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Is it time to screen for the Haptoglobin genotype to assess the cardiovascular risk profile and vitamin E therapy responsiveness in patients with diabetes?

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Abstract

Diabetes mellitus (DM) carries an increased risk for cardiovascular complications. Haptoglobin (Hp) is an abundant plasma protein with an anti-oxidant function by virtue of its ability to block the oxidative activity of extracorposcular hemoglobin. There exist two common functional alleles at the Hp genetic locus, denoted 1 and 2, with three Hp genotypes (Hp 1-1, 2-1 and 2-2). The Hp protein expressed in Hp 2-2 individuals is markedly inferior in protecting against hemoglobin induced oxidative stress. Hp 2-2 DM individuals have been shown to be at increased risk for the development of diabetes complications, particularly diabetic cardiovascular disease (CVD). We review here the biological mechanisms underlying the interaction between the Hp genotype and DM on CVD and the accumulating evidence in favor of Hp genotyping all individuals with DM and providing antioxidant vitamin E supplementation specifically to Hp 2-2 DM individuals in order to reduce their CVD morbidity and mortality.

Keywords

Diabetes mellitus; cardiovascular risk; haptoglobin; vitamin E

Introduction

People suffering from diabetes mellitus (DM) are prone to an array of complications in target organs. Accelerated atherosclerosis is prevalent in this population, and is a leading cause of morbidity and mortality. Interventions to tightly control plasma glucose levels have been proven vital in the control of microvascular complications[1, 2]. However, the importance of strict glycemic control on macrovascular clinical outcomes is a matter of considerable debate[3]. Additionally, interventions to control cardiovascular (CV) risk such as life-style interventions and pharmacotherapy with statins and angiotensin converting enzyme inhibitors are not always applicable, due to patient preferences or related costs[4], as well as questionable effectiveness[5, 6]. In this respect, it is of paramount importance to assess new and novel approaches to control atherosclerosis in DM, outside the scope of traditional health-care.

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Disclosure Statement. Dr Levy is the author of a series of patents which claim that the Hp genotype is predictive of CVD in individuals with DM and that vitamin E may be used in combination with the Hp genotype to reduce CVD risk. He is also the chief scientific officer of Haptocure which has licensed these patents from his university.

Atherosclerosis, cardiovascular risk, and DM

Atherosclerosis is one of the direst consequences of DM, and over 75% of DM patients die of atherovascular disease[7]. Indeed, when compared to individuals without DM, patients with DM are not only at increased risk for atherosclerosis, but also carry a greater extent of disease burden [8-10]. The pathogenesis of atherosclerosis in DM is multifactorial. Endothelial dysfunction is the hallmark of the pathological insult inflicted on blood vessels of DM individuals. It is aggravated by conditions such as hyperglycemia, hypertension, hyperlipidemia and smoking, and results in the loss of the ability to autoregulate vascular tone via reduced nitric oxide (NO) release, in increased endothelial wall permeability, and in the accumulation of lipids, monocytes/macrophages, and platelets in the subendothelium. These pathologic changes eventually lead to the formation of atherosclerotic plaques and its clinical implications[11, 12]. The role of oxidative stress in mediating the development of atherosclerosis has been formulated in the oxidative hypothesis[13]. In this model the most prominent target for oxidative modification is the LDL molecule. Oxidized LDL is not recognized by the LDL receptor but is readily taken up by the CD36 scavenger receptor pathway in macrophages leading to appreciable cholesterol ester accumulation and foam cell formation[14]. Oxidized LDL has multiple biological consequences. It is pro-inflammatory, causes inhibition of endothelial nitric oxide synthetase, promotes vasoconstriction and monocyte adhesion, and promotes platelet aggregation and thrombosis[15]. DM is known to be associated with increased oxidative stress and LDL oxidation[16].

Many patients with DM have additional cardiovascular risk factors[17]. These confer a risk which is not only additive, but often synergistic, for vascular complications[18, 19]. Additionally, it is speculated that metabolic alterations associated with DM may impair the energetic and functional adaptation of the heart to ischemia or hemodynamic overload, thus conferring worse clinical outcomes in the event of a macrovascular-driven event[20].

