

**The study of Mean Platelet Volume
(MPV) as a Potential Risk Factor for
Macrovascular Complications (Ischemic
Heart Disease and Cerebrovascular
Stroke) in Type 2 Diabetes Mellitus**

Thesis

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of M.D degree in Internal Medicine*

By

Yasmeen Abd El majeed Mohammed
Master degree of Internal Medicine

Under Supervision of

Prof. Dr. / Hanan Mohammed Amer

*Professor of Internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University*

Prof. Dr. / Khaled Mahmoud Makboul

*Professor of Internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University*

Dr. / Bassem Murad Mostafa

*Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University*

Dr. / Caroline Adel Girgis

*Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University*

Faculty of Medicine – Ain Shams University

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبب انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
<i>ADA</i>	<i>American Diabetes Association</i>
<i>AGE</i>	<i>Advanced glycation end product</i>
<i>BFU-E</i>	<i>Burst-forming unit-erythroid</i>
<i>BFU-MK</i>	<i>Burst forming units – megakaryocytes</i>
<i>CFRD</i>	<i>Cystic fibrosis-related diabetes</i>
<i>CFU-GEMM</i>	<i>Colony-forming unit–granulocyte-erythrocyte-monocyte-megakaryocyte</i>
<i>CFU-MK</i>	<i>Colony-forming unit–megakaryocyte</i>
<i>CMP</i>	<i>Common myeloid progenitor</i>
<i>CVD</i>	<i>Cardiovascular disease</i>
<i>DAN</i>	<i>Diabetic autonomic neuropathy</i>
<i>DC</i>	<i>Dendritic cell</i>
<i>DM</i>	<i>Diabetes Mellitus</i>
<i>DSPN</i>	<i>Distal symmetrical sensorimotor polyneuropathy</i>
<i>DV</i>	<i>Diabetic vasculopathy</i>
<i>EDTA</i>	<i>Ethylenediaminetetra-acid</i>
<i>FOG-1</i>	<i>Friend of GATA</i>
<i>GAD</i>	<i>Glutamic Acid Decarboxylase</i>
<i>GDM</i>	<i>Gestational diabetes mellitus</i>
<i>GP</i>	<i>Glycoproteins</i>
<i>HbA1c</i>	<i>Glycated hemoglobin</i>
<i>HDL</i>	<i>High-density lipoprotein</i>
<i>HLA</i>	<i>Human leukocyte antigen</i>
<i>HSC</i>	<i>Hematopoietic stem cell</i>
<i>IDF</i>	<i>International Diabetes Federation</i>
<i>IFG</i>	<i>Impaired fasting glucose</i>
<i>IGT</i>	<i>Impaired glucose tolerance</i>
<i>IMT</i>	<i>Intima-media thickness</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>IR</i>	<i>Insulin resistance</i>
<i>kDa</i>	<i>Kilodalton</i>
<i>MAPK</i>	<i>Mitogen activated protein kinase</i>
<i>MODY</i>	<i>Maturity onset diabetes of the young</i>
<i>MPV</i>	<i>Mean platelet volume</i>
<i>NPDR</i>	<i>Nonproliferative diabetic retinopathy</i>
<i>NSTEMI</i>	<i>Non ST elevaton MI</i>
<i>PAF</i>	<i>Platelet activating factor</i>
<i>PARs</i>	<i>Protease-activated receptors</i>
<i>PCT</i>	<i>Plateletcrit</i>
<i>PDGF</i>	<i>Platelet derived growth factor</i>
<i>PDR</i>	<i>Proliferative diabetic retinopathy</i>
<i>PDW</i>	<i>Platelet distribution width</i>
<i>PI3-K</i>	<i>Phosphoinositide 3-kinase</i>
<i>PKC</i>	<i>Protein kinase C</i>
<i>SDF-1</i>	<i>Stromal cell-derived factor1</i>
<i>STEMI</i>	<i>ST elevaton MI</i>
<i>T1DM</i>	<i>Type 1 diabetes mellitus</i>
<i>T2DM</i>	<i>Type 2 diabetes mellitus</i>
<i>TARC</i>	<i>Thymus- and activation-regulated chemokine</i>
<i>TGF-B</i>	<i>Transforming growth factor B</i>
<i>TLR</i>	<i>Toll-like receptors</i>
<i>UA</i>	<i>Unstable angina</i>
<i>VEGF</i>	<i>Vascular endothelial growth factor</i>
<i>VLDL</i>	<i>Very low-density lipoprotein</i>
<i>ZnT8</i>	<i>Zinc transporter 8</i>

