Published in final edited form as:

Eur J Intern Med. 2012 October ; 23(7): 628–632. doi:10.1016/j.ejim.2012.04.009.

Haptoglobin genotype and cardiovascular outcomes in diabetes mellitus — natural history of the disease and the effect of vitamin E treatment. Meta-analysis of the medical literature

Moshe Vardi^{a,b,*}, Shany Blum^c, and Andrew P. Levy^c

^aDepartment of Medicine, Carmel Medical Center, Haifa, Israel

^bHarvard Clinical Research Institute, Boston, USA

^cThe Ruth and Bruce Rappaport Faculty of Medicine. Technion — Israel Institute of Technology, Haifa, Israel

Abstract

Background—Diabetes mellitus carries a high risk for vascular events. Diabetics with different haptoglobin (Hp) types may carry different risk profiles, and may respond differently to vitamin E treatment. We aim to summarize the evidence about cardiovascular risk in diabetic patients, according to their Hp type, and the effect of vitamin E treatment on these sub-groups.

Methods—We searched MEDLINE and on-going trials' databases until February 2011; gray literature; reference lists of identified articles; and experts. Two investigators screened and selected studies that prospectively followed cardiovascular outcomes in diabetic patients with different Hp types (natural history analysis), and randomized controlled trials reporting the effect of vitamin E on cardiovascular outcomes in diabetics, in which Hp typing was performed (interventional analysis).

Results—Five and three studies, comprising 1829 and 2110 patients, were eligible for the natural history and the interventional analyses, respectively. The percentage of diabetic patients experiencing non-fatal MI, stroke, or cardiovascular death was significantly higher in the Hp 2–2 population (odds ratio (OR) 2.03 (95% confidence interval (CI) 1.46 to 2.81)). In patients with Hp 2–2 genotype, the OR for a combined endpoint was 0.66 in favor of the vitamin E treated group (95% CI 0.48 to 0.9). This effect was not shown in other Hp types.

Conclusion—Hp type 2–2 carries a high risk of cardiovascular events in diabetic patients. A pharmacogenomic approach towards treatment of diabetic patients with vitamin E may be warranted.

Keywords

Diabetes mellitus; Haptoglobin; Vitamin E; Cardiovascular complications

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*Corresponding author at: Harvard Clinical Research Institute, 930 Commonwealth Avenue, Boston, MA 02215, USA. Tel.: +1 617 307 5567. vardi.moshe@gmail.com (M. Vardi).

Conflict of interest

Dr. Vardi has no conflicts of interests. Dr. Blum is the CEO of Haptocure. Dr. Levy is presently on the board of Haptocure. Dr. Levy is the owner and Dr. Blum is co-author of patents which are owned by the university in which he works which claim that the Hp genotype can predict the development of diabetic complications and that vitamin E can reduce these complications in individuals with the Hp 2–2 genotype.

1. Background

Diabetes mellitus is a chronic and deleterious disease, with short and long term complications. Not only is the current public health and economic burden of diabetic CVD overwhelming, but the prevalence of DM is increasing at an alarming rate, particularly among individuals of lower socioeconomic status in the US and Europe, as well as in the developing world [1–4]. Accelerated atherosclerosis is one of the direst consequences of diabetes, and over 75% of diabetic patients die of atherosclerotic disease [5]. The goals of therapy for diabetic patients are to eliminate the symptoms of hyperglycemia, reduce the long term microvascular and macrovascular complications and allow the patients to achieve a normal life-style. These are traditionally achieved with hypoglycemic medication, and control of concomitant cardiovascular risk factors using best standard of care medications. These standard-of-care medications (e.g. statins and ACE inhibitors) to prevent diabetes-related CVD complications are neither affordable nor accessible to these populations [6]. Moreover, recent data from the ACCORD [7] and ADVANCE [8] studies and data from satellite publications [9,10] assessing these strategies in type 2 diabetics raise serious doubts regarding the effectiveness and even more the safety of these interventions and their clinical goals.