Haptoglobin genotype and activity

Haptoglobin (Hp) is an abundant plasma glycoprotein synthesized by hepatocytes. Two classes of functional alleles (1 and 2) have been identified at the Hp locus on chromosome 16q22, with homozygous (1-1 or 2-2) and heterozygous (2-1) genotypes possible[21, 22]. Structurally, Hp is found as a dimer in Hp 1-1 individuals, a linear polymer in Hp 2-1 individuals and a cyclic polymer in Hp 2-2 individuals[23]. The frequency of the 3 Hp genotypes in western counties is approximately 16% Hp 1-1, 48% Hp 2-1 and 36% Hp 2-2[21, 22] and is the same in individuals with and without DM[24].

The best known function of Hp is to bind free hemoglobin (Hb) released from red blood cells[21], which is released into the blood during the natural turn-over of red cells. Free Hb is capable of causing considerable oxidative tissue damage as a result of its heme iron. However, whenever Hb is released into the circulation it immediately binds to Hp with extremely high affinity (Kd ~10^{-15}) to form an Hp-Hb complex. The binding of Hp to Hb serves to inhibit the oxidative potential of Hb by preventing the release of heme iron from Hb[25-27]. Hp is normally found in the blood in a more than 400-fold molar excess to free Hb (10 μM vs. 25 nM) and therefore Hp is capable of binding all of the Hb that is released during normal red blood cell turnover[22, 28]. Once Hb is bound to Hp it is rapidly cleared from the bloodstream via the CD163 scavenger receptor expressed on monocyte/macrophages.

Hp gene polymorphism in patients with DM

The pathophysiological mechanism by which the Hp genetic polymorphism is translated into a pathological insult in DM is a result of functional differences between the Hp allele 1 and Hp allele 2 protein products. As described above, Hp is essential to the clearance of Hb. By

forming the Hp-Hb complex, Hp prevents oxidative stress on the vasculature exerted by Hb iron. Hp-Hb clearance is mediated by the scavenger receptor CD163[29]. Studies have shown that Hp 2-2-Hb complexes are cleared less efficiently than non Hp 2-2-Hb complexes [25, 27]. In DM individuals this phenomenon is more pronounced due to the down regulation of CD163, particularly in Hp 2-2 individuals[30]. Hp-Hb deficient clearance in Hp 2-2 DM individuals results in increased Hp-Hb binding to Apo A1 on high-density lipoprotein (HDL), thereby tethering the prooxidative heme moiety to HDL[31]. HDL in Hp 2-2 DM individuals is deficient in its ability to stimulate the reverse transfer of cholesterol from macrophages[31]. Oxidative modification of the HDL appears to be responsible for these alterations in HDL function in DM individuals with Hp 2-2[32].

One case-control and five prospective longitudinal studies have assessed the association between Hp genotype and the event rates of stroke, non-fatal MI, cardiovascular death, heart failure and mortality, in DM (Table 1). In the Strong Heart Study (SHS), a population based longitudinal study in Native Americans, 206 incident cases (over an interval of six years) and 206 matched controls were analyzed[33]. In a multivariate analyses controlling for conventional CV risk factors, the Hp genotype was a highly statistically significant, independent predictor of CV outcomes in DM. The odds ratio (OR) in the SHS study of having CV disease in DM with the Hp-2-2 genotype was 5.0 times greater than in DM individuals with the Hp-1-1 genotype.

