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Review

Effect of statin therapy on paraoxonase-1 status: A systematic review and meta-analysis of 25 clinical trials

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ABSTRACT

Background: Decreased activity of the enzyme paraoxonase-1 (PON1) has been demonstrated in cardiovascular diseases. Statins, the forefront of pharmacotherapy for dyslipidemia, have been shown to enhance PON1 activity but clinical findings have not been conclusive.
Objective: To systematically review the clinical findings on the impact of statin therapy on PON1 status (protein concentrations and activities of paraoxonase and arylesterase) and calculate an effect size for the mentioned effects through meta-analysis of available data.
Methods: Scopus and Medline databases were searched to identify clinical trials. A random-effects model and the generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the one-study remove approach. Random-effects meta-regression was performed to assess the impact of potential confounders on the estimated effect sizes.
Results: Meta-analysis suggested that statin therapy is associated with a significant elevation of PON1 paraoxonase and arylesterase activities, but not PON1 protein concentration. The PON1-enhancing effects of statins were robust in the sensitivity analyses and were independent of statin dose, treatment duration and changes in plasma low-density lipoprotein cholesterol concentration.
Conclusion: The increase of paraoxonase and arylesterase activities with statins is a pleiotropic lipid-independent clinical benefit that may partly explain the putative effects of statins in preventing cardiovascular outcomes.

Contents

Abbreviations: ACVD, atherosclerotic cardiovascular disease, BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CMA, Comprehensive Meta-Analysis; CVD, cardiovascular disease; NO, nitric oxide; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HTL, homocysteine-thiolactone; LDL-C, low-density lipoprotein cholesterol; PON1, paraoxonase-1; MAPKs, mitogen-activated protein kinases; ox-LDL, oxidized LDL; RCT, randomized controlled trial; ROS, reactive oxygen species; Sp1, specificity protein 1; SREBP-2, sterol regulatory element binding transcription factor 2.

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1. Introduction

Hypercholesterolaemia plays a key role in promoting atherosclerotic cardiovascular disease (ACVD) [1]. Lowering low-density lipoprotein cholesterol (LDL-C) is an established strategy to reduce the risk of cardiovascular disease: each 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C reduces the incidence of major coronary events and ischemic stroke by approximately 20% [2,3]. Oxidative stress and inflammation are also integral in the pathophysiology of atherosclerosis and cardiovascular disease [4]. Reactive oxygen species (ROS) are involved in all stages of the disease, from endothelial dysfunction to atheromatous plaque formation and rupture. There is increasing evidence that indicate the involvement of LDL oxidation (by free radicals or cellular enzymes) in the development of atherosclerotic lesions [1,5–7]. These detrimental effects of oxidative stress are due to increased levels of lipid peroxidation products that stimulate the synthesis of pro-inflammatory cytokines and adhesion of monocytes to endothelial surface [8]. On the contrary, an inverse association exists between plasma high-density lipoprotein cholesterol (HDL-C) levels and the risk for coronary artery disease (CAD) [9,10]. HDL exerts several physiological roles, prevents oxidation of LDL, and inhibits expression of pro-inflammatory cytokines by macrophages, as well as expression of adhesion molecules by endothelial cells [11–13]. The pleiotropic properties exerted by HDL have been recently reviewed [14,15].

