Asymmetric Dimethylarginine in Relation to Vascular Complications in Type 1 Diabetic Children and Adolescents

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علاقة مستوى ثنائى ميثيل الأرجنين الغير متماثل بالدم مع مضاعفات الأوعية الدموية فى مرض البول السكرى من النوع الأول فى الأطفال والمراهقين

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Summary

Renewed attention has been given to the endothelium system dysfunction as a potential contributor in the pathogenesis of diabetic vascular complications because of its association with cardiovascular and renal diseases. Endothelial nitric oxide synthase (eNOS) converts L-Arginine to nitric oxide (NO). ADMA is a competitive inhibitor of eNOS, which thus reduces the production of NO and might possibly cause endothelial dysfunction and vascular complication.

This study aimed to assess the role of ADMA in relation to vascular complications in type 1 diabetic children and adolescents.

The study was conducted in the Specialized Pediatric Diabetes clinic, Children's Hospital, Ain Shams University. It included 35 children and adolescents with type 1 DM, with disease duration 5 years or more and mean glycated hemoglobin level $\geq$ 8 %. There were 15 patients with vascular complications, 20 patients without, and thirty healthy children and adolescents as a control group.

Patients and controls were subjected to: full history taking, thorough clinical examination, fundus examination and laboratory investigations including: microalbuminuria, HbAc1, lipid profile and serum ADMA with estimation of carotid intimal thickness.

The results revealed patients and controls were comparable regarding age and gender. There was no significant difference in mean insulin dose, duration of diabetes or lipid profiles between diabetic patients with and those without vascular complications. No significant difference was found in mean blood pressure, BMI or carotid intimal thickness measurement among the three studied groups. Meanwhile, there was a significant difference in mean serum ADMA, and urinary microalbumin levels among the three studied groups. Mean serum cholesterol and LDL values were significantly higher in patients with VC than healthy controls.

The results showed a significant positive correlation between ADMA and both microalbuminuria and HbA1c in diabetic patients' group (n=35). Carotid intimal thickness levels correlated with age in the latter group. Significant negative correlation was found between ADMA and LDL levels. No correlation was observed between ADMA and BMI, BP, total cholesterol, triglyceride, HDL or carotid intimal thickness, either.

Introduction

Asymmetric dimethyl arginine (ADMA) is a naturally occurring amino acid that competitively inhibits the activity of nitric oxide synthase ***(Kielstein et al., 2007).*** Endothelial derived nitric oxide (NO) is a potent endogenous vasodilator that suppresses vascular smooth muscle proliferation, inhibits platelet adhesion and aggregation and interferes with leukocyte-endothelial cell interaction ***(Boger et al., 1998).*** The competitive inhibition of NO synthase by ADMA may explain the fact that high circulating ADMA level is associated with endothelial dysfunction and increased risk of atherosclerosis ***(Boger, 2003)***.

Asymmetric dimethyl arginine is produced by methylation of arginine residues in intracellular proteins via protein arginine N-methyl transferases (PRMT) where these proteins are hydrolyzed, ADMA is released and 20% of it is excreted in urine ***(Achan et al., 2003).*** More than 80% of ADMA is cleared by enzymatic degradation of dimethylamine dimethylaminohydrolase ***(Kielstein and Fliser, 2007)***.

It has been shown that ADMA level is elevated in diabetes mellitus and is associated with increased risk of cardiovascular morbidity in type 1 diabetes mellitus (DM) ***(Abbasi et al., 2001 and Sibal et al., 2009).*** Moreover, ADMA level is found to be elevated in patients suffering from diabetic nephropathy with micro- and macroalbuminuria ***(Tarnow et al., 2004).*** Elevated plasma ADMA level has also been reported in patients with hypercholesterolemia and hypertension ***(Altinova et al., 2007).***

Recently, a large community-based study observed that higher ADMA concentrations were associated with greater internal carotid artery intimal thickness which is consistent with the notion that ADMA promotes subclinical atherosclerosis with a greater influence at known vulnerable sites in the arterial tree ***(Maas et al., 2009).***

Aim of The Work

To assess the role of ADMA in relation to vascular complications in type I diabetic children and adolescents.

Diabetes Mellitus

Definition:

Diabetes mellitus is a group of metabolic diseases characterized by abnormal metabolism of carbohydrates, fats and proteins, resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidney, nerves, heart and blood vessels ***(American Diabetic Association, 2004)***.

Type 1 diabetes mellitus (DM) is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack ***(Rother, 2007)***.

