Apolipoprotein B/A-I Ratio in Diabetic Patients with Acute Coronary Syndrome - The Importance and Predictive Value

Thesis

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in Cardiology

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AIM OF THE WORK

- To study the risk ratio of Apolipoprotein B/A-I in type 2 diabetic patients with ACS as compared to such a ratio in diabetic patients with stable ischemic coronary artery disease.

- To study the risk ratio of Apolipoprotein B/A-I in type 2 diabetic patients as compared to conventional lipid profile in both group.

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LIST OF ABBREVIATIONS

NRH	Nodular regenerative hyperplasia
FNH	Focal Nodular Hyperplasia
HA	Hepatocellular Adenoma
HCC	Hepatocellular carcinoma
FHCC	Fibrolamellar Variant of HCC
IHE	Infantile Hemangioendothelioma
AML	Angiomyolipoma
EHE	Epithelioid hemangioendothelioma
HB	Hepatoblastoma
IPT	Inflammatory Pseudotumor
SE	Spin echo sequence
GRE	Gradient recalled echo sequence
FOV	Field of View
STIR	Short T1 inversion recovery
FLAIR	Fluid attenuated inversion recovery
MAST	Motion artifact suppression technique
FLASH	Fast Low-Angle Shot
GRASS	Gradient-Recalled Acquisition in the steady state
HASTE	Half Fourier Acquisition Single Shot Turbo Spin Echo
VIBE	Volumetric Interpolated Breath-Hold Examination
FIRM	Fast inversion-recovery motion-insensitive
DWI	Diffusion-weighted Imaging
SENSE	Sensitivity Encoding
SMASH	Simultaneous Acquisition of Spatial Harmonics
Gd-DTPA	Gadopentate dimeglumine
Gd-DTPA-BMA	Gadodiamide
Gd-DOTA	Gadoterate meglumine
Gd-HP-DO3A	Gadoteridol
Gd-BOPTA	Gadobenate dimeglumine
Gd-EOB-DTPA	Gadoxetic acid(Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid)
Mn-DPDP	Mangafodipir trisodium
CMC-001	Copenhagen Malmö Contrast
SPIO	Superparamagnetic iron oxide
USPIO	Ultrasmall superparamagnetic iron oxide
VSOP-C184	Very small SPIO particle, citrate coating, 184th formulation

INTRODUCTION

Worldwide, cardiovascular diseases are estimated to be the leading cause of death and disability. Although age adjusted cardiovascular death rates have declined in several developed countries in past decades, rates of cardiovascular disease have raised greatly in low income and middle income countries. ***(Salim et al, 2004)***

Acute coronary syndromes (ACS) can be defined as a triad of clinical presentation: a history of coronary artery disease, electrocardiographic changes and biochemical cardiac markers. Patients presenting with ACS can be divided into those with ST elevation myocardial infarction (STEMI), new left bundle branch block (LBBB), non ST elevation myocardial infarction (NSTEMI) or unstable angina (UA). ***(Topol and Eric, 2007)***

Estimation of cardiovascular risk has become the cornerstone of cardiovascular diseases' prevention. Although atherogenesis is a multi-factorial process, abnormalities in lipoprotein metabolism are one of the key factors, representing around 50% of the population-attributable risk of developing cardiovascular disease. ***(Jesus et al, 2009)***

Despite of the considerable progress made in cardiovascular disease management in recent decades, there is almost unanimous agreement among epidemiologists and clinicians that coronary risk assessment based exclusively on low density lipoprotein (LDL) is not optimal particularly in individuals at intermediate risk. And efforts have been made

for seeking emergent of new cardiovascular risk factors to improve cardiovascular disease prediction. ***(Jesus et al, 2009)***

Indices such as total cholesterol/HDL, LDL/HDL and apolipoprotein B/A-I ratios are considered to be more powerful predictors (especially apolipoprotein B/A-I ratio) of IHD than plasma LDL and HDL alone. ***(Benoit et al, 1996)***

Apolipoprotein B and apolipoprotein A-I are the main structural proteins of atherogenic lipoproteins and HDL particles, respectively. Apolipoprotein B levels reflect the entire spectrum of pro-atherogenic particles, including very low density, intermediate density, and low density lipoproteins, whereas LDL levels do not reflect theses indices. Apolipoprotein B levels also provide a good measure of the number of LDL particles, which reflects the atherogenicity of LDL. On the other hand, apolipoprotein A-I is more important than HDL cholesterol content for biochemical pathways that make HDL antiatherogenic. ***(Wim et al, 2007)***.

