

ROLE OF F2 ISOPROSTANES AS A BIOLOGICAL MARKER FOR THE EARLY ONSET OF TYPE 2 DIABETES MELLITUS IN THE MALAYSIAN POPULATION

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INTRODUCTION

Diabetes is one the most common non communicable disease affecting millions of the people globally. It is one of the most challenging health problems in many developing and industrialised countries and the exact cause is not known. One of the foremost challenges we face is to account mechanistically not only for the definition of hyperglycemia but also for other biochemical and physiological abnormalities which are the characteristics of the disease. Type 2 diabetes is a chronic disease that leads to complications such as cardiovascular disease, peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness resulting in increase disability, reduced life expectancy and enormous health cost for everybody.

There has been a recent explosion of interest in the notion low grade inflammation and activation in the innate immune system closely involved in the pathogenesis of Type 2 diabetes. In general, Type 2 diabetes develops when pancreatic β cells fail to secrete sufficient amount of insulin to meet the metabolic demand. An increased metabolic demand for insulin due to insulin resistance in several tissues usually precedes the development of hyperglycemia. An increased oxidative stress is a likely mechanism linking acute hyperglycemia to diabetic complications via cytokine secretion. Lipid peroxidation is a central feature of oxidative stress and an important feature in the development of atherosclerosis in Type 2 diabetes. Data continue to accrue supporting the hypothesis that oxidative stress is pivotal in the genesis of the atherosclerosis lesions. One hypothesis for the accelerated atherosclerosis of diabetes is the modification of lipoproteins particularly the low density lipoprotein (LDL) by oxidation or glycosylation or both may induce endothelial injury and accelerate foam cell formation.

Although oxidative stress plays a crucial role in the genesis and progression of the atherosclerosis lesions, there have not been any suitable biomarkers that could be quantified to measure of oxidative stress. On the other hand, direct assays such as measurement of urinary F2 Isoprostanes have shown great promises as bioactive products of lipid peroxidation. F2 isoprostanes are prostaglandin like compounds formed *in vivo* from free radical catalysed peroxidation of arachidonic acid mainly via a non cyclooxygenase dependent mechanism.

Enhanced formation of F2 isoprostanes has been reported in association with several cardiovascular risk factor including hypercholesterolemia, and diabetes mellitus, that are characterised by increased lipid peroxidation in response to complex abnormalities. It is widely accepted that frank clinical type diabetes is preceded by long pre-diabetic state and the events preceding the onset of NIDDM may contribute to the complications on Type 2 diabetes. The risk factors in Type 2 diabetes which lead to microvasuclar and macrovascular complications are similar in persons with frank diabetes and in persons with impaired glucose tolerance (IGT) whose glucose concentrations are relatively normal.

The identification of people at high risk group of Type 2 diabetes and cardiovascular disease is a major challenge. In the majority of populations, both genetic and environmental factors interact to determine individual risk for Type 2 diabetes. Non diabetic first degree relatives of Type 2 diabetic patients have an approximately 3 fold increased life time risk of developing the condition in comparison with the background population. Therefore, it could be expected that normoglycemic and IGT subjects with a family history of diabetes are subjected to risk factors relating to Type 2 diabetic complication. The risk factors could be the same as those found in pre-diabetic subjects. However, there is no reliable biological marker that could exactly identify the pre-diabetic stage. Impaired glucose tolerance is currently used to identify the pre-diabetic stage. However, IGT is not a homogenous condition.

The measurement of oxidative stress is hampered by methodological problem associated with the highly reactive species. However the measurement of F2 isoprostanes in urine and serum provides a direct measure of *in vivo* lipid peroxidation. Enhanced formation of F2 isoprostanes has been reported in Type 2 diabetes.

OBJECTIVES

The objective of this study is to measure the F2 isoprostanes as an oxidative marker in children from one diabetic parent. Early detection may be helpful in deviating from full blown diabetes by changing the life style.

METHODOLOGY

Anthropometric

Measurements were done to determine the weight, height and BMI

Clinical Estimations

After an overnight fast, venous blood samples were drawn from each patient in sterile EDTA tubes. Samples were assayed for plasma glucose, HbA1C, total cholesterol triglycerides, HDL and LDL cholesterol.

Measurement of F2 Isoprostanes

Serum was acidified and eluted through C18 cartridges. The eluates were evaporated and quantified using competitive immuno assay.

RESULTS

There were no differences in the biochemical profiles between NGT and IGT subjects from one parent diabetic family. However, the age, BMI, fasting plasma glucose, HbA1C, total cholesterol and LDL cholesterol was significantly higher amongst the diabetic subjects as compared to subjects from diabetic family with IGT and NGT. From our studies, we observed a negative correlation between F2 isoprostanes, clinical characteristics and the progression to IGT or T2DM which imply that F2 isoprostanes might be involved in the development of complications of Diabetes but not on the onset.