The classical symptoms of diabetes are polyuria, polydipsia and polyphagia ***(Cooke and Plotnick, 2008).***

Prevelance and incidence of type 1 DM

The World Health Organization estimates that more than 180 million people worldwide have diabetes mellitus and this number is likely to more than double by 2030; about 10% have type 1 diabetes mellitus ***(Jensen et al., 2011)***. DM is the most common metabolic disease in childhood ***(Ross, 2003).*** Approximately 50–60% of patients with type1 DM are diagnosed before the age of 15 years ***(International Diabetes Federation, 2007).*** Incidence rate varies greatly between different countries, within countries, and between different ethnic populations. The incidence of type 1 DM increased worldwide in the closing decades of the 20th century. Steep rises in the age group under 5 years has been recorded ***(Gale, 2002).*** Diabetes prevalence in some Eastern Mediterranean countries is among the highest in the world. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar where the incidence of type 1 diabetes is reported to be 8–10 per 100000 population per year in children aged <15 years ***(Elsamahy et al., 2008).*** In Egypt, the prevalence rate of type 1 DM among school children in Heliopolis district in Cairo was 1.09/1000 with male predominance and the study showed that age, seasonal variations, viral infections, emotional stress, high birth order, consanguinity between the parents and family history of diabetes were risk factors for development of type 1 DM ***(Salem et al., 1990).***

There is a clear seasonal variation in diagnosis of diabetes, and among children who had a preceding, perhaps precipitating, infection. However, seasonal factors could influence not only precipitating mechanisms just before diagnosis, but also initiating or promoting mechanisms very early in the disease process ***(Moony et al., 2004).***

Complications of type 1 diabetes

Complications can be acute or chronic:

- **Acute complications** include the following:
  - Hypoglycemia.
  - Local allergic reactions.
  - DKA.
- **Chronic complications** are further subdivided into macrovascular and microvascular.

  Microvascular complications
  - Peripheral neuropathy.
  - Diabetic retinopathy, cataract, glaucoma.
  - Diabetic nephropathy.

(Hussain and Vincent , 2010).

Macrovascular complications

Macrovascular disease is the leading cause of death in patients with diabetes, causing 65-75% of deaths in this group, compared with approximately 35% of deaths in people without diabetes. Diabetes increases the risk of myocardial infarction

(MI) 2-fold in men and 4-fold in women, and many patients have other risk factors for MI as well ***(Gerstein et al .,2010).*** The risk of stroke in patients with diabetes is double that of non diabetic people, and the risk of peripheral vascular disease is 4 times that of people without diabetes ***(Khardori et al., 2011).***

Prevention of complications

Glucose control

Glycated haemoglobin (HbA1c) should be as low as possible but avoid undue hypoglycaemia. A reduction of 1% of HbA1c could prevent 30-35% of microvascular and 14-16% of macrovascular complications ***(Haddadinezhad and Ghazaleh , 2010).***

Other factors

Blood pressure should be as low as possible (avoiding symptoms of postural hypotension), patients should be encouraged to stop smoking, eat healthily, lose weight and to exercise **(*Marshall and Flyvbjerg, 2006).*** Exercise is an indispensable component in the medical treatment of patients with type 1DM as it improves glycemic control and decreases cardiovascular risk factors among them **(*Salem et al., 2010).***

Diabetic Nephropathy

Epidemiology

Diabetic nephropathy (DN) is a serious microvascular complication of diabetes and has become the most common cause of end-stage renal disease (ESRD). Approximately one third of diabetic individuals will develop clinically apparent diabetic nephropathy ***(Bell et al., 2010).***

The peak incidence of diabetic nephropathy is around 15-20 years from the development of diabetes **(*Hovind et al., 2004*).**

Stages and clinical course

Diabetic nephropathy has been didactically categorized into stages based on the values of urinary albumin excretion (UAE) into three categories: no microalbuminuria, microalbuminuria (30–300 mg/24 h), or macroalbuminuria (>300 mg/24 h) ***(Rani et al., 2011).*** It has generally been thought that increases in urine albumin excretion rate (AER) precede a fall in glomerular filtration rate (GFR) in patients developing diabetic chronic kidney disease ***(Molitch et al., 2010).***

Persistent microalbuminuria was defined when two of three samples showed urinary albumin excretion rate of 30-300 µg/mg creatinine ***(Mogensen et al., 1995).***

Although microalbuminuria has been considered a risk factor for macroalbuminuria, not all patients progress to this stage and some may regress to normoalbuminuria ***(Caramori et al., 2003).***

