffice to distinguish the three types of ACS from one another. Patients without persistent (>20 minutes) ST-segment elevation in two or more contiguous leads but with biomarker evidence of myocardial necrosis are classified as having NSTEMI, whereas in patients without such evidence of myocardial necrosis, UA is diagnosed—a condition generally carrying a better prognosis [10].

Clinical diagnosis of MI requires a clinical syndrome indicative of myocardial ischemia with some combination of evidence of myocardial necrosis on biochemical, electrocardiographic, or imaging modalities. Cardiac professional societies have jointly established updated criteria for the diagnosis of MI (**Table-1**) [11]. These revisions to the definition of MI and a shift to more sensitive biomarkers of myocardial injury have important implications not only for the clinical care of patients but also for epidemiologic study, public policy, and clinical trials [12, 13].

Table 1: Universal Definition of Myocardial Infarction

Criteria for Acute Myocardial Infarction

The term *acute MI* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any of the following criteria meet the diagnosis for MI:

- Detection of a rise and/or fall in cardiac biomarker values (preferably Cardiac troponinT (cTn)), with at least one value above the 99th percentile of the upper reference level (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment T wave (ST-T) changes or new LBBB
  - Development of pathologic Q waves on the ECG

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

- **Cardiac death** with symptoms suggestive of myocardial ischemia and presumed new ischemic changes on the ECG or new LBBB but death occurred before cardiac biomarkers were determined or before cardiac biomarker values would be increased.
- **PCI-related MI** is arbitrarily defined by elevation of cTn values (to >5 × the 99th percentile of the URL) in patients with normal baseline values (≤99th percentile of the URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.reference
- **Stent thrombosis** associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall in cardiac biomarker values and at least one value higher than the 99th percentile of the URL.
- **CABG-related MI** is arbitrarily defined by elevation of cardiac biomarker values (to >10 × the 99th percentile of the URL) in patients with normal baseline cTn values (≤99th percentile of the URL). In addition, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.

Criteria for Previous Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathologic Q waves with or without symptoms in the absence of nonischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a nonischemic cause
- Pathologic findings of previous MI

CABG = coronary artery bypass grafting; cTn = cardiac troponin; LBBB = left bundle branch block; URL = upper reference limit. *From Thygesen K, Alpert JS, White HD, et al: Universal definition of myocardial infarction. J Am Coll Cardiol 60:1581, 2012.*