

جامعة عين شمس  
٢٠٠٧

**PREVALENCE OF HYPERHOMOCYSTEINEMIA IN TYPE  
٢ DIABETIC PATIENTS AND ITS RELATION TO THE  
DIFFERENT THERAPEUTIC MODALITIES FOR  
DIABETES**

Thesis  
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## **LIST OF ABBREVIATION**

<b>ACEI</b>	Angiotensin converting enzyme inhibitor.
<b>ADMA</b>	Asymmetric dimethyl arginine.
<b>AT</b>	Alpha tocopherol.
<b>BHMT</b>	Betaine homocysteine methyltransferase.
<b>BMI</b>	Body mass index.
<b>BMD</b>	Bone Mineral Density
<b>BNP</b>	B-type natriuretic peptide.
<b>CAD</b>	Coronary artery disease.
<b>CAN</b>	Cardiac autonomic neuropathy.
<b>CBS</b>	Cystathionine- $\beta$ synthase.
<b>CGL</b>	Cystathionine- $\delta$ lyase.
<b>CHD</b>	Coronary heart disease.
<b>CRF</b>	Chronic renal failure.
<b>CRP</b>	C-reactive protein.
<b>CVD</b>	Cardiovascular disease.
<b>DM</b>	Diabetes mellitus.
<b>E gr. 1</b>	Early growth response gene-1
<b>eNOS</b>	Endothelial nitric oxide synthase.
<b>ESRD</b>	End-stage renal disease.
<b>FFAs</b>	Free fatty acids.
<b>FMD</b>	Flow mediated dilatation.
<b>FPG</b>	Fasting plasma glucose.
<b>FPIA</b>	Fluorescence polarization immunoassay.
<b>GDM</b>	Gestational diabetes mellitus.
<b>GFR</b>	Glomerular filtration rate.
<b>Hcy</b>	Homocysteine.
<b>HDL</b>	High- density lipoprotein.
<b>HMG CoA</b>	Hydroxy methyl glutryl Co A.
<b>HOPE</b>	Heart Outcome Prevention Evaluation.
<b>ICAM</b>	Intercellular adhesion molecule.
<b>IFG</b>	Impaired fasting glucose.
<b>IGF-1</b>	Insulin growth factor-1.
<b>IGT</b>	Impaired glucose tolerance.
<b>IHD</b>	Ischemic heart disease.
<b>IL-6</b>	Interleukin-6.
<b>IMT</b>	Intima-media thickness.
<b>IRS</b>	Insulin resistance syndrome.
<b>LDL</b>	Low-density lipoprotein.
<b>Lp (a)</b>	Lipoprotein (a).
<b>MAT</b>	Methionine adenosyltransferase.
<b>MeTHF</b>	Methyltetrahydrofolate.
<b>MI</b>	Myocardial infarction.

<b>MICRO-HOPE</b>	Microalbuminuria, Cardiovascular and Renal Outcomes in HOPE.
<b>MNC</b>	Mononuclear cells
<b>MS</b>	Methionine synthase.
<b>NAC</b>	N-acetylcysteine.
<b>NO</b>	Nitric oxide.
<b>NOS</b>	Nitric oxide synthase.
<b>NPDR</b>	Non-proliferative diabetic retinopathy.
<b>OC</b>	Oral contraceptives.
<b>PAI-1</b>	Plasminogen activator inhibitor type 1.
<b>PDR</b>	Proliferative diabetic retinopathy.
<b>PPAR</b>	Peroxisome proliferators-activated receptors.
<b>SAH</b>	S-adenosylhomocysteine.
<b>SAM</b>	S-adenosylmethionine.
<b>TF</b>	Tissue factor.
<b>tHcy</b>	Total homocysteine.
<b>TGF-<math>\beta</math></b>	Transforming growth factor $\beta$ .
<b>TNF-<math>\alpha</math></b>	Tumor necrosis factor $\alpha$ .
<b>TZDs</b>	Thiazolidinediones.
<b>UKPDS</b>	United Kingdom Prospective Diabetes Study.
<b>VCAM</b>	Vascular cell adhesion molecule.
<b>VLDL</b>	Very low density lipoprotein.
<b>vWF</b>	von Willebrand factor.

## INTRODUCTION

Diabetes mellitus has been defined as a coronary heart disease risk equivalent. Therefore, there has been a major focus on preventing cardiovascular disease and controlling cardiovascular disease risk factors in the diabetic patient, and more aggressive treatment goals have been proposed for diabetic patients (*American Diabetes Association, 1997*).

Traditional risk factor such as hypertension, dyslipidemia and poor metabolic control has been well identified in type 2 diabetic patients. However, they do not fully explain the acceleration in macro-vascular disease in those patients (*Hoogeveen et al., 1999a*). Thus, non traditional risk factors came into focus.

Hyperhomocysteinemia is an independent risk factor for cardiovascular disease (*Guilliams, 1994*). It has been identified also as a modest predictor and stroke risk in healthy population (*The Homocysteine Studies Collaboration, 1999*), and even correlated with the angiographic extent of coronary artery disease (*Bozkurt, 1994*).

Diabetes mellitus is associated with impaired homocysteine metabolism which might contribute to endothelial- myocyte dysfunction in the heart of diabetic patients (*Tyagi et al., 1999b*). In addition, metformin; a key treatment option in type 2 diabetes, decreases vitamin B<sub>12</sub>

levels and subsequently increases homocysteine levels (*Wulffele et al.*, 2007). On the contrary, sulfonylureas were associated with lower serum levels of homocysteine when compared to diet and physical activity alone (*Hellgren et al.*, 2009).

## **AIM OF THE WORK**

To study the prevalence of hyperhomocysteinemia among type 2 diabetic patients receiving different anti-diabetic therapies.

## **NON TRADITIONAL RISK FACTORS & MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS**

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, insulin action or both (*American Diabetes Association, 2007*).

Several distinct types of diabetes mellitus (DM) exist and are caused by a complex interaction of genetics, environmental factors, and life-style choices. Depending on the etiology of the DM, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiological changes in multiple organ systems that impose burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non traumatic lower extremity amputations, and adult blindness. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future (*Gillam & Landsberg, 2007*).

**\*Etiologic Classification of Diabetes Mellitus: By**  
(*American Diabetes Association, 2007*).

- I. Type 1 diabetes** ( $\beta$ -cell destruction, usually leading to absolute insulin deficiency):
  - A. Immune-mediated.**