Apolipoprotein B/A-I ratio reflects the balance between two completely opposite processes: transport of cholesterol to peripheral tissues with its subsequent arterial internalization and reverse transport to the liver. The greater the ratio, the larger will be the amount of cholesterol from atherogenic lipoproteins circulating through the plasma compartment and likely to induce endothelial dysfunction and trigger the atherogenic process. On the other hand, a lower apolipoprotein B/A-I ratio will lead to less vascular aggression by plasma cholesterol and increased and more effective reverse transport of cholesterol, as well as other beneficial effects, thereby reducing the risk of cardiovascular disease. ***(Jesus et al, 2009)***.

At present, plasma apolipoprotein B and A-I levels have been described as better predictors of atherosclerotic diseases than lipid and lipoprotein concentrations. It has been also suggested that the apolipoprotein B/A-I ratio represents a superior parameter for predicting cardiovascular risk as compared with other lipid ratios, such as total cholesterol/HDL, LDL/HDL and non-HDL cholesterol/HDL. ***(Luciana et al, 2006)***.

ISCHEMIC HEART DISEASES

Definitions:

Ischemic heart disease (IHD) is a state of an imbalance between oxygen supply and demand in the heart. It is mainly caused by atherosclerosis. Since atherosclerosis can be well progressed before symptoms are felt, angina pectoris is usually the first symptom. ***(Selwyn et al, 1992)***

Coronary Artery Disease (CAD) is narrowing of the coronary arteries sufficiently to prevent adequate blood supply to the myocardium. The narrowing is usually caused by atherosclerosis. ***(Wexler et al, 1996)***

Epidemiology:

The incidence of angina, acute myocardial infarction and the major clinical manifestations of CHD that were assessed epidemiologically varies according to risk factors, age, gender, and ethnicity at the individual level and among countries, regions, and social strata within countries at the population level and it has varied markedly over time. ***(Tyroler, 2000)***

Mortality rates:

Coronary heart disease is the most common cause of death and premature death in the UK. There are 94,000 deaths from CHD in the UK each year. 1 in 5 men and 1 in 7 women die from CHD. ***(Willacy, 2010)***

Morbidity rates:

About 4% of men and 0.5% of women in the UK have had coronary heart disease. Prevalence increases with age being higher in men. There are about 52,000 new cases of angina per year in all men living in the UK and about 43,000 new cases in women. The average incidence of myocardial infarction is 600 per 100,000 in men aged 30-69 and 200 per 100,000 in women. The incidence increases with age. ***(Willacy, 2010)***

The prevalence of ischemic heart diseases is higher in lower socioeconomic groups. And its mortality is falling but morbidity appears to be rising. ***(Willacy, 2010)***

Risk Factors:

A cardiovascular risk factor is a condition that is associated with an increased risk of developing cardiovascular disease. The association is almost always a statistical one and so the fact that a particular person has a particular factor merely increases the probability of developing a certain type of cardiovascular disease. It does not mean that he or she is certain to develop heart or blood vessel disease. ***(Barry et al, 1992)***

Over 300 risk factors have been associated with coronary heart disease and stroke (Table 1). The major established risk factors meet three criteria: a high prevalence in many populations, a significant independent impact on the risk of coronary heart disease or stroke and their treatment and control result in reduced risk. ***(WHO website, 2002)***

Table 1: WHO classification of cardiovascular Risk Factors according to its implication and modifiability *(WHO website, 2002)*