In prospective longitudinal trials, 1829 patients with DM and the Hp 2-2 genotype and 3135 patients with DM and the Hp 1-1 or Hp 2-1 genotypes, were followed for periods ranging between 30 days and a mean of 18.8 years. Patients enrolled in the ICARE study[34], and a subset of patients from the Women's Health Study (WHS)[35, 36] and the Heart Outcomes Prevention Evaluation (HOPE)[37, 38] trials, were studied for total mortality, CV mortality, non-fatal MI and stroke. When comparing DM patients with Hp 2-2 to a group of non-2-2 Hp type patients (Hp 1-1 and 2-1), a harmful effect of Hp 2-2 genotype was observed. For CV mortality, the pooled percentage of patients experiencing an event was 3.4% versus 1.2%, for the Hp 2-2 versus the non-2-2 Hp groups, respectively. For stroke, the percentages were 2.8% versus 1.7%, respectively. For non-fatal MI data from a fourth trial was available[39], and the combination of these 4 studies have shown that the percentage of patients experiencing an event in the Hp 2-2 group was 6.29%, versus 3.74% in non-2-2 Hp patients. The odd ratios (ORs) for CV mortality, stroke, and non-fatal myocardial infarction all suggest a harmful effect for Hp 2-2 genotype with statistical significance (2.37 (95% confidence interval (CI) 1.32 to 4.24), 2.08 (95% CI 1.22 to 3.55), 1.94 (95% CI 1.39 to 2.71), respectively). Combining a total of CV mortality, strokes and non-fatal MIs also shows a striking difference in events of 9.35% versus 5.76% (OR of 2.03 (95% CI 1.46 to 2.81). Total mortality assessed in three trials [39-41] was higher in the Hp 2-2 group (10.54% versus 6.97%, OR 1.53 (95% CI 1.17 to 2.00)). These effects were maintained after adjusting for the duration of follow-up.

Vitamin E, Hp, and cardiovascular risk reduction

Functional differences between the Hp 1 and Hp 2 allelic protein products particularly in DM can explain why there are differences in susceptibility to DM complications in non Hp 2-2 and Hp 2-2 DM individuals and why these groups may differ in the ability of vitamin E supplementation to provide clinical benefit. The main reason why Hp 2-2 DM individuals appear to uniquely derive benefit from vitamin E is that redox active Hb is associated with HDL only in Hp 2-2 DM individuals[27].

There have been only three interventional randomized controlled trials (RCTs) in which the only antioxidant which the DM participants received was vitamin E and in which the Hp type of study participants was determined. The ICARE[34] study was a RCT aimed to

evaluate this intervention in DM patients for which the Hp genotype was prospectively collected. Additionally, blood samples from a subset of patients recruited for the WHS [35,36] and HOPE[37, 38] studies were analyzed for Hp polymorphism, and the outcomes were re-assessed according to the patient's Hp type. In all of these studies, it was found that Hp 2-2 DM conferred a higher risk for cardiovascular mortality without intervention (compared to the non-2-2 Hp cohort), and that intervention with vitamin E significantly decreased this risk. Meta-analysis of the HOPE and ICARE data showed that vitamin E significantly reduces a composite of CV mortality, MI and stroke in Hp 2-2 diabetes patients (OR 0.58, confidence interval (CI) 0.4-0.86), while having no influence in Hp 1-1 or Hp 1-2 diabetes patients[42]. In the WHS cohort, Vitamin E supplementation was associated with an approximately 15% reduction in composite CV outcomes in Hp 2-2 DM individuals, compared to a 20–25% increase in non-Hp 2-2 DM individuals [36].

Simulation of the results from ICARE and HOPE studies over 50 years in the Kaiser Permanente Northwest region population (California, USA), has shown that screening diabetic patients and treating Hp 2-2 patients with vitamin E, would add 1.09 and 3.04 years/person and 0.89 and 2.49 quality-adjusted life years/person to the whole population and to Hp 2-2 diabetics, respectively. Per 1000 Hp 2-2 individuals, treatment would prevent 75 myocardial infarctions, 31 cardiac surgical procedures and 19 per cutaneous cardiac interventions[42].

Conclusions

The clinical outcomes of patients with DM and Hp 2-2 genotype, together with the understanding of the reasons for their increased vulnerability for cardiovascular events, and the apparent risk reduction with vitamin E therapy in Hp 2-2 DM, has given rise to a possible novel pharmacogenomic approach to reduce Diabetic CV disease.

