Mean Platelet Volume: Relation to Glycemic Control and Cardiovascular Complications in Patients with Type 2 Diabetes Mellitus

Thesis

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by

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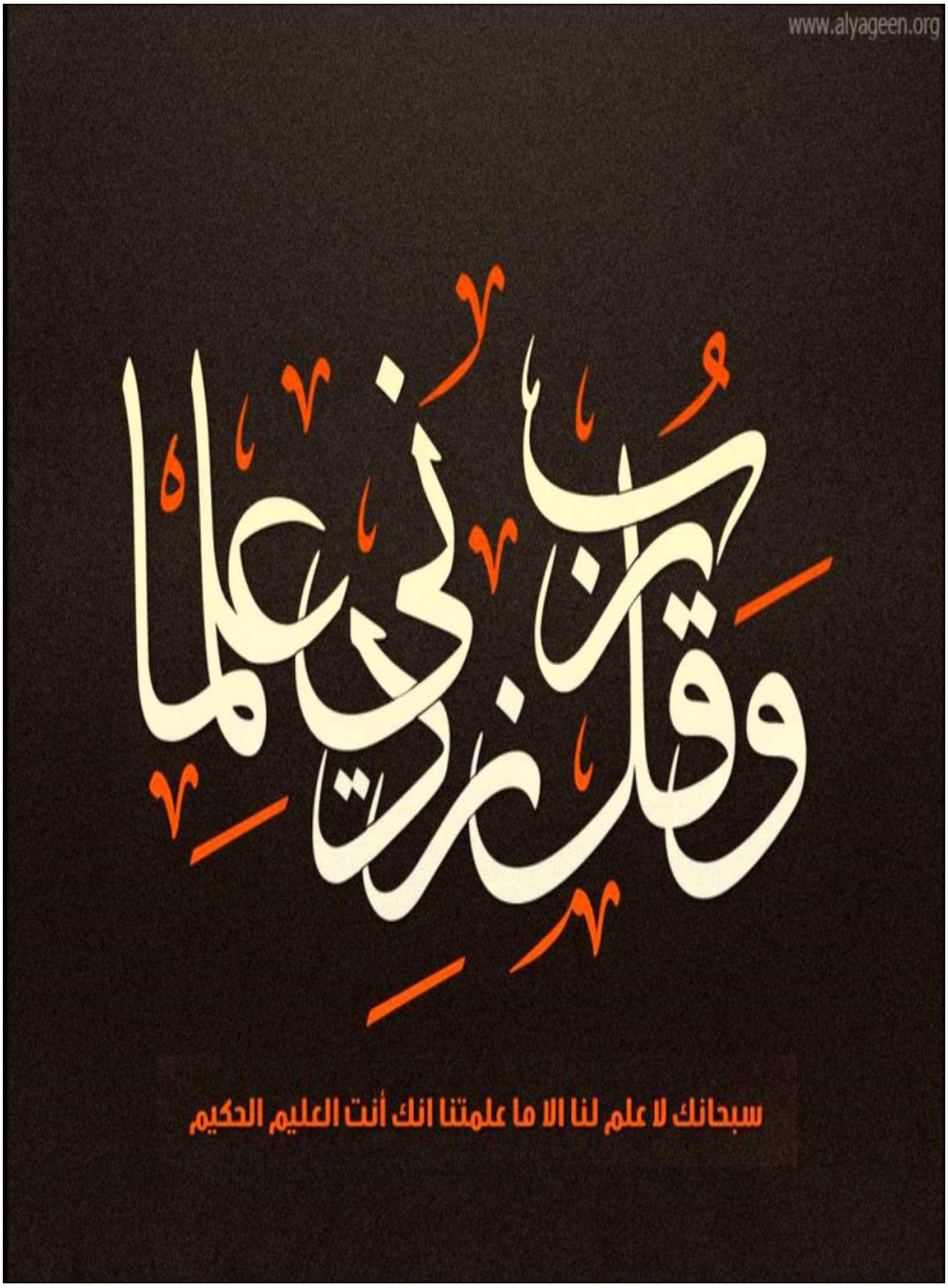

