Correlation between on admission serum uric acid level and corrected TIMI frame count, Myocardial Blush Grade in patients with STEMI undergoing primary PCI

Thesis

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بسم الله الرحمن الرحيم

وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ والْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ اللهِ
عَلَيْكَ عَظِيمًا

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List of Abbreviations

Abb.	Full word
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CK	Cereatine Kinase
COX	Cyclo-Oxygenase Enzyme
CTFC	Corrected TIMI Frame Count
CVD	Cardio-Vascular Disease
DAPT	Dual Anti-Platelet Therapy
DES	Drug Eluting Stent
DM	Diabetes Mellitus
ECG	Electrocardiography
GFR	Glomerular Filteration Rate
GRACE	Global Registry of Acute Coronary Events
HIT	Heparin Induced Thrombocytopenia
HTN	Hypertension
IABP	Intra Aortic Balloon Pump
IRA	Infarct Related Artery
LBBB	Left Bundle Branch Block
LV	Left Ventricle
MACE	Major Adverse Cardiac Events

List of Abbreviations **(Cont...)**

Abb.	Full word
MAPK	Mitogen Activated Protein Kinase
MBG	Myocardial Blush Grade
MCP	Monocyte Chemo-attractant Protein
MI	Myocardial Infarction
NO	Nitric Oxide
OAT	Occluded Artery Trial
PCI	Percutaneous Coronary Intervention
PDGF	Platelet Derived Growth Factor
SCD	Sudden Cardiac Death
STEMI	ST-Elevation Myocardial Infarction
TFC	TIMI Frame Count
TFG	TIMI Flow Grade
TIMI	Thrombolysis In Myocardial Infarction
TXA2	Thromboxane A2
UFH	Un Fractionated Heparin
URL	Upper Reference Limit
VF	Ventricular Fibrillation
Vs	Versus

INTRODUCTION

Acute Myocardial Infarction (MI) is one of the most predominant causes of mortality worldwide ***(Antman et al., 2008)***. ST-elevation Myocardial Infarction (STEMI) remains the principle cause of death in developed countries ***(De Luca et al., 2008)*.**

Rapid restoration of Infarct Related Arterial (IRA) flow is associated with improved ventricular performance and lower mortality among patients with myocardial infarction ***(Kaya et al., 2005)*.**

Primary interventions used to treat STEMI in its acute phase are thrombolytic and Percutaneous Coronary Intervention (PCI). While both are effective, research indicates a significant benefit of using PCI as the primary reperfusion therapy over fibrinolytics in acute myocardial infarction ***(Eckstein et al., 2009).*** Furthermore, analysis of the multinational Global Registry of Acute Coronary Events (GRACE) has shown that an increasing use of primary PCI combined with decreased use of thrombolytics is associated with improved short-term outcomes, resulting in less recurrent ischemia and angina, less cardiogenic shock, and a decreased length of stay ***(Nallamothu et al., 2007; Concannon et al., 2010).*** However, poor arterial flow and no reflow phenomena may limit the benefits of recanalization of the IRA ***(Ito et al., 1999)*.**

Several biomarkers are associated with poorer outcomes in STEMI ***(Hong et al., 2009).*** Uric acid is one of those markers and it has been shown as an independent risk factor for cardiovascular events and coronary artery diseases ***(Culleton et al., 1999).***

Uric acid is produced by the enzymatic activity of xanthine oxidase and is the final product of purine metabolism ***(Wasserman et al., 2010)***. Xanthine oxidase produces oxidants and oxygen free radicals in this process that may have a role in cardiovascular disease. Some studies suggested that uric acid can cause intracellular stress and inflammation leading to endothelial injury and enhancement of vasoconstrictor effects ***(Basar et al., 2011).***

It has been shown that coronary flow reserve - a marker of coronary microvascular function - is significantly greater in patients with lower serum uric acid concentration ***(Erdogan et al., 2006).***

It has been also demonstrated that high serum uric acid level is associated with slow coronary flow in patients underwent elective angiography ***(Yildiz et al., 2007)*** but little is known regarding the association of uric acid level with coronary blood flow in the setting of STEMI.

Reperfusion can be assessed using angiographic (Thrombolysis in Myocardial Infarction) [TIMI] flow grade, Corrected TIMI Frame Count [CTFC] or Myocardial Blush Grade [MBG] ***(Gibson and Schömig, 2004).***

The conventional (TIMI) flow grade classification scheme has been a valuable tool to compare angiographic and clinical outcomes after thrombolysis ***(The GUSTO Investigators, 1993).*** However, this classification scheme is limited by interobserver variability, its limited statistical power, and the fact that nonculprit flow (used to gauge TIMI grade 3 flow) is abnormal. So, TIMI Frame Count (TFC) and Myocardial Blush Grade (MBG) are more accurate ***(Gibson et al., 1999)***.