Major modifiable risk factors	
• **High blood pressure** Major risk for heart attack and the most important risk factor for stroke. • **Abnormal blood lipids** High total cholesterol, LDL-cholesterol and triglyceride levels, and low levels of HDL-cholesterol increase risk of coronary heart disease and ischaemic stroke. • **Tobacco use** Increases risks of cardiovascular disease, especially in people who started young, and heavy smokers. Passive smoking an additional risk. • **Physical inactivity** Increases risk of heart disease and stroke by 50%.	• **Obesity** Major risk for coronary heart disease and diabetes. • **Unhealthy diets** Low fruit and vegetable intake is estimated to cause about 31% of coronary heart disease and 11% of stroke worldwide; high saturated fat intake increases the risk of heart disease and stroke through its effect on blood lipids and thrombosis. • **Diabetes mellitus** Major risk for coronary heart disease and stroke.
Other modifiable risk factors	
• **Low socioeconomic status (SES)** Consistent inverse relationship with risk of heart disease and stroke. • **Mental ill-health** Depression is associated with an increased risk of coronary heart disease. • **Psychosocial stress** Chronic life stress, social isolation and anxiety increase the risk of heart disease and stroke.	• **Alcohol use** One to two drinks per day may lead to a 30% reduction in heart disease, but heavy drinking damages the heart muscle. • **Use of certain medication** Some oral contraceptives and hormone replacement therapy increase risk of heart disease. • **Lipoprotein(a)** Increases risk of heart attacks especially in presence of high LDL-cholesterol. • **Left ventricular hypertrophy (LVH)** A powerful marker of cardiovascular death.
Non-modifiable risk factors	
• **Advancing age** Most powerful independent risk factor for cardiovascular disease; risk of stroke doubles every decade after age 55. • **Heredity or family history** Increased risk if a first-degree blood relative has had coronary heart disease or stroke before the age of 55 years (for a male relative) or 65 years (for a female relative).	• **Gender** Higher rates of coronary heart disease among men compared with women (premenopausal age); risk of stroke is similar for men and women. • **Ethnicity or race** Increased stroke noted for Blacks, some Hispanic Americans, Chinese, and Japanese populations. Increased cardiovascular disease deaths noted for South Asians and American Blacks in comparison

Taking action that modifies a risk factor does not necessarily imply that the probability of a heart disease or stroke will be eliminated. Furthermore, when a strong risk factor is present, treating it even if the treatment is very effective does not necessarily mean that the risk is reduced. Fortunately, treatment of the major risk factors (smoking, high blood pressure, and elevated cholesterol) has been shown to reduce the possibility of a heart attack. ***(Barry et al, 1992)***

Some major risks are modifiable in that they can be prevented, treated, and controlled. There are considerable health benefits at all ages, for both men and women, in stopping smoking, reducing cholesterol and blood pressure, eating a healthy diet and increasing physical activity. ***(Barry et al, 1992)***

Risk factors for cardiovascular disease are now significant in all populations. In the developed countries, at least one-third of all CVD is attributable to five risk factors: tobacco use, alcohol use, high blood pressure, high cholesterol and obesity (Figure 1). ***(WHO website, 2002)***