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has reached global epidemic proportions, with more than 382 million people affected according to a 2013 estimate. By 2035, its prevalence is expected to reach 471 million, meaning that 10% of the world's population will have diabetes (*International Diabetes Federation, 2013*). Patients with diabetes often suffer from metabolic abnormalities, poor glycemic control, oxidative stress, insulin resistance, and low-grade inflammation. These conditions trigger vascular dysfunction, which predisposes them to atherothrombosis (*Pignone et al., 2010*).

The coronary risks associated with T2DM are similar to those of nondiabetic patients with previous myocardial infarction (MI) (*Haffner et al., 2010*). Diabetes almost doubles the risk of having a stroke. This is because high levels of glucose in blood can damage the blood vessels, making them harder and narrower and more likely to become blocked. If this happens in the cerebral blood vessels it could cause a stroke (*Stroke Association Factsheet, 2015*).

Diabetic subjects have a very high risk of death from stroke. More than one fifth of stroke deaths in the population can be attributed to diabetes, more in women than in men. Diabetes should be taken into account when the stroke risk profile of a population is analyzed (*Stroke, 2005*). The cardiovascular risks remain high, even after optimal glycemic

and metabolic control has been achieved. Thus, identifying novel risk factors can provide better preventive strategies for individuals at high risk of cardiovascular events (*Sansanayudh et al., 2014*). Platelets have a key role in the development of acute complications of atherosclerosis. The first step in the development of atherosclerosis is the platelets' adhesion to the endothelium. As larger platelets are metabolically more active, the volume of the platelet is one of the determinants of platelet function.

Mean platelet volume (MPV) is a measure of the average size of platelets in the circulation. Considerable evidence suggests that MPV can be used as a potential biomarker of cardiovascular disease (CVD) (*Sansanayudh et al., 2014*).

In addition to the studies reporting that increase in the mean platelet volume (MPV) is an early indicator of inflammatory process and increased platelet activation, there are publications claiming that it constitutes a new risk factor for atherosclerosis (*Murat et al., 2015*).

Recent studies reported that increased MPV is associated with the presence of angina pectoris, severity of coronary artery occlusion, and even poor prognosis for acute MI (*Sansanayudh et al., 2014*).

Arterial stiffness is a manifestation of structural and functional changes in the vascular wall and a strong predictor

of cardiovascular events and mortality. It is also a link between diabetes and increased cardiovascular risks (*Stehouwer et al., 2008*).

Carotid B-mode high resolution ultrasonography is a noninvasive tool to assess intima-media thickness (IMT) and plaque presence in carotid arteries, visualizing changes in vascular morphology (*Naqvi and Lee, 2014*).

In clinical practice, carotid ultrasonography is widely accepted as efficient tool for identifying individuals at high risk for Cardiovascular diseases with predictive power for cardiovascular outcomes (*Den Ruijter et al., 2012*).

Murat et al., studied the relation between Aortic Intima-Media Thickness and Mean Platelet Volume in Children With Type 1 Diabetes Mellitus, and a positive correlation was found between them (*Murat et al., 2015*).

Several studies reported that increased MPV is closely associated with cardiovascular risks in patients with diabetes; however, this remains controversial because others failed to observe an association between MPV and Cardiovascular diseases (*Lekston et al., 2014*).