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Glucose-6-Phosphate Dehydrogenase Deficiency and Coronary Artery Disease

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Abstract: Glucose-6-phosphatase dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in humans, affecting 400 million people worldwide. It is inherited as an X-recessive linked disorder. Evidence indicates that G6PD-deficient patients are protected against cardiovascular disease. Thus we decided to test this hypothesis in male subjects expressing the G6PD deficiency phenotyp. We evaluated 420 man patients with CoronaryAartery Disease (CAD) admitted for angiography in Ahvaz Golestan Hospital. The G6PD phenotype was determined using fluorescent spot test method. Twenty-eight out of 420 (6.7%) patients were G6PD deficient. In addition, the frequency of dyslipidemia in patients with G6PD deficiency was lower than patients with normal enzyme activity ($p<0.05$). Our findings confirmed the hypothesis that susceptibility to CAD in G6PD-deficient patients is less. We suggest that protective efect may reduce LDL and total cholesterol level by inhibiting of cholesterol biosynthesis.

Key words: G6PD deficiency, coronary artery disease, cholesterol, X-recessive, LDL

INTRODUCTION

Glucose-6-phosphate Dehydrogenase (G6PD) is a cytoplasmic enzyme that present in all cells, it plays the key role in pentose phosphate pathway. Specifically, the enzyme affects the production of the reduced form of the extra mitochondrial Nicotine-Adenosine Dinucleotide Phosphate (NADPH) coenzyme by controlling the step from glucose-6-phosphate to 6-phosphogluconate in the pentose phosphate pathway. In erythrocytes, defense against oxidative damage is heavily dependent on G6PD activity, because it is the only source of NADPH, which helps to maintain the stability of catalase and preserves and regenerates the reduced form of glutathione (GSH) (Luzzatto *et al*., 2001; Beutler, 1994). The gene encoding G6PD is located in the distal long arm of the X chromosome (band Xq28). Therefore, polymorphism is more frequently observed among hemizygous men. G6PD deficiency is one of the most common human genetic abnormalities, affecting 400 million people worldwide, with a high prevalence in Sardinia, Italy (Luzzatto *et al*., 2001). According to the World Health Organization (WHO), Iran is located in an area that the enzymatic deficiency is estimated 10-14.9% (Khalesy *et al*., 2012). Based on a study, the prevalence of G6PD deficiency has been reported 7.6% in Khuzestan Province of Iran (Nezhad *et al*., 2009). More than 400 variants of the enzyme have been known, G6PD B is the wild type of allele (normal variant) (Beutler, 1991). The G6PD A+variant is associated with high enzyme levels and hence, no hemolysis. G6PD A- is associated with lower enzyme levels and acute intermittent hemolysis. G6PD A-occurs in high frequency in African, Mediterranean, and Asian variants. Mediterranean G6PD A-(also called G6PD Mediterranean) is characterized by enzyme deficiencies that are more severe than in the other G6PD A- alleles (Kirkman, 1968; Sanna *et al*.,). Beside erythrocytes, nucleated cells are also affected, including leukocytes (Chan *et al*., 1965), liver cells (Oluboyede *et al*., 1979) and cells in many other tissues (Battistuzzi *et al*., 1985).

G6PD deficiency may provoke the sudden destruction of red blood cells and lead to hemolytic anemia with jaundice following the intake of fava beans, certain legumes known as favism, or intake of some drugs (Beutler, 1991; Kirkman, 1968). Furthermore,have been reported that patients with G6PD deficient phenotype develop have lower LDL (8.8%) and apolipoprotein B (6.7%) than wild-type phenotype and suggested a 20-30% reduction in coronary risk (Muntoni *et al*., 1992).A 3% reduction in coronary risk for any 1% decrease in serum cholesterol is suggested in predictive models indicating that considerably reduce CAD risk among G6PD- deficient

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individuals (Blackburn, 1991.).In previous studiesthe less mortality rate of cardiovascular diseases than expected in G6PD deficient patients (Cocco *et al*., 1998) and we have a report of a reduction in the prevalence of coronary artery disease among patients with G6PD A phenotype (Long *et al*., 1967). We conducted a hospital-based cross-sectional study to test the primary hypothesis of a reduction in risk of CAD among G6PD deficient patients.