A key role in the protective antioxidant effects of HDL against peroxidation of LDL is exerted by the HDL-associated enzyme paraoxonase-1 (PON1) [16]. The best known protective function of PON1 is its ability to hydrolyze organophosphate nerve agents and insecticides, and the term paraoxonase is related to the ability of PON1 to hydrolyze paraoxon (diethyl p-nitrophenyl phosphate, E600), the toxic oxon metabolite of parathion. Mackness et al. [17] were the first to suggest that serum paraoxonase may be able to protect against the initial stage of atherogenesis through inhibiting the oxidation of LDL phospholipids. The lack of atheroprotective effects of the HDL fraction obtained from PON1 knockout mice, compared with HDL from wild type mice [18], confirms the crucial role of PON1 in the protective effects of HDL on LDL oxidation. Concerning the molecular mechanisms involved in the protective effects exerted by PON1 against lipid peroxidation, Rosenblat et al. [19] proposed hydrolysis of oxidized lipids by PON1 based on the lactonizing (lactone formation) and lactonase (lactone hydrolysis) activities of the enzyme. Other authors have attributed the protective effects of PON1 to its peroxidase activity on cholesteryl ester hydroperoxides, fatty acids hydroperoxides and hydrogen peroxide (H_2O_2) [20]. The lactonase activity of PON1 allows the hydrolysis of a variety of endogenous lactones such as homocysteine–thiolactone (HTL). Therefore, PON1 could exert a protective effect against homocysteinylation of LDL and other proteins by detoxifying HTL [21]. Recent studies have demonstrated that two statins widely used in human clinical trials (lovastatin and simvastatin) are hydrolyzed by purified PON1 [22]. Moreover, the ability of PON1 to metabolize atorvastatin–lactone, a toxic atorvastatin metabolite, in human liver has been demonstrated [23].

PON1 also plays a key role in other properties of HDL related to the prevention of ACVD [24,25]. *In vitro* studies have shown that PON1 inhibits macrophage cholesterol biosynthesis rate and stimulates HDL-mediated cholesterol efflux from macrophage [26,27]. HDL-associated PON1 has been identified as an important determinant of the capacity of HDL to stimulate endothelial nitric oxide (NO) production, and also exerts NO-dependent endothelial-atheroprotective effects [28].

Due to the physio-pathological relevance of PON1, several studies have evaluated its activity by spectrophotometric assays and it has been directly quantified in serum using immunological methods with specific antibodies. The spectrophotometric assays based on the ability of PON1 to hydrolyze different substrates are currently more widely used, owing to their low cost and availability. A non-phosphorous arylester such as phenyl acetate or 4 (p)-nitrophenyl acetate is used as a substrate to evaluate PON1 arylesterase activity. Moreover, more recently the lactonase activity has been studied using 5-thiobutyl butyrolactone or other lactones such as dihydrocoumarin as substrates.

Paraoxon and phenyl acetate are the most widely used substrates to study the paraoxonase and arylesterase activities of PON1, respectively. Several studies have demonstrated a decrease of PON1 activities in human diseases associated with oxidative stress. A decrease in PON1 activities has been demonstrated in human diseases with accelerated atherogenesis, such as familial hypercholesterolaemia [29], diabetes mellitus [30] and obesity [31,32]. This has led to the hypothesis that the lower the PON1 activity is, the higher will be the accumulation of oxidized LDL and risk of coronary heart disease (CHD). Case-control studies have shown a clear association between CHD and low serum PON1 activity [33]. This relationship has been further strengthened by the publication of the first prospective study showing that low serum PON1 activity is an independent predictor of CHD events [33]. Further experiments with transgenic PON1 knockout mice confirmed the potential role of PON1 to protect against atherogenesis [34,35].

A large variability in serum PON1 activities has been reported. However, direct measurements of PON1 protein levels by ELISA showed variations of only 5 folds [36]. This discrepancy results from the fact that most activities reflect not only the differences in total PON1 levels but also the differences in the degree of catalytic stimulation exerted by HDL and/or in the specific activities of various PON1 genetic polymorphisms in the coding and promoter regions [37,38].

Two common polymorphisms in the coding region of the *PON1* gene lead to a glutamine → arginine substitution at the position 192 (Q192R) or leucine → methionine substitution at the position 55 (L55M) [39]. The T to C exchange in position −107 is one of the several polymorphisms identified in the promoter region of *PON1*. The coding region PON1-Q192R polymorphism has the most significant impact on the enzyme activity [39]. Some substrates *e.g.* paraoxon are hydrolyzed faster by the R isoform while the arylesterase activity is similar in both