

**Methylene Tetrahydrofolate Reductase Gene
Polymorphism and Its Relationship To
Microvascular Complications In Patients With
Type-I Diabetes Mellitus**

Thesis

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List of Abbreviations

| | |
|-------------|---|
| aa | : Amino acids |
| Ab | : Antibodies |
| ADA | : American Diabetes Association |
| Ag | : Antigen |
| AIRE | : Autoimmune regulator gene |
| ALP | : Alkaline phosphatase enzyme |
| Anti-IL2 | : Anti interleukin two |
| APS-I | : Autoimmune polyendocrine syndrome |
| bl | : Blood |
| CBV | : Coxsackie B virus |
| CGMS | : Continuous glucose monitoring system |
| CHO | : Carbohydrates |
| DCCT | : Diabetes control and complication trial |
| DKA | : Diabetic ketoacidosis |
| DM | : Diabetes mellitus |
| DN | : Diabetic nephropathy |
| EV | : Enterovirus |
| FA | : Fatty acid |
| Fa | : Folic acid |
| FOX P3.gene | : Forkhead box P3 gene |
| GAD | : Glutamic acid decarboxylase |
| GBM | : Glomerular basement membrane |
| GFR | : Glomerular filtration rate |
| gl | : Glucose |
| Hb | : Haemoglobin |
| HbA1c | : Haemoglobin A, C (glycosylated haemoglobin) |
| HDL | : High density lipoprotein |
| HLA | : Human leukocytes antigen |
| hr | : Hour |
| IAA | : Insulin auto-antibodies |
| ICA | : Islet cell antibodies |
| ICU | : Intensive care unit |
| IDDM | : Insulin dependent diabetes mellitus |
| IFG | : Impaired fasting glucose |

List of Abbreviations (cont.)

| | |
|----------------|--|
| IGT | : Impaired glucose tolerance |
| IPEX syndrome: | Immune dysregulation polyendocrinopathy, enteropathy, X-linked syndrome |
| IV | : Intravenous |
| IZS | : Insulin zinc suspension |
| LDL | : Low density lipoprotein |
| MA | : Microalbumin |
| MODY | : Maturity onset diabetes of the young |
| MTHF | : Methyline tetrahydro folate |
| MTHFR | : Methyline tetrahydro folate reductase |
| NDDM | : Non-insulin dependant diabetes mellitus |
| NPH | : Neutral protamine Hagedorn insulin |
| OGTT | : Oral glucose tolerance test |
| PCR | : Polymerase chain reaction |
| PN | : Peripheral neutritis |
| RBCs | : Red blood cells |
| SC | : Sub-cutaneous |
| SMG | : Self monitoring of blood glucose |
| T3 | : Thyroxin hormone (3) |
| T4 | : Thyroxin hormone (4) |
| T1DM | : Type I diabetes mellitus |
| T2DM | : Type II diabetes mellitus |
| TSH | : Thyroid stimulating hormone |
| U/S | : Ultrasound |
| UTI | : Urinary tract infection |
| VEGF | : Vascular endothelial growth factor |
| WHO | : World Health Organization |
| wks | : weeks |
| Wt. | : Weight |
| yrs | : years |

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بحث العلاقة بين تغيرات جين ميثايلين رباعي
هيدروفوليت ريذاكتيز ومضاعفات الأوعية الدموية
الدقيقة في المرضى المصابين بالبول السكري من
النوع الأول

رسالة

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طب الأطفال

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الملخص العربي

مرض البول السكري من النوع الأول هو مرض شائع جداً في الأطفال والمراهقين، وهو مرض من أمراض المناعة الذاتية الذي يؤدي إلى تكسير خلايا بيتا بالبنكرياس المفرزة للأنسولين، مما يؤدي إلى ارتفاع السكر في الدم. وتؤثر العوامل الوراثية في حدوث هذا المرض تأثيراً كبيراً.

ومن أهم مضاعفات هذا المرض حدوث تغييرات في الأوعية الدموية الدقيقة وهذه التغييرات لها علاقة وثيقة بطول فترة المرض وضبط السكر بالدم، ومرة أخرى تؤثر هذه العوامل الوراثية في حدوث هذه المضاعفات، وهذه المضاعفات تؤثر على الكلى وقاع العين والأعصاب.

