The Egyptian Journal of Medical Human Genetics (2014) 15, 257–264

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com

ORIGINAL ARTICLE

Haptoglobin phenotypes as a risk factor for coronary artery disease in type 2 diabetes mellitus: An Egyptian study

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Received 24 February 2014; accepted 30 March 2014
Available online 22 April 2014

KEYWORDS

Type 2 DM;
Haptoglobin polymorphism;
CAD;
Oxidative stress;
Polymerase chain reaction (PCR)

Abstract *Objective:* Diabetes has long been known to be an independent risk factor for cardiovascular disease. Recognition of diabetic individuals at greatest risk of developing coronary artery disease (CAD) would have important public health importance by allowing the distribution of limited resources to be directed on those who would most benefit from aggressive management. Several functional differences between haptoglobin (Hp) phenotypes have been demonstrated that appear to have important biological and clinical consequences in the development of CAD in patients with type 2 DM. The present study was conducted to demonstrate the relationship between

Abbreviations: Hp, haptoglobin; CAD, coronary artery disease; DM, diabetes mellitus; CRP, serum C-reactive protein; PCR, polymerase chain reaction; ECG, electro-cardiograph; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; 2hsBS, 2 hours postprandial blood glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; LDL-c, low density Lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol.

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Peer review under responsibility of Ain Shams University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejmhg.2014.03.003

the Hp phenotypes and the development of CAD among Egyptian patients with type 2 DM. To our knowledge this work had not been carried out in Egypt before.

Subjects and methods: The study included 160 subjects divided into three groups. Group I: 72 type 2 DM patients without CAD, Group II: 48 type 2DM patients with developed CAD, Group III: 40 age and gender matched apparently healthy subjects to serve as controls. All patients and controls were subjected to full history taking, complete clinical examination, and routine laboratory investigations. Serum C-reactive protein (CRP) levels and serum haptoglobin levels were measured. Polymerase chain reaction (PCR) was used for Hp phenotypes' determination.

Results: Analysis revealed association between Hp2-2 phenotype and the presence of CAD in type 2 DM. Hp and CRP serum levels were significantly higher in patients with CAD. Although the levels of Hp did not reach significance among patients with different Hp phenotypes yet the individual with Hp2-2 phenotype had trend toward higher level.

Conclusion: Hp2-2 phenotype is considered to be a major susceptibility gene for the development of CAD in type 2 DM. Awareness of this gene susceptibility should raise future research for proper treatment and prevention of CAD development in type 2 DM.

1. Introduction

Regardless of efforts and advances in management, patients with type 2 diabetes Mellitus (type 2 DM) represent a significant global health problem and continue to be at high risk of cardiovascular complications. Risk factors such as hypertension, hyperlipidemia, and cigarette smoking independently increase the risk to the DM patient of developing CAD, but the effect of DM appears to be independent of conventional risk factors [1]. Identifying genes that contribute to complication development has been challenging. The susceptibility to diabetic complications is partially controlled by complex unknown genetic factors. One such genetic factor appears to be a functional allelic polymorphism in the haptoglobin (Hp) gene [2–4].

Haptoglobin (Hp) is an acute phase protein synthesized primarily in the liver, and to a lesser extent in other tissues including the lung, skin, spleen, and kidney in response to inflammatory cytokines [5]. It is a plasma α2-glycoprotein. Hp possesses an innate phenotype-dependent antioxidant, one of its main functions is to bind oxygenated, free hemoglobin with stabilization of the heme iron within hemoglobin (Hb) [6] and thereby prevents the oxidative tissue damage in areas of inflammation that may be mediated or catalyzed by free hemoglobin through the generation of highly reactive oxygen species which promotes endothelial activation and inflammation leading to endothelial dysfunction [7]. The Hp–Hb complex is rapidly removed from circulation via monocyte–macrophage cell surface scavenger receptor (CD163) mediated endocytosis by hepatic Kupfer cells [8]. Several lines of evidence have suggested the role for pro-inflammatory cytokines in regulating insulin action and glucose homeostasis. Type 2 diabetic patients exhibit higher serum levels of pro-inflammatory cytokines and acute-phase reactants [9]. Diabetes mellitus is also associated with increased oxidative stress and imbalance of antioxidant defense mechanism, that results in damage of several cellular bio molecules [10] .The role of Hp in regulation of inflammation suggests a potential role in type 2DM pathogenesis [11–12]. The ability of haptoglobin to protect against hemoglobin driven oxidative injury is abrogated when hemoglobin becomes glycated, a process that is markedly accelerated in the diabetic state. Glycohemoglobin–haptoglobin complexes are catalytically redox active and therefore the rate at which haptoglobin–hemoglobin complexes are cleared from the serum and extravascular space is of heightened importance in the diabetic state [13].

Hp is composed of four chains: 2 α chains and 2 β-chains. α and β chains are encoded by a single gene and are synthesized as a single polypeptide chain that is proteolytically cleaved into a short α chain and a long β chain that remain connected through a disulfide bond [14]. In humans, Hp is characterized by a genetic polymorphism which arises from differences in α chains while β chains are identical in all Hp types. The Hp locus is located on chromosome 16 (16q22.1). Two common alleles exist for Hp, Hp1 and Hp2 that give rise to three major phenotypes. Individuals homozygous for allele Hp1 express the phenotype 1-1, those homozygous for allele Hp2, express phenotype Hp2-2, and heterozygous individuals express phenotype Hp1-2 [15–16]. A link between Hp polymorphism and a broad range of pathological conditions has been demonstrated, and such associations probably reflect functional differences among the phenotypes [17].

A key discrepancy between the alleles is that the protein product of the Hp1 allele has a more potent antioxidant compared with that produced by the Hp2 allele [18]. This functional allelic polymorphism in the haptoglobin gene, may determine susceptibility to a wide variety of vascular disorders associated with an increase in oxidative stress [4,19–20].

There exists a growing body of evidence that diabetic vascular disease develops only in those patients who are genetically susceptible. Diabetic individuals homozygous for the haptoglobin 2 allele (Hp2-2) are at significantly greater risk of developing cardiovascular disease as compared with diabetic individuals homozygous for the haptoglobin 1 allele (Hp1-1) with an intermediate risk being found in the heterozygote [2]. Hp1-1–Hb complexes are cleared much more rapidly than Hp2-2–Hb complexes by CD163 (monocyte–macrophage scavenger receptor) providing one mechanism for decreased oxidative stress and cardiovascular disease in Hp1-1 diabetic patients [13].

To our knowledge, there is no study conducted to clarify the relationship between haptoglobin polymorphisms of Egyptian type 2 DM and the development of CAD. Therefore this study is designed to investigate the distribution of Hp