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Clinica Chimica Acta 366 (2006) 293 – 298

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Homocysteine and other biochemical parameters in Type 2 diabetes mellitus with different diabetic duration or diabetic retinopathy

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Received 10 October 2005; received in revised form 28 October 2005; accepted 29 October 2005
Available online 15 December 2005

Abstract

Background: Cardiovascular risk-related markers in type 2 diabetes mellitus (DM) have not been well understood.
Methods: Serum and urine samples for biochemical and immunologic analysis were collected from 204 normal subjects and 257 type 2 DM patients, the latter of which were further classified by different diabetic duration with or without retinopathy.
Results: Glycosylated hemoglobin A1c, triglyceride, lipase, free fatty acid, albumin creatinine ratio (ACR), lactate dehydrogenase (LDH) and homocysteine were significantly increased in DM patients, whereas high density lipoprotein cholesterol and bilirubin were significantly decreased in DM patients, compared with normal subjects. Lipid profiles, ACR, bilirubin, uric acid, creatine kinase, and hsCRP were not changed in DM patients with different diabetic duration or diabetic retinopathy. Lactate dehydrogenase in DM patients with duration >20 years and homocysteine in patients with duration >10 years was significantly higher than those with duration <5 years. Homocysteine was significantly increased in DM patients with retinopathy, compared with DM patients without retinopathy.
Conclusion: The increased triglyceride, lipase, free fatty acid, albumin creatinine ratio, lactate dehydrogenase and homocysteine as well as decreased high density lipoprotein cholesterol and anti-oxidative bilirubin in DM patients should be cautious and considered as risks for increasing DM complication. Homocysteine might be associated with longer diabetic duration and microvascular complication of retinopathy in diabetes.

Keywords: NIDDM; Hyperhomocysteinemia; Lactate dehydrogenase; Retinopathy

1. Introduction

Type 2 diabetes mellitus (DM) is a complex disease combining various other metabolic abnormalities. Increased cardiovascular (CV) disease is the major risk to cause morbidity and mortality in the complication of DM. Glycosylated hemoglobin A1c (HbA1c) is the pre-eminent factor for quantifying the risk of complications in patients

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doi:10.1016/j.cca.2005.10.025

with diabetes and for monitoring glycemia [1]. Measurement of HbA1c remains the gold standard for the assessment of glycemic control in patients with type 2 DM [2].

Dyslipidemia is characterized by increases in triglyceride concentrations, increased blood concentrations of low-density lipoprotein (LDL) cholesterol and lower concentrations of high-density lipoprotein (HDL) cholesterol in patients with DM [3–5]. Lipase is an enzyme secreted by the pancreas and catalyzes the breakdown of triglycerides (TG) into free fatty acids (FFA) and glycerol [6]. Lipid profiles are strongly associated with CV risks. However, it is unclear whether free fatty acid and lipase are associated with different diabetic duration or diabetic retinopathy.

Urinary albumin to creatinine ratio (ACR) in a single urine sample has been proposed to provide an estimate of microalbuminuria by adjusting for variability in urine concentrations [7]. Any degree of albuminuria is a risk factor for CV events in individuals with DM. Screening for albuminuria was suggested to identify people at high risk for CV events [8]. Bilirubin was long considered as a useless or potentially toxic metabolite of jaundice, especially in high doses, particularly in neonates. On the other side, bilirubin exhibits potent anti-oxidant properties preventing the oxidative damage triggered by a wide range of oxidant-related stimuli [9]. However, it is unclear whether albuminuria ACR and anti-oxidant bilirubin are associated different diabetic duration or diabetic retinopathy.

Increased uric acid concentration is a significant and independent risk factor for peripheral arterial diseases in Taiwanese patients with Type 2 DM [10]. On the other side, serum uric acid concentration is associated with an increased risk for hypertension but not for Type 2 DM in Japanese men [11]. Hyperuricemia is a strong predictor of stroke events in middle-aged patients with Type 2 DM independently of other cardiovascular risk factors [12]. Lactate dehydrogenase (LDH) is an enzyme of special interest due to its key position in anaerobic metabolic pathways as well as total serum LDH and creatine kinase (CK) activities were regarded as cardiac markers for myocardial infarction or cardiac damage [13]. Mild DM has no effect on LDH, but raised plasma levels of LDH in severe DM are found to be highly significant [14]. C-reactive protein (CRP), a nonspecific acute-phase reactant that is easily and reliably measured, has strong predictive power for cardiovascular events. DM patients with macrovascular disease do not had higher CRP [15]. Among various cardiovascular risk factors, hyperhomocysteinemia has recently emerged as an important one [16]. Hyperhomocysteinemia is one of the newly recognized risk factors of coronary artery disease (CAD) [17]. However, it is unclear whether the changes of ACR, bilirubin, uric acid, LDH, CK, CRP, and homocysteine are associated with different diabetic duration or diabetic retinopathy.

The aims of this study were to identify the concentrations of HbA1c, lipid profile (cholesterol, triglyceride, HDL-C, LDL-C, TC/HDL-C, lipase, and FFA), ACR, bilirubin, uric acid, LDH, CK, hsCRP, and homocysteine in DM patients and to clarify the related roles in DM patient with different diabetic duration or diabetic retinopathy.

2. Patients and methods

2.1. Subjects

Two hundred fifty-seven patients with Type 2 DM from the first time of diagnosis were recruited from the Endocrine Clinic in St. Joseph's Hospital, Taiwan. The diagnosis of type 2 DM was made based on 1985 World Health Organization criteria [18]. The diabetic duration was defined as the duration from the first diagnosis of type 2 DM to the time of blood sampling. Exclusion criteria included acute myocardial infarction, any organ failure, pregnancy, liver disease, stroke, current use of cholesterol-lowering agents, and uncertained diabetic duration. The healthy subjects recruited from the division of health examination were all non-smokers who had no history of DM, hypercholesterolemia, hypertension or coronary heart diseases, nor a family history of diabetes or heart diseases. This study and informed consent was approved by Research Ethics Board of the St. Joseph's Hospital. Every participant signed the informed consent.

2.2. Examination of diabetic retinopathy

The diabetic retinopathy was determined by ophthalmoscopy and fluorescein angiography through dilated pupils by a retinal specialist prior to the examination of the blood samples, and the patients were classified according to the presence or absence of diabetic retinopathy, regardless of its degrees of severity.

2.3. Blood and urine sampling

Overnight fasting blood samples were drawn from 7:00 to 9:00 a.m. by a trained phlebotomist via a venipuncture of an antecubital vein with the patient in the supine position and the patients' usual medications were withheld until after venesection. The blood samples were drawn and used for biochemical assay and HPLC. In addition, the first voided morning urine sample was collected.

2.4. Biochemical assay and High Performance Liquid Chromatography (HPLC)

Glucose, total cholesterol, triglycerides (TG) and high-density lipoprotein (HDL), low-density lipoprotein (LDL), uric acid, and total bilirubin, lactate dehydrogenase (LDH), creatine kinase (CK), creatine, and lipase were analyzed based on a spectrophotometric method using the Cobas Integra 700 Analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). Free fatty acid (FFA) concentrations were measured with Hitachi-7170 automatic Analyzer (Hitachi