والميثالين رباعي هيدروفوليت ريداكتيز هو إنزيم هام جداً في أيض حمض الفوليك وهو هام جداً في التفاعلات الميثالية وأيض الهوموسيستين. وحدث خلل في التفاعلات الميثالية قد يؤدي إلى عيوب خلقية، كما أن ارتفاع نسبة الهوموسيستين يؤدي إلى حدوث مشاكل في الأوعية الدموية.

ومما سبق يمكن استنتاج أن تغييرات الميثالين رباعي هيدروفوليت ريداكتيز جين قد يؤدي إلى نتائج خطيرة.

وفي مرض السكر من النوع الأول يؤدي نقص حمض الفوليك إلى خلل في وظائف الخلايا المبطنة للأوعية الدموية، وبالتالي فإن التغيرات في الجينات المسؤولة عن أيض حمض الفوليك قد تكون مسئولة أو مشاركة في حدوث أمراض الأوعية الدموية، كما أن وجود المضاعفات الخاصة بمرض السكر وخاصة في الكلى والعين عند عائلات بعينها يؤكد أن للجينات دور في حدوث هذه المضاعفات.

الهدف من الدراسة :

تهدف هذه الدراسة إلى بحث العلاقة بين تغيرات جين ميثايلين رباعي هيدروفوليت ريداكنتيز ومضاعفات الأوعية الدموية الدقيقة في المرضى المصابين بالبول السكري من النوع الأول.

المرضى وطرق البحث :

سوف يتم إجراء هذه الدراسة على عدد مائة مريض من مرضى البول السكري من النوع الأول .. وسوف يتم عمل الآتي لهؤلاء المرضى:

- أخذ التاريخ المرضي الكامل والكشف الطبي الدقيق.
- عمل الفحوصات والاختبارات المعملية الآتية :
 - متوسط نسبة الجلوكوز في الدم صائم وبعد ساعتين من الأكل.
 - متوسط الهيموجلوبين السكري في الدم خلال العام الماضي.
 - قياس الزلال المجهرى في البول.
 - فحص قاع العين.
 - قياس سرعة توصيل النبضات العصبية في الأعصاب.
 - قياس تغيرات ميثايلين رباعي هيدروفوليت ريداكنتيز جين.

المقياس الضمني :

تشمل هذه الدراسة الأطفال المصابين بمرضى البول السكري من النوع الأول الذين تم تشخيصهم منذ أكثر من خمس سنوات.

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INTRODUCTION

Diabetes mellitus is a common chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. Type-I D.M is the most common form of D.M. in children and adolescents (90% of cases) and account for only 5-10% of all cases of D.M (*Wyatt, 2008*).

It's an autoimmune disorder characterized by T-cell mediated destruction and progressive loss of pancreatic β -cells leading to eventual insulin deficiency and hyperglycemia. This disorder has a strong genetic component, inherited mainly through HLA complex, but the factors that trigger onset of clinical disease remain largely unknown (*Denis-Deneman, 2006*).

The risk of developing microvascular complications is related mainly to the duration of diabetes and degree of glycemic control achieved over time (i.e./ Hb A1C 7.0% or less). Genetic factors also may influence the risk of complications. These complications are mainly renal microvascular complication (microalbuminurea or diabetic nephropathy), retinopathy and neuropathy (peripheral or autonomic) (*Robert et al., 2007*).

Methylene tetrahydrofolate reductase is a key enzyme in folic acid metabolism. Folic acid has recently gained a great deal of attention as a biologically important molecules. Methylene tetrahydrofolate reductase is the enzyme responsible for reduction of methylene tetrahydrofolate, which

is the key single carbon donor required for thymidine synthesis, to methylene tetrahydrofolate, which is essential for homocysteine remethylation to methionine (**Boushey et al., 1995; James et al., 1999 and Kim, 2000**).

Defect in methylation reaction is involved in the etiology of some birth defects and elevated homocysteine is a known risk factor for vascular disease. So the polymorphism in methylene tetrahydrofolate reductase may have a detrimental consequences. The range of disorders that have been studied and linked to methylene tetrahydrofolate gene polymorphism include : diabetes mellitus, vascular diseases, leukaemia, birth defects, colon cancer, preeclampsia, Alzheimer disease, Down syndrome and many others (**Wiltshine et al., 2008**).

In patients with type-I diabetes mellitus folate deficiency is associated with endothelial dysfunction and folate supplementation improves the endothelial functions in these patients. The familial clustering of nephropathy and retinopathy found in diabetes control and complications trial supports a contribution of genetic factors in their development. So, polymorphism in genes involved in folate metabolism may have a role in vascular disease (**Wiltshine et al., 2008**).