METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 609–622

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Meta-analysis

Systematic review and meta-analysis deciphering the impact of fibrates on paraoxonase-1 status

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ARTICLE INFO

Article history:
Received 29 July 2015
Accepted 5 January 2016

Keywords:
Cardiovascular risk
HDL
Hypertriglyceridemia
Lipoprotein metabolism
Oxidation

ABSTRACT

Objective. A significant residual cardiovascular risk is consistently observed in patients treated with statins. A combined treatment with fibrates reduces cardiovascular events in very high-risk patients. Because this is apparently unconnected to an improvement in lipid-related outcomes we hypothesized that the cardioprotective effects of fibrates might be associated with an improvement in paraoxonase-1 (PON1) status.

Method. The search for existing evidence, using the Medline, Scopus and Cochrane databases, was systematic and followed the PRISMA statement without restrictions on publication date. We excluded non-clinical and observational studies and we extracted data on baseline and post-treatment values of serum PON1 activity and other measurements of PON1 status.

Results. Nine studies (including 12 treatment arms) in patients with hyperlipidemia, diabetes or metabolic syndrome treated with fibrates, alone or in combination with statins, were included to synthesize results. A meta-analysis of the data using a random-effects model revealed a significant increase in serum PON1 activity following fibrate therapy (WMD: 15.64 U/L, 95% CI: 6.94, 24.34, $p < 0.001$), an effect that was robust and not sensitive to any particular study. Subgroup analysis indicated differences in the effect size among types of fibrates and that PON1 alterations were associated with high-density lipoprotein cholesterol changes following fibrate therapy.

Conclusions. Results indicate a significant PON1-enhancing effect of fibrates. Whether this effect is associated with a clinical benefit, although likely, remains to be further investigated.

Abbreviation: ABCA1, ATP-binding cassette A1; CI, confidence interval; CV, cardiovascular; HDL, high-density lipoprotein; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PON1, paraoxonase-1; PON2, paraoxonase-2; PON3, paraoxonase-3; PPARα, peroxisome proliferator-activated receptor alpha; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation; SEM, standard errors of the mean; SIGLE, system for information on gray literature; WMD, weighted mean differences.

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http://dx.doi.org/10.1016/j.metabol.2016.01.002
0026-0495/

1. Introduction

The addition of fibrates to statin therapy aimed to control residual vascular risk in selected patients provides reductions in cardiovascular events. Beneficial effects are limited to individuals with high risk of cardiovascular (CV) disease and/or those with atherogenic dyslipidemia (i.e., combined hypertriglyceridemia and low plasma high-density lipoprotein cholesterol (HDL-C) concentrations) [1,2]. The likely mechanisms for the cardioprotective effects of fibrates are, however, not restricted to the effects of these drugs in reducing plasma triglyceride and/or increasing HDL-C levels [3–5]. Interpretation from clinical trials is difficult [4–6] because data are probably modulated by changes in lifestyle factors and secondary pharmacological treatments with anti-inflammatory and antioxidant effects [7–9]. Factors considering the heterogeneous structure, different intravascular metabolism and, more importantly, biological activity of lipoproteins should be included in the clinical assessment [10,11]. The reduction in inflammation and oxidation, under these circumstances, is likely associated with an increase in antioxidant protection by paraoxonase-1 (PON1) and significant effects in the functional complexity of circulating lipoproteins [10]. PON1 is responsible for several functional properties of HDL, including antioxidant, anti-inflammatory and homocysteine-thiolactone detoxification activities [12]. Some in vitro data have strongly suggested that triglycerides decrease PON1 catalytic activity and have deleterious effects on HDL biological activity [13,14]. Hence, the effects of fibrate therapy, which corrects these alterations, might provide a theoretical basis for exploring the PON1 status in CV disease especially because these effects overlap with the action of statins and the combination of these drugs might result in efficient enhancement of PON1 status and mitigation of oxidative burden [13–15].