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List of Contents

List of Abbreviations

ADA	**The American Diabetes Association**
ADP	**Adenosine 5'-diphosphate**
ATP	**Adenosine triphosphate**
BFU-E	**Burst-forming unit-erythroid**
BMI	**Body mass index**
CD62P	**P-Selectin**
CE	**Cholesterol esterase**
CFU-MK	**Colony-forming unit–megakaryocyte**
CHD	**Coronary heart disease**
c-Mpl	**Thrombopoietin receptor (Myeloproliferative leukemia virus oncogene)**
CVD	**Cardiovascular disease**
CXC	**Chemokine**
DM	**Diabetes mellitus**
DTS	**Dense tubular system**
DVT	**Deep venous thrombosis**
EDTA	**Ethylenediaminetetraacetic acid**
FBS	**Fasting blood sugar**
FOG-1	**Friend of GATA**
FPG	**Fasting plasma glucose**
GATA-1	**GATA-binding factor 1**
GDM	**Gestational Diabetes Mellitus**
GP	**Glycoproteins**
GPIb	**Glycoprotein 1b**
GPIbα	**Glycoprotein Ibα**

List of Abbreviations (Con.)	
GPIIb	**Glycoprotein IIb**
GPIX	**Glycoprotein IX**
GPV	**Glycoprotein V**
HbA1c	**Hemoglobin A1c**
HDL	**High-density lipoprotein**
HPLC	**High Performance Liquid Chromatography**
HSC	**Hematopoietic stem cell**
IDF	**International Diabetes Federation**
IFG	**Impaired Fasting Glucose**
IGT	**Impaired glucose tolerance**
IL-3	**Interleukin-3**
ITP	**Immune thrombocytopenic purpura**
LDL	**Low-density lipoprotein**
LIF	**Leukemia-inhibitory factor**
MCV	**Mean red cell volume**
MEP	**Megakaryocyte-erythroid progenitor**
MODY	**Maturity–onset diabetes of the young**
MPV	**Mean platelet volume**
NDDG	**The national diabetes data group**
OCS	**Open canalicular system**
OGTT	**Oral glucose tolerance test**
PAF	**Platelet activating factor**
PCT	**Plateletcrit**
PDGF	**Platelet derived growth factor**
PDW	**Platelet distribution width**
PF4	**Platelet factor**

List of Abbreviations (Con.)	
P-LCR	**Platelet large cell ratio**
PS	**Phosphatidylserine**
SD	**Standard deviation**
SDF-1	**Stromal cell-derived factor 1**
TG	**Triglycerides**
TPO	**Thrombopoietin**
TXA2	**Thromboxane A2**
VLDL	**Very low density lipoprotein**
VWF	**Von Willebrand Factor**
WHO	**World Health Organization**
β-TG	**Plasma beta-thromboglobulin**

List of Tables

List of Figures

INTRODUCTION

Diabetes mellitus (DM) is a major global health problem affecting children, adolescents, and adults. According to the World Health Organization, approximately 180 million people worldwide currently have type 2 DM, the number of people with type 2 DM is estimated to double by 2030 ***(Mahsud et al., 2010)***. Diabetes mellitus is a complex metabolic health syndrome characterized by chronic hyperglycemia ***(Dermirtunc et al., 2009)***. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) **(*Fowler, 2008).***

Vascular disorders, such as coronary artery disease enhance the morbidity and the mortality of type 2 DM ***(Chiha et al., 2012)***, accounting for more than 17.5 million deaths worldwide ***(Moore et al., 2009)***. The prevalence of diabetic vascular complications is higher in people with poor glycemic control, longer duration of DM, associated hypertension and obesity ***(zuberi et al., 2008).***

Platelets are known to have a major effect on the formation of atherosclerotic plaques and, therefore, play an essential role in the pathogenesis of atherothrombosis. Larger and hyper-reactive platelets accelerate the formation of an intracoronary thrombus, leading to a cascade of clinical events, such as, acute coronary syndrome ***(Elsenberg et al., 2009)***. An increase in platelet aggregability is associated with unstable angina and myocardial infarction. Platelet size and activity are correlated, and mean platelet volume (MPV) was found to be increased before acute myocardial infarction ***(Perege et al., 2010).***

Platelet volume is a marker of platelet function and activation. It can be quantified as mean platelet volume by clinical hematology analyzers ***(Hekimsoy et al., 2004)***. ***Kakouros et al. (2011)*** reported that hyperglycemia causes larger platelets, which can synthesize more prothrombotic factors such as thromboxane A2, than normal platelets**.** It is also suggested that the increased platelet activity enhances vascular complications in those patients ***(Ulutas et al. 2014)***. Moreover, cardiovascular complication prevalence of type 2 DM may be associated with increased hemoglobin A1c (HbA1c) and MPV ***(Han et al., 2013)***.