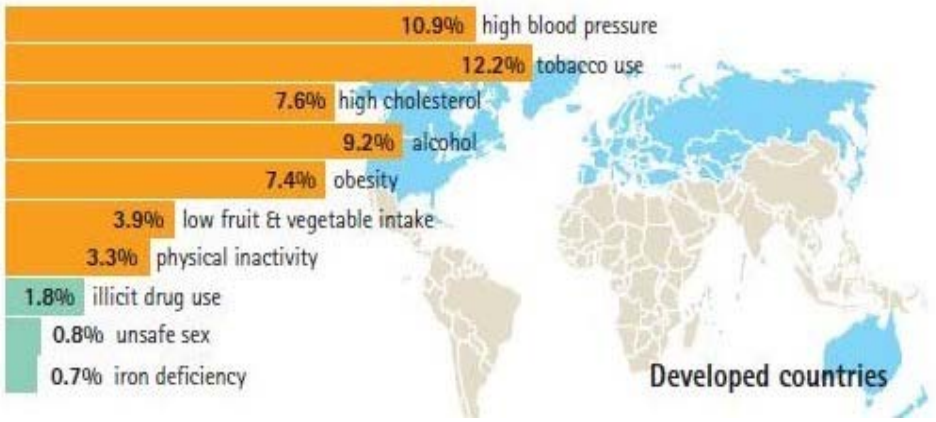

Figure 1: Main risk factors in developed countries ***(WHO website, 2002)***

In developing countries with high mortality rates, such as those in sub-Saharan Africa (e.g. Egypt), high blood pressure, high cholesterol, tobacco and alcohol use, as well as low vegetable and fruit intake, already figures among the top risk factors (Figure 2). ***(WHO website, 2002)***

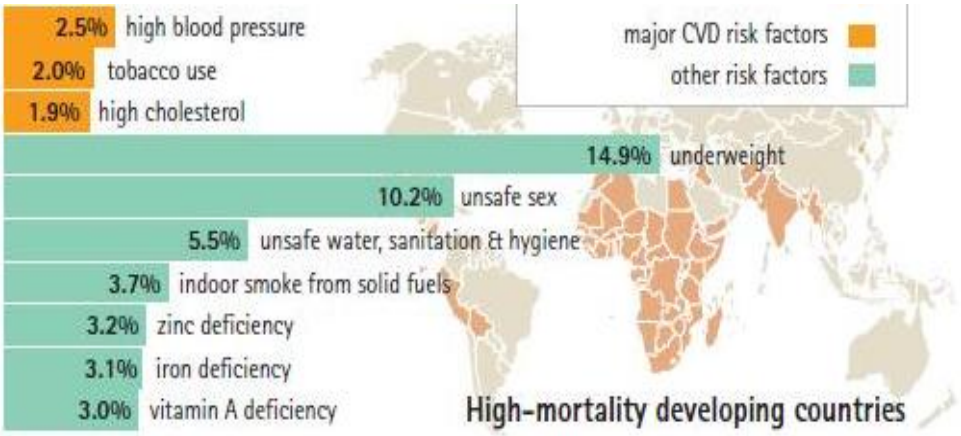

Figure 2: Main risk factors in developing countries with high mortality rates. ***(WHO website, 2002)***

1) Male gender:

Cardiovascular disease, which includes coronary artery disease, cerebrovascular disease and congestive heart failure, is one area of population health where gender impacts significantly on health and disease outcomes. ***(Weiss, 2009)***

Men are more likely than women to develop coronary heart disease, stroke and other cardiovascular diseases that are manifestations of atherosclerosis. Whether this is because male hormones increase the risk or because female hormones protect against atherosclerosis is not completely understood. It is likely that both play a role, but that the protective role of

estrogens is the predominant factor. This seems to be supported by the fact that heart disease risk for women rises dramatically after menopause. ***(Barry et al, 1992)***

Female sex is associated with higher in-hospital mortality, while long term mortality is low without difference between the two genders. ***(Sederholm et al, 2010)***

The reasons for high case fatality and poor outcomes in women include a later age of onset of the disease, suboptimal treatment and psychological factors, such as depression and anxiety. ***(Hayes, 2006)***

Some studies have suggested that much of the difference in life expectancy can be explained by the fact that more men than women smoke cigarettes. As more teenage girls are starting to smoke than are teenage boys, this advantage may disappear. So, women may soon have as much coronary heart disease and other complications of cigarette smoking as do men or more. ***(Barry et al, 1992)***

2) Old age:

In many epidemiologic surveys, age remains one of the strongest predictors of disease. More than half of those who have heart attacks are 65 or older and about four out of five who die of such attacks are over age 65. ***(Barry et al, 1992)***

An increase in risk factor levels was associated with the age related increase in CHD incidence and mortality in both sexes but to a larger extent in women. ***(Jousilahti et al, 1999)***