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High density lipoprotein cholesterol function improves after successful treatment of psoriasis: a step forward in the right direction

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Several lines of evidence have demonstrated that psoriasis, a chronic Th1-17 inflammatory skin disease, is associated with systemic inflammation(Mehta *et al.*, 2011), metabolic diseases(Armstrong *et al.*, 2013; Azfar *et al.*, 2012; Langan *et al.*, 2012), predisposition to cardiovascular (CV) risk factors(Neimann *et al.*, 2006) and cardiovascular disease(Armstrong *et al.*, 2012; Gelfand *et al.*, 2006; Mehta *et al.*, 2010; Yeung *et al.*, 2013). Indeed, these lines of evidence span from basic cellular models(Nestle *et al.*, 2009), animal models(Davidovici *et al.*) and observational human studies(Mehta *et al.*, 2013). The weight of the evidence, mechanistically, biologically and epidemiologically, support the notion that systemic inflammation, either induced experimentally in humans or that which is observed in psoriasis, is associated with a heightened state of CV risk.

What factors may play roles in increasing CV risk for patients with psoriasis? Indeed, conventional cardiovascular risk factors such as hypertension, tobacco use, obesity and diabetes are more prevalent in psoriasis, but the association with CV outcomes persists even after adjusting for these factors in large, population-based studies(Ahlehoff *et al.*, 2011; Gelfand *et al.*, 2006; Langan *et al.*, 2012; Li *et al.*, 2012). Furthermore, dyslipidemia, defined by the conventional assessment of lipids has been shown to be increased in psoriasis(Ma *et al.*, 2013), and most recently, triglycerides were found to be increased in a dose-dependent fashion with increasing body surface areas affected by psoriasis,

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Conflict of Interest

NNM is a full time United States government employee. JMG has received grants from Amgen, Pfizer, Eli Lilly, Novartis, and Abbott, and is or has been a consultant for Amgen, Novartis, Pfizer, Eli Lilly, Abbott, Merck, Celgene, and Centocor; neither of the authors has a conflict of interest to declare.

independent of the usual risk factors, such as body mass index(Langan *et al.*, 2012). Lipid panels usually rely on direct concentration measurements of total cholesterol (TC), high-density lipoproteins (HDL), triglycerides (TGs), with calculation to estimate low density lipoproteins (LDL). However, these metrics have variable responsex to anti-psoriatic treatments, despite a large body of pre-clinical and human evidence demonstrating that induction of inflammation worsens HDL levels in humans(de la Llera Moya *et al.*, 2012; McGillicuddy *et al.*, 2009). Furthermore, it would be expected that with improvements in known CV markers and direct measurement of vascular inflammation following open-label anti-psoriatic treatment(Bissonnette *et al.*, 2013) lipids, namely HDL, would improve; however in these studies this relationship was observed inconsistently. These findings reinforce the idea that changes in HDL-C levels are an inadequate surrogate for responses to therapy(Schwartz *et al.*, 2012) and that more precise techniques to understand cholesterol composition and function are needed(Rosenson *et al.*, 2012). These new measures include lipid particle size and number measured by nuclear magnetic resonance spectroscopy, which provides an assessment of the *composition* of the lipid content beyond concentration alone (Jeyarajah *et al.*, 2006). These metrics predicted first myocardial infarction within a prospective population-based study with equivalent performance as LDL concentration(Mora et al., 2009). In psoriasis, lipid particle size and number have also been demonstrated to be more atherogenic in a study of 100 patients (Mehta et al.,2012b) and also associated with vascular inflammation (Yu, 2012). Conventional lipid measures in these patients were ‘normal’, including HDL levels. However, the function of HDL cholesterol, which performs a process called “reverse cholesterol transport” (RCT), was impaired in psoriasis as well (Mehta et al., 2012b). This pathway involves efflux of cholesterol from macrophages (such as those within atherosclerotic plaque) to HDL acceptor particles for ultimate return to the liver and biliary excretion. HDL efflux is thought to be a central function that makes HDL the “good” cholesterol(Khera *et al.*). In fact, recent studies demonstrate that raising HDL pharmacologically is not protective against CV events, most likely because these approaches do not improve HDL function(Khera *et al.*, 2013; Schwartz *et al.*, 2012). Thus, the developing new approaches to targeting the HDL pathway to lower cardiovascular risk is an area of intense scientific and medical interest.