TFC is defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel. The number is expressed based upon a cinefilming rate of 30 frames/ second. Thus, a frame count of 30 would mean that 1 second was required for dye to traverse the artery, the TIMI Frame Count is counted using an electronic frame counter. Selected anatomic endpoints (landmarks) are used for the analysis.

The angiographic Myocardial Blush Grade is based on the visually assessed contrast density in the infarcted myocardium after reperfusion therapy. This information can be obtained during routine high-quality coronary angiography ***(Dodge et al., 1988)*.**

AIM OF THE WORK

The study aim is to determine the association between serum uric acid levels on admission and coronary blood flow following primary PCI among patients presented with STEMI.

Chapter 1

Uric Acid

Uric acid is a final product of purine metabolism by the enzymatic activity of Xanthine Oxidase ***(Wu et al., 1992)***.

Hyperuricemia is defined as serum uric acid level > 7.0 mg/dL in men and >6.0 mg/dL in women ***(Enomoto et al., 2002)***. In adults, serum uric acid levels vary with height and body weight ***(Nishioka et al., 1980)***. It is also influenced by the rate of production due to high protein diets, alcohol consumption or conditions with high cell turnover ***(Gutman et al., 1952)*** and the rate of elimination ***(Steele, 1971)***. The changing level of serum uric acid concentration in women at menopause suggests an interaction with sex hormones ***(Levine et al., 1989).***

The association between uric acid and Cardiovascular Diseases (CVD) was largely ignored until the mid-1950s and early 1960s, when it was rediscovered ***(Cannon et al., 1966; Gertler et al., 1951)***. Since then, a number of epidemiologic studies have reported a relation between serum uric acid levels and a wide variety of cardiovascular conditions, including hypertension ***(Cannon et al., 1966)***, metabolic syndrome ***(Ford et al., 2007)***, coronary artery disease ***(Tuttle et al., 2001)***, and cerebrovascular diseases. The relation between uric acid and cardiovascular disease is observed not only with frank

hyperuricemia, but also with uric acid levels considered to be in the normal to high range (>5.2 to 5.5 mg per deciliter) ***(Feig et al., 2003; Nakagawa et al., 2005; Niskanen et al., 2004)***. Nevertheless, debate arose from early times whether uric acid is an independent predictor of CVD or not. This controversy caused uric acid to be no longer regarded as a true CV risk factor ***(Culleton, 2001)***. However, epidemiological studies have revealed that uric acid concentrations predict the progression of chronic kidney disease ***(Kang et al., 2002)***, the development of stroke ***(Kim et al., 2009)***, and a recent meta-analysis reported that uric acid is associated with the presence of hypertension ***(Grayson et al., 2011)***, diabetes ***(Kodama et al., 2009)***, and metabolic syndrome ***(Nakagawa et al., 2006)***.

Conflicting information has put forward that uric acid could be a prognostic marker of CV events including myocardial infarction, heart failure, stroke, and death ***(Strasak et al., 2008)***. Finally, in patients with heart failure there is significant confirmation that elevated uric acid levels predict an increase in morbidity and mortality both in acute and chronic heart failure patients ***(Thanassoulis et al., 2010)***.

Recent evidence has emerged in parallel suggesting that uric acid is an inflammatory factor that also plays a role in endothelial dysfunction. Thus, uric acid can induce proinflammatory changes in the adipocyte similar to those observed in the prediabetic subject ***(Sautin et al.,***

2007). Finally, most of these trials suggested that cardiorenal effects of uric acid are due to its intracellular effects ***(Schlesinger, 2004)***, unlike gout and stones.

Uric acid is increased in Subjects at Cardiovascular Risk:

Serum uric acid is frequently elevated in subjects at cardiovascular risk. Uric acid is higher in men and postmenopausal women because estrogen is uricosuric ***(Galvan et al., 1995)***. In subjects with obesity, insulin resistance and dyslipidemia (Metabolic Syndrome), hyperuricemia frequently occurs because insulin stimulates sodium and urate reabsorption in the proximal tubule ***(Galvan et al., 195)***. Uric acid is increased in subjects with renal disease as the result of reduction in Glomerular Filteration Rate (GFR) and renal urate excretion. Diuretics such as thiazides increase serum uric acid by stimulating both sodium and urate reabsorption in the proximal tubule. Alcohol intake results in elevated uric acid levels due to increased urate generation (from increased adenine nucleotide turnover) and decreased excretion (due to lactate blocking tubular transport of urate) ***(Faller et al., 1982; Lieber et al., 1962)***.

Uric acid is also commonly associated with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension ***(Cannon et al., 1966).*** The increase in