Preclinical *in vitro* and *in vivo* studies have provided a strong rationale for this pharmacogenomic paradigm. These studies have provided an understanding of the unique pathological cascade related to Hp 2-2 particularly in the setting of hyperglycemia, resulting in increased atherosclerosis. These preclinical studies have also provided a reasonable explanation for the responsiveness of Hp 2-2 DM patients to vitamin E. Moreover, data from human subjects from three independent RCTs have shown that individuals with Hp 2-2 significantly benefit from vitamin E intervention.

This pharmacogenomic modality of treatment is of a unique nature in view of its low cost and wide availability. Cardiovascular complications of DM cost over $174 billion annually in the US alone and account for 80% of all deaths in individuals with DM[4, 43, 44]. The prevalence of DM is increasing at an alarming rate, particularly among individuals of lower socioeconomic status in the US as well as in the developing world[43,45,46]. The requirements for Hp typing, although not readily available for commercial use, are expected to be simple and inexpensive. In the broader context of public, policy-makers', and professionals' attention moving towards personalized medicine[47], and with growing budget constraints, this pharmacogenomic paradigm seems even more sound. If these results are validated in another RCT, Hp genotyping and the subsequent prescription of vitamin E based on the Hp genotype may become a part of routine medical care for all DM individuals.

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Longitudinal studies assessing CV outcomes according to Hp phenotype in patients with DM

Trial	Vitamin E	Follow-up [years]	Specific patient characteristics	Number of patients	Clinical outcomes	Results
Levy 2002[33]	No	6	Native Americans	412	CV disease event	OR [95% CI] for CVD event: Hp 2-2 vs. 1-1: 5.08[2.37-10.89], p<0.001 Hp 2-2 vs. 2-1: 3.26[1.67-6.37], p<0.001
Burbea 2004[40]	No	3	Hemodyalisis	392	Total mortality	Kaplan–Meier 3 years survival, age< 60: Hp 2-2: 45.1%; Hp non 2-2: 50%; p < 0.003.
Costacou 2008[48]	No	18	CV disease free, type 1 diabetics	453	CV disease events	Cox proportional model, HR [95% CI]: Hp 2-2 vs. non 2-2: 2.21[1.05-4.65], p =0.04
Roguin 2003 [39]	No	1	Post PTCA	935	Total MI, total mortality, target vessel revasculation, MACE (= combination of all)	Cox proportional model: Hp 1-1: 20.9%; Hp 2-1, 26.4%; Hp 2-2: 31.4%; p = 0.015
Suleiman 2005 [41]	No	30 days	Acute MI	506	Composite (30 days mortality + heart failure)	Multivariate linear regression, OR [95% CI]: Hp 1-1 vs. Hp 2-2: 0.35[0.15-0.86], p = 0.018

HOPE- Heart Outcomes Prevention Evaluation; WHS- Women's health study. CV= Cardiovascular, DM= diabetes mellitus, Hp= haptoglobin, OR= Odds Ratio, HR= Hazard Ratio

Table 1b

Longitudinal studies assessing CV outcomes according to Hp phenotype with and without vitamin E treatment

Trial	Vitamin E	Follow-up [years]	Specific patient characteristics	Number of patients	Clinical outcomes	OR [95% CI]+ in Hp 2-2 patients	OR [95% CI]+ in non Hp 2-2 patients
WHS study data [36, 35]	Yes, 600IU QD	8	CV disease free, women	721	Total MI, total stroke, CV mortality, composite (= first MI + first stroke + CV mortality), cancer	0.87 [0.49, 1.53]	1.02 [0.69, 1.50]
Milman 2008 [34]	Yes, 400IU QD	1.5	CV disease free	2967	Total MI, total stroke, CV mortality, composite (= first MI + first stroke + CV mortality)	0.46 [0.25, 0.85]	N/A
HOPE study data [37, 38]	Yes, 400IU QD	4.5	CV disease free	530	First MI, first stroke, CV mortality, composite (= first MI + first stroke + CV mortality)	0.69 [0.42, 1.13]	1.02 [0.69, 1.50]

CV= cardiovascular; MI= myocardial infarction.

+OR for for a composite outcome of first MI, first stroke and cardiovascular mortality, vitamin E vs. placebo.