In this issue of the *JID*, Holzer and colleagues follow up on a previous observation that HDL efflux is abnormal in psoriasis(Holzer *et al.*, 2012) by performing an open-label study of psoriasis treatment to understand the effect on HDL characteristics (Holzer *et al.*, 2013). HDL was isolated from 15 patients with moderate to severe psoriasis at baseline and after effective topical and/or systemic anti-psoriatic therapy; they were compared to 15 age- and sex-matched controls. HDL efflux was measured using two validated techniques: 1) by depleting serum of all apoB containing lipids; 2) by isolating HDL directly, using centrifugation techniques. Other known important characteristics of HDL such as HDL phospholipid content and enzymatic mediators within the RCT pathway, including HDL paraoxanase and Lp-PLA2, were also measured before and after therapy. The investigators confirmed earlier observations that HDL efflux was reduced in patients, consistent with the hypothesis that increased systemic inflammation impairs the RCT pathway(Holzer *et al.*, 2012; Mehta *et al.*, 2012b). They also observed, after 56–100 weeks of treatment, that the reduction in PASI scores was associated with improvement in HDL efflux from isolated

HDL. Furthermore, supporting the notion of improvement in HDL characteristics, PON and LP-PLA2 enzyme activity were modulated in a favorable direction. The authors also reported that there was an increase in HDL size by NMR, suggesting that phospholipid content increased within the HDL, also supporting the observation that HDL characteristics were more favorable after successful treatment of psoriasis. Finally, all of these improvements in HDL function and composition occurred, despite the lack of change in blood lipid levels and including HDL.

These findings are largely consistent with earlier observations in healthy humans that experimental inflammation *in vivo* modulates HDL function and composition(de la Llera Moya *et al.*, 2012; McGillicuddy *et al.*, 2009; Mehta *et al.*, 2009). Our group has demonstrated that HDL efflux decreases after administration of lipopolysaccharide, a known stimulator of innate immune pathways known to be activated in psoriasis. Furthermore, in that study, LPS led to a decrease in HDL phospholipid content, and this correlated highly with HDL efflux. Holzer and colleagues extend these findings by demonstrating that HDL phospholipid was reduced in psoriasis compared to healthy controls and that this content tended to improve following successful treatment. Furthermore, the increase in LCAT activity suggests that cholesterol esterfication improved following therapy, which would facilitate exit of cholesterol from the body. However, these findings must be interpreted with caution. The authors do not provide free cholesterol and cholesterol ester data before and after therapy, which are more precise measures of LCAT activity(Vaisman and Remaley, 2013). Moreover, the small sample size, lack of a randomized placebo controlled design, and inability to determine which specific treatment improved HDL function all remain to be addressed.

The strengths of the study are that authors used rigorous lab methods to provide the initial characterization of treatment effects on HDL properties in patients with psoriasis. The study brings to center stage the concept that the conventional methods of assessing CV risk in psoriasis may be in need of refinement (Mehta *et al.*, 2012a). This concept of residual risk for CV disease, despite improvement in the usual risk factors suggests use of newly developed functional measures. Furthermore, there is still limited data on whether treatment of psoriasis will improve outcomes for CV disease or for the risk factors alone. Another small open label study demonstrated in humans that treatment of psoriasis utilizing anti-TNF therapy led to improvement in carotid intimal medial thickness, a surrogate marker of CV disease(Jokai *et al.*, 2013). However, whether improvement in such surrogate markers would hold up under a more rigorous randomized placebo controlled trial design and ultimately translate into improvement in CV outcome is unknown. This approach of utilizing a validated surrogate marker to understand whether there is improvement in an outcome was widely used in earlier studies of lipid treatment, using rigorous randomized controlled trials(Taylor *et al.*, 2009). Reduction in cholesterol levels as well as improvement in imaging of atherosclerosis served as proxies for lower CV outcomes. However, if psoriasis is in the causal pathway for CV diseases (i.e. an intermediate risk factor), a strategy to tease out disease treatment effects on CV outcomes will require concomitant use of surrogate endpoints as well as outcome studies to understand *how* treatment modulates short and long term CV risk.

A strategy currently underway to advance understanding of CV risk, treatment effects and outcomes in psoriasis includes performance of a randomized, placebo-controlled trial of psoriasis treatment (anti-TNF, UVB therapy and placebo) with a primary outcome of vascular inflammation by FDG PET CT (http://clinicaltrials.gov/ct2/show/NCT01553058, http://clinicaltrials.gov/show/NCT01866592), a novel imaging biomarker which measures CV risk for both short (Fayad *et al.*, 2011) and long term events(Arauz *et al.*, 2007; Rominger *et al.*, 2009). However, larger simple trials studying CV outcomes in psoriasis such as those currently underway in non-psoriasis patients evaluating the effect of very low dose methotrexate in patients with CVD (Ridker, 2009) will also need to be planned. Until then, we can certainly gain insight from this and other recent studies which suggest that successful treatment of inflammation *in vivo* leads to improvement in cardiometabolic diseases(Maki-Petaja *et al.*, 2012), the most potent source of mortality in psoriasis.

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Clinical Implications

1. Recent studies demonstrate that raising HDL pharmacologically is not protective of CV events likely in psoriasis, [NNM1] because these approaches do not improve HDL function(Khera et al., 2013; Schwartz et al., 2012).
2. Developing new approaches to targeting the HDL pathway to lower cardiovascular risk is an area of intense scientific and medical interest.
3. The results by Holzer et al in this issue of the JID may be a step in the right direction as they suggest that successful treatment of psoriasis may improve HDL function.