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Prednisone and Its Active Metabolite Prednisolone Attenuate Lipid Accumulation in Macrophages

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Abstract : Background: Synthetic forms of glucocorticoids (e.g., prednisone, prednisolone) are anti-inflammatory drugs which are widely used in clinical practice. The role of glucocorticoids (GCs) in cardiovascular diseases including atherosclerosis is highly controversial, and their impact on macrophage foam cell formation is still unknown. Our aim was to investigate the effects of prednisone or its active metabolite, prednisolone, on macrophage oxidative stress and lipid metabolism using in-vivo, ex-vivo and in-vitro systems. Methods: The in-vivo study included C57BL/6 mice which were intraperitoneally injected with prednisone or prednisolone (5mg/kg) for 4 weeks, followed by lipid metabolism analyses in the mice aorta, and in peritoneal macrophages (MPM). In the ex-vivo study, we analyzed the effect of serum samples obtained from 9 healthy volunteers before or after treatment with oral prednisone (20mg for 5 days), on J774A.1 macrophage atherogenicity. In-vitro studies were conducted using J774A.1 macrophages, human monocyte derived macrophages (HMDM) and fibroblasts. Cells were incubated with increasing concentrations (0-200 ng/ml) of prednisone or prednisolone, followed by determination of cellular oxidative status, triglyceride and cholesterol metabolism. Results: Prednisone or prednisolone treatment resulted in a significant reduction in triglycerides and mainly in cholesterol cellular accumulation in MPM or in J774A.1 macrophages incubated with human serum. Similar resulted were noted in HMDM or in J774A.1 macrophages which were directly incubated with the GCs. These effects were associated with GCs inhibitory effect on triglycerides and cholesterol biosynthesis rates, throughout downregulation of diacylglycerol acyltransferase1 (DGAT1) expression, and of the sterol regulatory element binding protein (SREBP2) and HMGCR expression, respectively. In parallel to prednisone or prednisolone induced reduction in macrophage triglyceride content, paraoxonase 2 (PON2) expression was significantly upregulated. GCs-induced reduction of cellular triglyceride and cholesterol mass was mediated by the GCs receptors on macrophages since the GCs receptor antagonist (RU 486) abolished these effects. In fibroblasts, unlike macrophages, prednisone or prednisolone showed no anti-atherogenic effects. Conclusions: Prednisone or prednisolone are anti-atherogenic since they protected macrophages from lipid accumulation and foam cell formation.

Keywords : atherosclerosis, cholesterol, foam cell, macrophage, prednisone, prednisolone, triglycerides
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