Targeting HDL Quality Rather than Quantity: Providing the Mechanistic Rationale for the Pharmacogenomic Interaction Between the Haptoglobin Genotype and Vitamin E on Cardiovascular Disease in Individuals with Diabetes Mellitus

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Objective. Pharmacogenomics is a key component of personalized medicine. ICARE, a prospective placebo controlled study, recently demonstrated vitamin E could dramatically reduce CVD in individuals with Diabetes Mellitus (DM) and the Haptoglobin (Hp) 2-2 genotype (40% of DM individuals). However, due to the large number of clinical trials which failed to demonstrate benefit from vitamin E coupled with the lack of a mechanistic explanation for why vitamin E should be beneficial only in DM individuals with the Hp 2-2 genotype, enthusiasm for this pharmacogenomic paradigm has been limited. In this study we sought to provide such a mechanistic explanation based on the hypothesis that the Hp 2-2 genotype and DM interact to promote HDL oxidative modification and dysfunction.

Research Design and Methods. Clearance of ^{125}I-Hp 1 or ^{125}I-Hp 2-hemoglobin (Hb) complexes were assessed in non-DM and DM mice after injection of the complexes in the tail vein. Hb association to HDL was assessed in HDL isolated by immunoprecipitation. Oxidative modification of HDL was assessed by measuring HDL associated lipid peroxides and redox active iron. HDL function was assessed based on its ability to promote cholesterol efflux from macrophages. A crossover placebo controlled study in Hp 2-2 DM humans and in Hp 1-1 and Hp 2-2 DM mice assessed the ability of vitamin E to reduce oxidative modification of HDL and improve HDL function.

Results. In DM mice, the half-life of the Hp 2-Hb complex was dramatically increased. Immunoprecipitation studies demonstrated specific binding of Hp-Hb complex to HDL with over 25% of the injected Hp 2-Hb complex associating with HDL. Hb was found to be associated with HDL in all Hp 2-2 DM individuals and mice by western blot. Redox active iron and lipid peroxides associated with HDL were significantly increased and HDL function was remarkably impaired in Hp 2-2 DM individuals and mice. Vitamin E significantly decreased oxidative modification of HDL and improved HDL function in Hp 2-2 DM but had no effect in Hp 1-1 DM.

Conclusions. In Hp 2-2 DM individuals, there is an increased amount of Hb bound to HDL which results in an oxidative modification of HDL and HDL dysfunction. Vitamin E significantly improves the quality of HDL and may explain the exclusive CVD benefit in this cohort.