MATERIALS AND METHODS

Patients and methods: The present study was carried out on 420 male patients with CAD admitted for angiography in Ahvaz Golestan Hospital from October 2014 to March 2015.Informed consent was given for inclusion of the patiens.A minimum of 2 ml of blood volume was taken from each patient. The samples had been stored for less than 5 days to testing for G6PD deficiency. Tests to diagnose G6PD deficiency was done by florescent spot method. This test is most reliable and highly sensitive and classified simply as normal, or.When test shows less than 30% of the normal activity is deficient.Activities above 30% are unlikely to be accompanied by clinical manifestations. Data obtained from clinical records included: age, drug history, coronary risk factors such as arterial hypertension (Q140/90 mmHg), dyslipidaemia, diabetes, tobacco smoking, and family history of CAD. Plasma lipid profile were also analyzed in patients during the first hours of hospital admission. To assess CAD risk associated with G6PD phenotype, we used a Chi-square model. Covariates in the Chi-square were the following: age (two categories: =40,>40 years), prevalence of the G6PD deficient phenotype, dyslipidemia, hypertension, diabetes and tobacco smoking (two categories: yes/no).

RESULTS AND DISCUSSION

The frequency of dyslipidemia, hypertension, diabetes, and smoking in G6PD deficient (G6PD-) and non deficient (G6PD+) phenotype is shown in Table 1. Twenty-eight out of 420 patients were G6PD deficient; therefore, a 6.7% frequency was obtained for G6PD deficiency. G6PD deficient patients were less frequently represented among patients with CAD (6.7%) than among normal population (7.6%) (Nezhad *et al*., 2009). In addition, the frequency of dyslipidemia in patients with G6PD deficiency was lower than patients with normal enzyme activity ($p<0.05$).

Our findings confirmed the hypothesis that a significant protective effect of G6PD deficiency against CAD is due to its genetic condition. Our results are consistent with the previous studies mortality in cohort men expressing the G6PD deficient phenotype (Cocco *et al*., 1998) and with a cross-sectional study of G6PD deficient phenotype A (Long *et al*., 1997).Experimental studies also, support the hypothesis (Matsui *et al*., 2006).In G6PD deficiency Due to reduced HMG-CoA reductase activity the biosynthesis of cholesterol reduced (Muntoni *et al*., 1992; Muntoni, 2003; Muntoni, 2001).It has been suggested for reducing the development of atherosclerosis (Abedi *et al*., 2012).

Table 1: Prevalence of the risk factors in G6PD deficient and non deficient patients

Risk Factor	G6PD-(N=28)	G6PD+(N=392)	p-value
	%	%	
Age			0.1
>40 Year	25	75	
=40 Year	8	92	
Dyslipidemia	14	34	0.02
Hypertension	17.5	34	0.5
Diabetes	32	32.5	0.5
Tobacco Smoking	50	36	0.1

Our analysis showed evidence among the study population of a significant reduction in blood levels of LDL and cholesterol in G6PD deficient phenotype. A total of 33% of our patients had dyslipidemia while only 3% of them were deficient. It should be noted that Statin drugs, used for the treatment and prevention of CAD, are potent HMG-CoA reductase and cholesterol biosynthesis inhibitors (Cannon *et al*., 2004 Sheperd *et al*., 1995) and down regulate NADPH oxidase (Endres, 2006) similar to G6PD deficiency. Indeed, there are evidences that the clinical benefits of these drugs in addition to the effect on blood cholesterol levels. Accordingly, treatment with statins and the G6PD deficient phenotype may delay development of atherosclerosis even independently of a reduction in cholesterol synthesis. We believe that the Prevention of the development of oxidative stress due to NADPH deficiency has protective effect of G6PD deficiency on CAD (Leopold *et al*., 2001;Meloni *et al*., 2008; Abedi and Rostami, 2012).

However more population studies are needed to better evaluated the effects of G6PD deficiency on atherosclerosis and pathophysiology of cardiovascular disease in humans.

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