The haptoglobin (Hp) protein is an antioxidant due to its ability to neutralize the oxidative activity of hemoglobin (Hb) [11]. There exist two classes of alleles at the Hp locus in man denoted 1 and 2. The protein product of the Hp 2 allele is an inferior antioxidant compared to the Hp 1 allele product [12]. We have shown in 7 independent longitudinal studies that the Hp 2–2 genotype is associated with a 2–5 fold increased risk of incident CVD in individuals with diabetes (DM) [13–18].

In addition, we have shown in 3 independent intervention trials with vitamin E in diabetic patients that there appears to exist a pharmacogenetic interaction between the Hp genotype and vitamin E on the development of CVD in individuals with DM [18]. Vitamin E appears to provide substantial cardiovascular benefit to Hp 2–2 DM [15,18] individuals, and it appears to promote CVD in Hp 2–1 DM individuals [18].

The purpose of this systematic review and meta-analysis of the medical literature is to summarize the data from prospective trials related to the incidence of cardiovascular complications in patients with diabetes mellitus, according to their Hp genotype. We also aimed to assess the influence of vitamin E treatment on the incidence of cardiovascular complications in diabetic patients, according to their Hp type, as projected from randomized controlled trials.

2. Research design and methods

2.1. Search

We searched *The Cochrane Library* and MEDLINE (until February 2011) to identify relevant trials. We also searched databases for ongoing trials: Current Controlled Trials, UK National Research Register, Center Watch Clinical Trials Listing Service and National Institute of Health. We tried to identify additional studies by searching the reference lists of relevant trials and reviews identified. The authors of published trials and experts in the field were contacted for further leads and clarifications. Search for identification of studies was not restricted by language. The search protocol was divided into two parts. In the first part, trials in which a prospective follow-up assessing cardiovascular outcomes in diabetic patients with Hp 2–2 genotype versus other genotypes (namely 1–1 and 1–2) were included (natural history meta-analysis). In the second part, randomized controlled trials (RCTs) in which diabetic patients were treated with vitamin E versus placebo, and in which Hp

genotypes were sought, were included (interventional meta-analysis). Studies in which Hp genotypes were not assessed, or in which vitamin E was given with additional supplements (e.g. vitamin C), were excluded. Trials with a follow-up period of any duration were included. Two reviewers (MV, SB) independently scanned the titles, abstract sections and keywords of every record retrieved. Full articles were retrieved for further assessment if the information given suggested that the study fulfilled the inclusion criteria and did not meet the exclusion criteria. Differences in opinion were resolved through open discussion.

The quality of RCTs was assessed with quality criteria specified by Schulz and by Jadad [19,20]: minimisation of selection bias, minimisation of performance bias, minimisation of attrition bias and minimisation of detection bias. Based on these criteria, RCTs were broadly subdivided into the following three categories: (A) all quality criteria met: low risk of bias; (B) one or more of the quality criteria only partly met: moderate risk of bias; and (C) one or more criteria not met: high risk of bias. Non-RCTs were not assessed for quality.

2.2. Statistical analysis

Data were summarized statistically if they were available, similar, and of sufficient quality. Heterogeneity was identified using the formal chi-square test, with a P value of less than 0.10 considered statistically significant. The Mantel-Haenszel method was used for fixed-effect analysis. The effect of treatment was expressed with relative effect measures due to the dichotomous nature of the data (events per population).

We aimed to perform a subgroup analysis, according to the following predefined groups: gender, baseline characteristics, type and dose of vitamin E supplements. We also performed a sensitivity analysis in order to explore the influence of the following factors on effect size: study quality, exclusion of large trials, and trials with different durations of follow-up. The robustness of the results was also tested by repeating the analysis using different measures of effect size (risk difference, odds ratio, etc.) and different statistical models (fixed and random effects models).

