Systemic chronic subclinical inflammation, adipose tissue dysfunction, and polycystic ovary syndrome: three major forces intertwined

Three major pathophysiologic forces, systemic chronic subclinical inflammation, dysfunctional adiposity, and polycystic ovary syndrome (PCOS), are brought together in the study by Juan et al. (1). Polycystic ovary syndrome is the single most frequent endocrine disorder of women, affecting at least one in every seven women globally. It also is the single most common cause of infertility and the single most common antecedent of type 2 diabetes mellitus in premenopausal women. The direct medical costs of PCOS exceed $8 billion yearly in the United States alone, not including the costs of associated mental health disorders, loss of productivity, and quality of life (i.e., indirect and intangible costs of disease). Yet the disorder is generally ignored, with patients often having difficulty finding quality health care, in some cases because the practitioners they see know little of PCOS, while in others because the clinicians they see treat all of them the same… and who also know little of this complex genetic trait. Even our National Institutes of Health, and its component institutes and centers, have done little to prioritize a disorder that affects at least 4 million women in the United States today.

Most patients with PCOS demonstrate insulin resistance and hyperinsulinemia, which in large part is responsible, along with other as yet undetermined factors, for the hyperandrogenism of the disorder. While some metabolic derangements may relate to excess adiposity, the vast majority appear to be related to insulin signaling and adipose tissue (AT) dysfunction. To wit, AT is not just storing unused calories in the form of lipids, it is a rich and complex tissue composed of adipocytes, blood vessels, and interstitial tissues that include preadipocytes, fibroblasts, macrophages, and much more. It is a tissue that produces a myriad of signaling agents and has extensive endocrine-metabolic actions. In fact, AT is the single largest endocrine organ in the human body. In PCOS, AT dysfunction appears to have a significant role in the metabolic and, consequently, hyperandrogenic features of the disorder (2).

Chronic subclinical inflammation is reflected in a continuous systemic increase in inflammatory immune mediators (e.g., higher concentrations of proinflammatory cytokines, such as adipocytokines, offending lipid fractions, etc.) in response to ongoing cellular damage (3, 4). Persistent damage that may be the result of unresolved hypoxic/oxidative, metabolic, infectious, foreign body, or other harmful tissue stress and stimuli. The inflammatory response to such unanswered tissue damage generally involves the upregulation of genes encoding for cytokines, chemokines, and other inflammatory mediators through the activation of various transcription factors (e.g., nuclear factor κB, nuclear factor of activated T cells, activator protein-1, and signal transducer and activator of transcription-3) or may result from the activation of the inflammasome, a multiprotein complex that serves as a platform for caspase-1 activation and results in the increased secretion of interleukin-1β and interleukin-18. Systemic chronic subclinical inflammation has been found to play key roles in the pathophysiology of many common diseases, including type 2 diabetes mellitus, cardiovascular diseases, cancer, rheumatoid arthritis, neurodegenerative diseases, and PCOS (5).

Juan et al. (1) reported that the concentrations of the chemotactic cytokine or chemokine CCL5 (i.e., C-C motif chemokine ligand 5, also known as 'regulated upon activation, normal T-cell expressed and secreted' or RANTES), an 8 kDa protein, was significantly higher in the plasma of women with PCOS. Plasma levels of CCL5 also significantly correlated with serum testosterone levels in women with PCOS. In turn, the expression of CCR5 (i.e., C-C chemokine receptor type 5), a receptor for CCL5 and other similar chemokines, was increased in the AT and peripheral blood mononuclear cells of women with PCOS when compared with matched controls. Additionally, the levels of CCR5 mRNA were correlated positively with fasting insulin, fasting glucose, testosterone, and C-reactive protein circulating levels, and with HOMA-IR. Interestingly, the expression of CCR5 in THP-1 cells (a spontaneously immortalized monocyte-like cell line) increased after exposure to testosterone, suggesting that, at least in part, the increased production of CCR5 could be secondary to hyperandrogenism.

Overall, albeit including a limited number of subjects, this report suggests how chronic subclinical inflammation may play a role in the AT dysfunction and hyperandrogenism of PCOS, and help account for the increased metabolic derangements evident in this highly prevalent disorder. Furthermore, the study reminds us that while systemic chronic subclinical inflammation is beginning to be recognized as an important pathophysiologic mechanism underlying many common disorders, its role in reproductive disorders is just beginning to be explored. An objective that will require collaboration with investigators from nonreproductive disciplines, and support and funding by institutes and centers of the National Institutes of Health that have not traditionally supported reproductive system research, including the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute.

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