Screening for diabetic nephropathy

The first manifestation of diabetic nephropathy (DN) is microalbuminuria, an elevated albumin excretion rate (AER). **(*Schultz et al., 2001).*** The measurement of UAE is the cornerstone for the diagnosis of diabetic nephropathy ***(Adler et al., 2003).*** For patients with type 1 diabetes, the first screening has been recommended at 5 years after diagnosis. However, the prevalence of microalbuminuria before 5 years in this group can reach 18%, especially in patients with poor glycemic and lipid control, high normal blood pressure levels and at puberty (**Figure 1**) ***(Gross et al.,2005).*** In patients with pubertal/post-pubertal onset of diabetes, screening for nephropathy is initiated 2 years after diagnosis. If microalbuminuria is absent, it must be repeated annually ***(Moore et al., 2009).***

The screening should not be performed in the presence of conditions that increase UAE, such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycemia, uncontrolled hypertension, and heart failure ***(Eknoyan et al., 2003).*** Recent study founded that moderate intensity exercise resulted in significant elevation of both systolic and diastolic blood pressure and urinary excretion of microalbumin in patients with type 1 diabetes ***(El Habashy et al., 2007).***

Immunoassays routinely used for albumin measurements present adequate diagnostic sensitivity for detection of diabetic nephropathy **(*Comper et al., 2004)***.

There are some patients with either type 1 or type 2 diabetes who have decreased glomerular filtration rate (GFR) in the presence of normal UAE. GFR is the best parameter of overall kidney function ***(Levey et al., 2003)*** and should be routinely estimated for a proper screening of diabetic nephropathy ***(*MacIsaac *et al., 2004).*** Proximal tubular dysfunction may occur independent of glomerular alteration as patients without microalbuminuria may have their tubular markers as n-acetyl-β-d-glucosaminidase(β-NAG) and retinol binding protein excreted in urine in significantly higher amounts than controls (***Salem et al., 2002).***

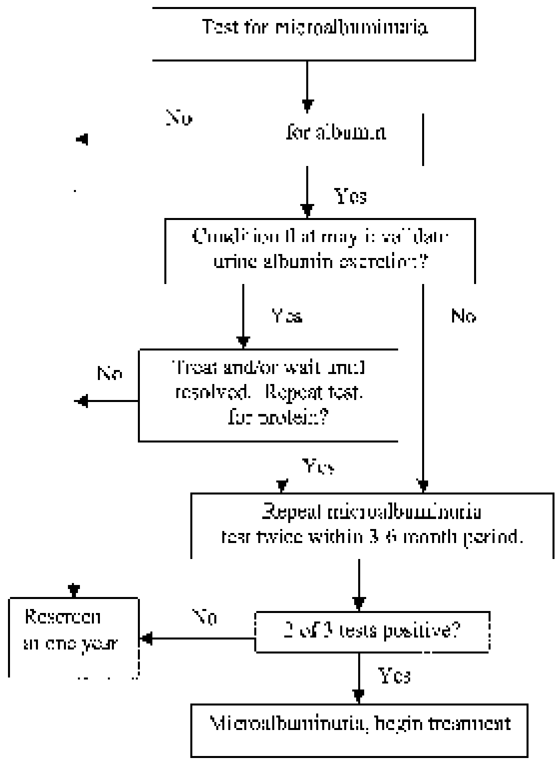

Figure (1): Algorithm for microalbuminuria screening ***(ADA, 2004a)***.

Risk factors of diabetic nephropathy

Hyperglycemia

A reduction of 1% in HbA1c is associated with a 37% decrease in microvascular endpoints ***(Stratton et al., 2000).*** Even though some studies showed a deleterious effect of high glucose levels on GFR ***(Hovind et al., 2003).*** Moreover, it was demonstrated that pancreas transplantation reversed renal damage in type 1 DM patients with mild to advanced DN lesions ***(Fioretto et al., 2007).*** Recently, a large trial also reinforced the importance of intensive treatment of DM to decrease the microvascular complications ***(Patel et al., 2008).***

Arterial Hypertension

Every 10 mmHg reduction in systolic blood pressure is associated with a 13% reduction in the risk of microvascular complications ***(Adler et al., 2000).***

Smoking

Several studies have shown the relationship between smoking and the development of diabetic nephropathy in diabetes. Progression of diabetic nephropathy was less common in non-smokers (11%) than in smokers (53%), and ex-smokers (33%) ***(Girach et al., 2006).***

Dyslipidemia

Lipid disturbances are well known to be associated with diabetic nephropathy and in type 1 DM patients increased serum triglycerides, total and LDL-cholesterol were associated with micro- and macroalbuminuria ***(Jenkins et al., 2003***).

The familial clustering of lipid disturbances may partly account for the reported familial clustering of cardiovascular disease in type 1 diabetic patients with nephropathy **(*Hadjadj et al., 2004*).**