Our research question (i.e., whether fibrates are potential modulators of PON1) is mostly relevant in the study of the metabolic syndrome as a low-grade proinflammatory and/or pro-oxidative state associated with high serum triglyceride concentrations, low HDL-C values and high cardiovascular risk [16–18]. Moreover, nutritional and lifestyle changes indicated in the management of metabolic syndrome can regulate PON1 activity [19,20]. Current data have derived from studies of PON1 but it is important to highlight the existence of three paraoxonase genes (and proteins), which probably evolved from a common ancestor [21,22]. In the blood, PON1 is mostly bound to HDL and the relative abundance and wide distribution of PON1 in human tissues is likely associated with HDL-related delivery of PON1 into cells [23,24]. Of note, PON1 is an enzyme that hydrolyzes a variety of substrates and promotes the degradation of oxidized lipids in both circulating lipoproteins and cells [25–28]. The enzyme is promiscuous and the developed spectrophotometric assays are based on the enzyme's capacity to hydrolyze different substrates. The choice of substrates is mostly based on low cost and availability, and paraoxon and phenyl acetate have been traditionally used as both paraoxonase and arylesterase activity are important determinants of PON1 status [27]. Indeed, accumulating evidence from clinical research has indicated that PON1 is an important contributor to CV health and consequently has proposed therapeutic strategies targeting the molecular regulation of PON1 [6,9,10]. Fibrates and other peroxisome proliferator-activated receptor alpha (PPARα) agonists are potential options for the stimulation of PON1 activity [29,30]. Specifically, there are some PPARα binding sites in the *PON1* gene promoter that could directly influence serum PON1 activity and PPARα activators induce the expression of apolipoprotein AI and the ATP-binding cassette A1 (ABCA1) controlling cellular cholesterol efflux [29–32]. We have systematically assessed and synthesized the clinical evidence, using meta-analysis, to clarify the potential role of fibrate therapy in antioxidant protection by paraoxonase.

2. Methods

2.1. *Eligibility Criteria, Protocol and Search Process*

The inclusion criteria were specified a priori including study designs, populations, interventions, comparisons and outcome measures. The protocol was limited to: 1) clinical trials (i.e., in humans) with concurrent control groups; 2) investigation of the impact of fibrates on PON1 status; 3) treatment duration of at least 2 weeks; and 4) the presentation of information on PON1 status at baseline and at the end of the treatment period (i.e., reported outcomes commonly accepted as meaningful to assess changes in PON1). We excluded non-clinical and observational studies and there were no geographic inclusion/exclusion criteria.

Following procedures outlined previously, as well as the PRISMA and STARLITE statements [10,33,34], we performed a search involving an expert chain-of-citations approach, followed by a keyword-based computerized search with no restrictions on publication date. We assumed, considering the included search terms, that English-language was sufficient to identify relevant non-English-language reports. We searched Medline (http://www.ncbi.nlm.nih.gov/pubmed) and SCOPUS (http://www.scopus.com) databases using an overlapping subsets approach and applying the following Boolean expression, which included suggested Mesh terms and wild-card terms to increase sensitivity: (fenofibrate OR bezafibrate OR ciprofibrate OR clofibrate OR gemfibrozil OR "fibrates" OR "fibrate therapy") AND (paraoxonase OR paraoxonase-1 OR "paraoxonase 1" OR "paraoxonase1" OR PON-1 OR "PON 1" OR "PON1" OR arylesterase). We found no search results in the Cochrane database of systematic reviews (http:/www.cochrane.org). Publication status was not a criterion and to avoid the exclusion of fugitive literature, an information retrieval specialist searched Google scholar, Dissertation Abstracts International (http://www.worldcat.org), conference proceedings (eric.ed.gov) and SIGLE (system for information on gray literature) database. Hand searching of references of the retrieved articles was performed to identify additional studies but this information was considered not relevant by the review team according to our criteria. When necessary, we contacted authors to confirm the accuracy of the data and to ensure whether preliminary results or special reports were taken from the original studies.