3. Results

3.1. Trials identified

For the natural history meta-analysis, 281 records were retrieved using the combined search strategy of this review. After screening the headings and abstracts, five studies finally met the inclusion criteria [15–17,21,13]. For the interventional meta-analysis, eight records were retrieved using the electronic search strategy of this review, of which one [15] was included. For these searches, the inter-rater agreements for study inclusion were 0.92 and 1, respectively. A search through databases of ongoing trials did not reveal additional eligible trials. Hand searching through reference lists yielded one additional article for full text evaluation [22], in which data from the Heart Outcomes Prevention Evaluation (HOPE) [23] study was analyzed. After contacting experts in the field, we identified another publication from which eligible data could be extracted [18], in which data from the Women's Health Study (WHS) study was analyzed [24]. In these two studies, Hp analysis was not defined as an outcome of the original study, and Hp subgroup genotyping was performed in arbitrary patients selected from these trials in a retrospective manner. They were eligible for both the natural history and the interventional arms (see Fig. 1 for details).

Table 1 summarizes the characteristics and quality of trial identified.

1829 patients with diabetes and Hp 2–2 genotype and 3135 patients with diabetes and Hp genotypes 1–1 or 1–2 were followed without intervention for a period ranging between 30 days and a mean of 18.8 years in the studies identified for the natural history meta-analysis.

In the interventional meta-analysis, a total of 1094 patients with diabetes and Hp 2-2 genotype were treated with vitamin E, compared to 1016 patients given placebo. In the group of diabetics with Hp genotypes 1-1 or 2-1, 541 were given vitamin E, while 2115 were given placebo.

For the natural history trials included, sub-groups from the ICARE and HOPE studies did not differ significantly with respect to age, medical history, weight, concomitant medication, and diabetes mellitus severity or duration. These data were not available for the WHS cohort. For the interventional trials, baseline characteristics of patients from HOPE and ICARE were similar. WHS included only female patients. Valid diagnostic criteria for diabetes mellitus were not described.

4. Outcome measures

4.1. Natural history meta-analysis

The combined endpoint of the number of patients experiencing non-fatal MI, stroke, or cardiovascular death was significantly more prevalent in the Hp 2-2 population, with an odds ratio (OR) of 2.03 (95% confidence interval (CI) 1.46 to 2.81), signifying Hp 2-2 genotype to be harmful (Fig. 2). The OR for stroke, cardiovascular death, and non-fatal myocardial infarction all suggest a harmful effect for Hp 2-2 genotype with statistical significance (2.08 (95% CI 1.22 to 3.55), 2.37 (95% CI 1.32 to 4.24), 1.94 (95% CI 1.39 to 2.71), respectively). The OR for total mortality was 1.53 (95% CI 1.17 to 2.00) with statistical significance suggesting higher death rates for patients with Hp 2-2. In the trials assessing coronary artery disease, heart failure combined with mortality at 30 days, and target vessel revascularization (one trial for each endpoint), Hp 2-2 genotype was harmful but without statistical significance. We also examined the event rate per 1000 patients per year for stroke, cardiovascular death, non-fatal myocardial infarction and the combined endpoint. The weighted mean difference for all these showed Hp 2-2 genotype to be harmful, all with statistical significance (Table 2).

4.2. Interventional meta-analysis

The combined endpoint in all trials was the number of patients experiencing non-fatal MI, stroke, and cardiovascular deaths. In patients with Hp 2-2 genotype, the OR for a combined endpoint was 0.66 in favor of the vitamin E treated group, with statistical significance (95% CI 0.48 to 0.9). In patients with Hp 1-1 and 1-2, the OR for the combined endpoint was 1.11 (95% CI 0.80 to 1.53). The minimal overlap between the confidence intervals signifies significant interaction between the type of Hp and the outcome (Fig. 3).

In the group of patients with Hp genotype 2-2, the ORs for a first stroke, non-fatal myocardial infarction, and cardiovascular death, were 0.78 (95% CI 0.45 to 1.35), 0.60 (95% CI 0.39 to 0.91), and 0.47 (95% CI 0.26 to 0.85), respectively, in favor of the vitamin E treatment group. The latter two were statistically significant. In the Hp 1-1 and 1-2 population, none of these outcomes was statistically significant or with a tendency towards favorable outcomes with vitamin E or placebo. Total mortality was not significantly altered in the two groups. When assessing these events per 1000 patients per year, the weighted mean difference between vitamin E and placebo treated patients with Hp 2-2 were all significantly in favor of the intervention group. These effects were significantly more prominent and without overlap of confidence intervals, in patients with Hp 2-2 genotype than in those with non 2-2 genotype. (Table 2)

4.3. Heterogeneity and subgroup analysis

The only parameter assessed with moderate heterogeneity was cardiovascular deaths in the natural history arm. This was explained by the very low death rate in diabetics with Hp 1–1 or 1–2 genotypes in one of the trials included [15], which was probably related to the shorter duration of follow-up in this trial.

