

Low density, high impact? Neutrophil changes in obesity and bariatric surgery

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The worldwide obesity pandemic continues to worsen, with an estimated 650 million adults with obesity according to the World Health Organization's most recent 2016 estimate.¹ While the morbidity of metabolic diseases, such as type 2 diabetes with obesity is well known, the impact of obesity-driven immune dysregulation is often less appreciated. Obesity increases susceptibility to infectious diseases, a fact most recently driven home by worse outcomes among obese patients with COVID-19,² and is also linked to autoimmune diseases such as psoriasis and psoriatic arthritis as well as cancer.³ Beginning with Weisberg's observation of increased macrophage infiltration into the adipose tissue in obesity,⁴ a large body of work has detailed the more subtle effects obesity has on innate and adaptive immunity, establishing links between the immune system and metabolism.

Recently in *eBiomedicine*, Sanchez-Pino et al. found that patients with morbid obesity (BMI > 40 kg/m²) have an increased number of low-density neutrophils (LDN) in the peripheral blood as compared to normal weight individuals.⁵ LDNs were first described in 1986 when investigators noted large numbers of neutrophils with abnormally low densities in the peripheral blood of patients with systemic lupus erythematosus, rheumatoid arthritis, and acute rheumatic fever.⁶ Despite further research into LDNs in the intervening years, fundamental questions about their origin, function, and role in health and disease remain unanswered. LDNs have also been found in high quantities in the peripheral blood of patients with psoriasis, HIV infection, and other chronic inflammatory diseases.⁶ On the contrary, other studies⁷ have demonstrated the presence of LDNs in healthy individuals, seemingly performing protective, homeostatic roles. As such, the data on LDN function remain mixed and work into understanding their precise lineage and their numerous effects, both protective and pathologic, is ongoing.

To better understand the effects of LDNs in the context of obesity, Sanchez-Pino et al. performed transcriptomic profiling of LDNs in obese patients, finding upregulation of primarily inflammatory pathways. While the authors also demonstrated upregulation of some immunosuppressive pathways found in myeloid-derived suppressor cells, LDNs isolated from obese patients did not demonstrate immunosuppressive properties on T cells *in vitro*, suggesting that LDNs in obesity are primarily pro-inflammatory. The authors go on to show that in a prospective cohort of patients, LDNs decrease substantially within months after bariatric surgery. Sanchez-Pino et al. confirm work demonstrating that bariatric surgery alters neutrophil numbers.⁸ This body of evidence also adds to potential cellular mediators for the observed benefits of bariatric surgery on COVID-19 infection severity² and protection against autoimmune disease.³

Strengths of this study include its analysis of multiple human patient cohorts, including an obese cohort, a control lean cohort, and a prospective bariatric surgery cohort, as well as analysis of both peripheral blood and visceral adipose tissue samples. The study also uses transcriptomics to molecularly characterize human obese LDNs, an important step given the known heterogeneity of LDN populations. Unfortunately, the number of samples included in the transcriptomic analysis of LDNs ($n = 5-8$ per group) is small, and these transcriptomic findings are not verified functionally in the larger cohort. Moreover, the authors only measure total neutrophils and not LDNs in the visceral adipose biopsies and do not perform any transcriptomic or functional analysis of LDNs in post-bariatric surgery patients. Thus, despite the compelling correlations between obesity, bariatric surgery, and LDNs identified in this study, both the functional consequences and mechanism of changes to LDN numbers in obesity remain to be determined in future work.

While questions abound, Sanchez-Pino et al. have opened an important line of inquiry into the role of LDNs in obesity, obesity-related comorbidities, and bariatric surgery. Could the change in LDN numbers affect infectious disease defense and contribute to metabolic disease, such as type 2 diabetes? What are the molecular signals that drive changes in LDNs and other immune subsets in obesity? Recent work has shown that gut

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microbial metabolites affect T cell function,⁹ while accumulation of lipids in natural killer cells in obesity affects their ability to mount antitumor responses.¹⁰ It is tempting to speculate that either the characteristic microbiome changes in obesity and/or direct effects on immune cell substrate metabolism may be contributing factors in LDN and other immune dysregulation in obesity.

Sanchez-Pino et al. have added LDNs to the list of immune cell subsets that are altered by both obesity and bariatric surgery, and importantly, have confirmed and translated pre-clinical animal findings to human patients. Whether LDNs play a causal role in obesity-related disease and how bariatric surgery alters LDN function remain open questions of importance to clinicians and, potentially, over 650 million obese adults worldwide. Continued investigation to clarify the molecular mechanisms and functional consequences of these immunologic changes will hopefully reveal novel targets for intervention to treat the complications of obesity.

Contributors

Cullen Roberts and Eric Sheu contributed equally in writing this commentary.

Declaration of interests

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