Few studies have been conducted on the association between MPV and HbA1c as a marker of glycemic control and cardiovascular complications in type 2 DM.

Aim of the Work

This study aims to measure MPV in relation to HbA1c to assess the usefulness of MPV as a marker of glycemic regulation and to detect its relation to cardiovascular complications in type 2 DM.

MEGAKARYOPOIESIS

Megakaryocytes, as all blood cells, originate from the hematopoietic stem cell (HSC). The HSC gives rise to progressively committed progenitors, involving the megakaryocyte-erythroid progenitor (MEP). MEPs are bipotential precursors that progress to cells of both megakaryocytic and erythroid lineages ***(Geddis, 2010).*** The MEP differentiates into the burst-forming unit-erythroid (BFU-E) and the colony-forming unit–megakaryocyte (CFU-MK). The CFU-MK is a cell that progresses to a simple colony containing from three to fifty mature megakaryocytes ***(Kaushansky, 2008)*** (figure1).

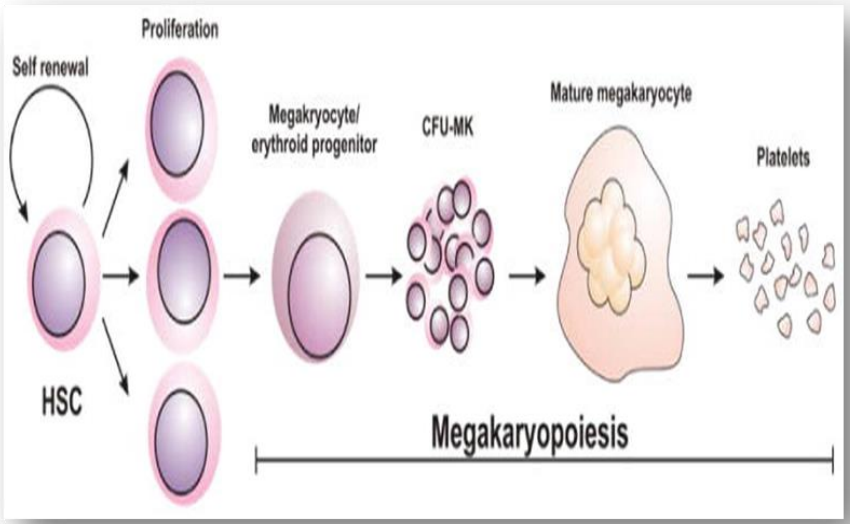

Figure (1): Overview of megakaryopoiesis. Megakaryocytes are derived from the hematopoietic stem cell and proliferate and differentiate under the influence of thrombopoietin (TPO) ***(Geddis, 2010).***

The megakaryocyte passes through a unique maturation process that involves polyploidization, formation of an extensive internal demarcation membrane system and lastly formation of proplatelet processes. Platelets are released from these processes to vascular sinusoids within the bone marrow ***(Geddis, 2010).*** The platelet life-span is 10 days, in the resting state about 30% of platelets are sequestered in the spleen ***(Briggs et al., 2007).***

Regulation of megakaryopoiesis and platelet production:

Extracellular mechanisms:

Thrombopoietin (TPO) is the primary controller of thrombopoiesis. It stimulates platelet production in a log-linear manner to levels 10-fold higher than baseline without the peripheral blood red or white cell counts are being affected ***(Kaushansky, 2008).*** The platelet counts can be reduced with an inhibitor against TPO with no impairment of primary hemostasis ***(Kaushansky 2006; Tucker et al. 2010).***

The revelation of TPO, and its megakaryocyte specific receptor c-Mpl, reformed the field of megakaryocyte and platelet biology. This discovery assisted development of in vitro cell culture systems that reconstruct megakaryocyte differentiation, maturation, proplatelet extension, and platelet