A formal subgroup analysis according to predefined criteria was not feasible due to lack of reporting regarding the clinical and interventional parameters.

A post hoc exclusion of studies assessing specific medical scenarios such as heart failure and acute coronary events [16,17,21] did not affect the robustness of the results.

4.4. Sensitivity analysis

The influence of quality of studies was assessed by a sensitivity analysis. The results did not change after assessing the influences of total study quality, specific quality criteria, length and size of the included trials. Two of the assessed outcomes had lost their statistical significance after different statistical methods had been employed: the rate of non-fatal myocardial infarction in the interventional arm (random effect analysis model), and the rate of cardiovascular death in the natural history arm (inverse-variance statistical method and random effect analysis model).

4.5. Assessment of publication bias

Funnel plots were symmetric for the combined endpoints.

5. Discussion

The role of oxidative stress in mediating the development of atherosclerosis has been formulated in the oxidative hypothesis [25]. However, large clinical trials assessing anti-oxidant supplementations in diabetic patients have failed to show clinical benefit with this sound intervention.

Hp is an antioxidant with variable efficacy to reduce oxidative stress, with Hp 1–1 being superior to Hp 2–2 in blocking the production of reactive oxygen species [12,26] mediated by hemoglobin. In this systematic review and meta-analysis of the medical literature we have shown that in trials in which Hp typing was performed, patients with Hp types 1–1 and 1–2 (non 2–2) had better short and long term cardiovascular outcomes. In this respect, the data presented implies that the inferiority of Hp 2–2 as an anti-oxidant may carry true clinical consequences in diabetic patients. When re-assessing interventional trials in which vitamin E was given to patients with diabetes mellitus, our results indicate with statistical significance that this intervention in patients with Hp type 2–2 altered the clinical course of their disease. Our results also imply that this change is truly the result of the Hp type, with an interaction which was either statistically significant or close to significance.

While evaluating the effect of Vitamin E treatment on diabetic individuals, we have excluded from the analysis any combination treatment and have concentrated on studies using natural source vitamin E as a single intervention. We have previously shown that vitamin C may in fact increase the risk of Hp 2–2 diabetic patients for cardiovascular complications due to the pro oxidative effect of vitamin C in the presence of labile (free) iron, as is the case in Hp 2–2 diabetic patients. Since not all antioxidants exert the same effect on diabetic patients and in order to eliminate bias and confusion in the interpretation of the results, we have decided to concentrate on one intervention which was also shown to be beneficial both in vitro, in vivo and in man.

Our study has several limitations. In the natural history analysis, clinical scenarios differed widely. In both analyses, the length of follow-up varied widely. We therefore calculated the event rate per 1000 patients per year, and showed that the results did not change. In the interventional analysis, two of the included trials did not specifically aim to assess Hp typing and its effect on outcomes, and the data were retrospectively analyzed. However, baseline characteristics for the patients from these trials (excluding gender) were similar.

In most western populations the prevalence of the Hp 1–1 genotype (homozygous for the Hp 1 allele) is 16%, the Hp 2–2 genotype is 36% and the Hp 2–1 genotype is 48% [11]. It is thus indicative that over a third of diabetic patients may benefit from vitamin E treatment and that commercial genotyping of diabetic patients to determine their Hp type is warranted. Although larger controlled clinical trials are indicated to substantiate the findings illustrated herein, we believe this innovative pharmacogenomic approach towards the reduction of cardiovascular complications in a major subset of diabetic patients may become an essential part in the arsenal of diabetes care.

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Learning points

1. Haptoglobin type 2-2 is prevalent in diabetics.
2. Haptoglobin type 2-2 is associated with increased risk for cardiovascular morbidity and mortality in diabetics.
3. Vitamin E is associated with a reduced risk for cardiovascular complications in patients with diabetes mellitus and haptoglobin type 2-2.

Fig. 1.
Studies identified.

Fig. 2.
 Combined endpoints for the natural history trials.

Fig. 3.
Combined endpoint Vitamin E versus placebo for Hp 2–2 and non Hp 2–2 patients.

Table 1

Characteristics and quality of included studies.

Trial	Meta analysis	Follow up in years	Specific patient characteristics	Number of patients	Vitamin E dose	Clinical outcomes	Total quality
Burbea 2004[21]	Natural history	3	Hemodialysis	392	N/A	Total mortality	Non-RCT
Costacou 2008 [13]	Natural history	18	CV disease free, type 1 diabetics	453	N/A		Non-RCT
Roguin 2003 [16]	Natural history	1	Post PTCA	935	N/A	Total MI, total death, target vessel revascularization, MACE (= combination of all)	Non-RCT
Suleiman 2005 [17]	Natural history	30 days	Acute MI	506	N/A	Composite (30 days mortality+heart failure)	Non-RCT
WHS study data [18,24]	Natural history and interventional	8	CV disease free, women	721	600 IU QD	Total MI, total stroke, CV death, composite (= first MI+first stroke+CV death), cancer	A
Milman 2008 [15]	Natural history and interventional	1.5	CV disease free	2967	400 IU QD	Total MI, total stroke, CV death, composite (= first MI+first stroke+CV death)	A
HOPE study data [22,23]	Natural history and interventional	4.5	CV disease free		400 IU QD	First MI, first stroke, CV death, composite (= first MI+first stroke+CV death)	A

CV — cardiovascular, HOPE — Heart Outcomes Prevention Evaluation, IU — international units, MI — myocardial infarction, PTCA — percutaneous coronary angiography, QD — once daily, RCT — randomized controlled trial, WHS — Women's Health Study.

Table 2

Summary of outcomes.

Outcome	Number of trials	Number of patients	Odds ratio (MH, fixed, 95% CI)	Mean difference (IV, fixed, 95% CI)	Statistical significance
Natural history arm					
Combined endpoint	3	2879	2.03 (1.46, 2.81)	14.8 (14.42, 15.18)	Y
Cardiovascular death	3	2879	2.37 (1.32, 4.24)	3.93 (3.78, 4.08)	Y
Stroke	3	2879	2.08 (1.22, 3.55)	4.10 (3.87, 4.33)	Y
Non-fatal myocardial infarction	4	3814	1.94 (1.39, 2.71)	8.75 (8.48, 9.01)	Y
Total mortality	6	4484	1.53 (1.17, 2.00)	7.24 (6.99, 7.49)	Y
Experimental arm					
Combined endpoint	3	2110	0.66 (0.48, 0.90)	-12.68 (-13.09, -12.27)	Y
Hp non 2-2		2656	1.11 (0.80, 1.53)	2.25 (1.71, 2.78)	N
Cardiovascular death	3	2110	0.47 (0.26, 0.85)	-2.39 (-2.56, -2.21)	Y
Hp non 2-2		2656	0.84 (0.51, 1.38)	-1.32 (-1.62, -1.03)	N
Stroke	3	2110	0.78 (0.45, 1.35)	-3.41 (-3.66, -3.17)	N
Hp non 2-2		2656	1.53 (0.85, 2.76)	2.66 (2.37, 2.95)	N
Non-fatal myocardial infarction	3	2110	0.60 (0.39, 0.91)	-7.51 (-7.80, -7.21)	Y
Hp non 2-2		2656	0.97 (0.66, 1.43)	-0.09 (-0.48, 0.30)	N
Total mortality	3	2110	0.81 (0.55, 1.20)	-1.18 (-1.47, -0.89)	±
Hp non 2-2		2656	0.82 (0.57, 1.19)	-3.04 (-3.53, -2.55)	±

Hp — haptoglobin, IV — inverse variance, MH — Mantel-Naenszel, ± — statistical significance for the events per 1000 patient years only