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The Emerging Role of Mesenteric Fat and Its Association with Crohn's Disease

by Razvan Arsenescu, Willem J.S. de Villiers and Trevor A. Winter

INTRODUCTION

Crohn's disease is a chronic inflammatory bowel disease, of uncertain etiology, characterized by transmural inflammation, with a predilection for the terminal ileum. In his original description of the disease, Burril Crohn described the characteristic mesenteric fat change (1). Although widely recognized, particularly by surgeons, the relevance of this fat hypertrophy and wrapping, referred to as "creeping fat," is unknown, and has received little research attention. Accumulation of mesenteric fat, with fat wrapping, appears to be specific for Crohn's disease, and occurs from the onset of disease (2). Fat wrapping has been defined as fat hypertrophy extending from the mesenteric attachment with >50% coverage of the intestinal surface (3). Fat wrapping occurs in both the small and large bowel, and correlates with transmural inflammation, ulceration, stricture formation, increased mesenteric wall thickness, and decreased internal bowel diameter (3). Fat wrapping and mural thickening is associated with mucosal ulceration in 86% of patients (4). In combination with serositis, it is associated with mucosal ulcers and cobblestones in 96% of patients and with strictures in 46% (4). Fat wrapping was noted in 100% of patients undergoing

Razvan Arsenescu, M.D., Willem J.S. de Villiers, M.D., Ph.D., and Trevor A. Winter, M.D., Ph.D., University of Kentucky, Lexington, KY.

resection, and correlated with the degree of acute and chronic inflammation (5).

The association of fat hypertrophy with Crohn's disease raises the question of whether the fat wrapping is a consequence of transmural inflammation, probably caused by cytokine release from lymphoid tissue (3,4), or whether the fat is in some way responsible for the inflammatory changes. Cytokines such as transforming growth factor beta-1 (TGF-β1) and TNF-α stimulate proliferation and activation of mesenchymal tissues. Peroxisome proliferators-activated receptor γ (PPAR-γ) is expressed by the intestine and adipose tissue, and can modulate the activity of the inflammatory cytokines (6). It is a major regulator of adipocyte differentiation, and may therefore play a significant role in the development of mesenteric fat hypertrophy in Crohn's disease.

ADIPOCYTES AND INFLAMMATION

The previously held notion that adipose tissue is merely an inert energy storage depot, releasing fatty acids only during times of hardship, such as fasting or starvation has been recently challenged. It has become clear that adipocytes are considerably more complex than previously considered, with the production of a multitude of hormones, proteins, peptides, compliment factors, cytokines, enzymes and receptors in response to specific extracellular stimuli, or changes

in metabolic status (7,8). The term adipocytokines has been introduced, and adipose tissue is correctly considered a major endocrine organ. Several of these adipocytokines, including adiponectin, leptin, resistin, interleukin 6 (IL-6), tumor necrosis factor (TNF-α), are directly involved in the inflammatory response, and have both metabolic as well as immune-regulatory functions. Obesity has reached epidemic proportions in the USA. The obese state has been associated with a low-grade systemic inflammatory state, with increased C-reactive protein (CRP), IL-6 and TNF-α, as well as with the metabolic syndrome (9). Studies have indicated that adipose tissue is infiltrated by macrophages, and that the pro-inflammatory cytokines are produced mainly by these macrophages (10,11). In another study, however, TNF-α secretion was noted to be predominantly from the mesenteric adipocytes (2). TNF-α increases the secretion of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 alpha (MIP-1α) from adipocytes, which function as chemoattractants for macrophage precursors. The secretion of macrophage colony-stimulating factor (M-CSF) by adipose tissue may then lead to expansion and differentiation of the macrophage pool (12). It is therefore apparent that adipose tissue links energy metabolism with immune function and host defence (Figure 1) (13,14).

ADIPOCYTES AND THE METABOLIC SYNDROME

It has been long recognized that obesity is associated with insulin resistance, and that accumulation of intra-abdominal visceral fat may contribute to the development of hyperlipidemia, diabetes mellitus and hypertension, in what is termed the metabolic syndrome (15). A number of inflammatory cytokines, secreted by adipose tissue, such as TNF-α, IL-1, IL-6 and MCP-1
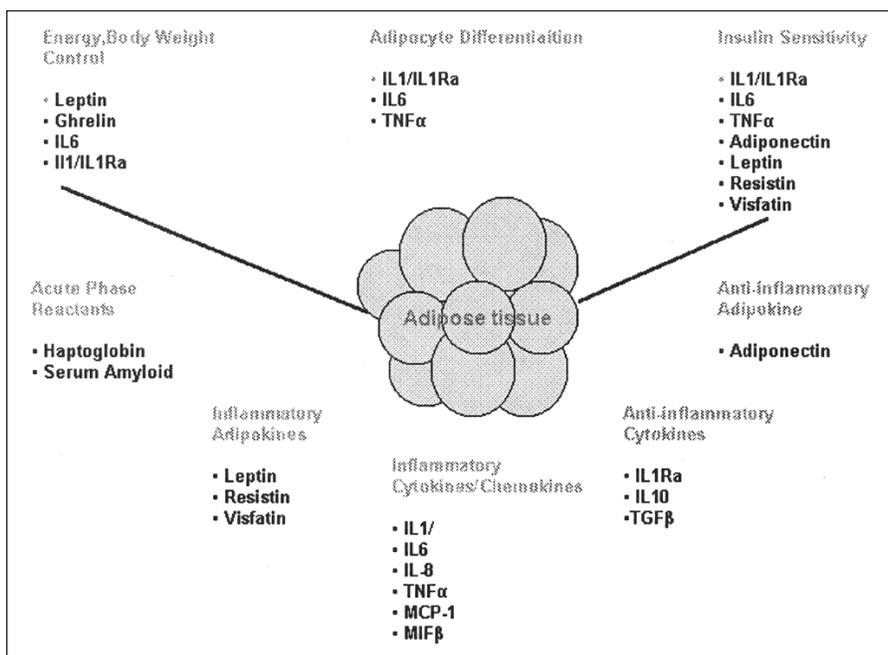

**Figure 1.** Regulation of metabolism and inflammation by the adipose tissue.

have been associated with insulin resistance. Adiponectin, also secreted by adipocytes, is, on the other hand associated with insulin sensitivity. Although secreted by adipocytes, adiponectin levels are in fact lower in obese subjects than in lean subjects (16). Plasma levels of adiponectin have been demonstrated to be lower in patients with type 2 diabetes, hypertension and coronary heart disease (17). Insulin resistance and the metabolic syndrome have been associated with obesity, and the production of adipocytokines may explain this relation (18).

VISCERAL ADIPOSE TISSUE

Visceral adipose tissue (VAT) has several characteristics, that may directly relate to intestinal disease (19). VAT is metabolically active, with a high free fatty acid (FFA) efflux into the portal vein (20). Visceral obesity leads to increased delivery of FFA's to the liver via the portal vein resulting in steatosis, dyslipidemia and hepatic insulin resistance. VAT secretes a specific pattern of adipocytokines. Plasminogen activator inhibitor-1, (PAI-1), IL-6,

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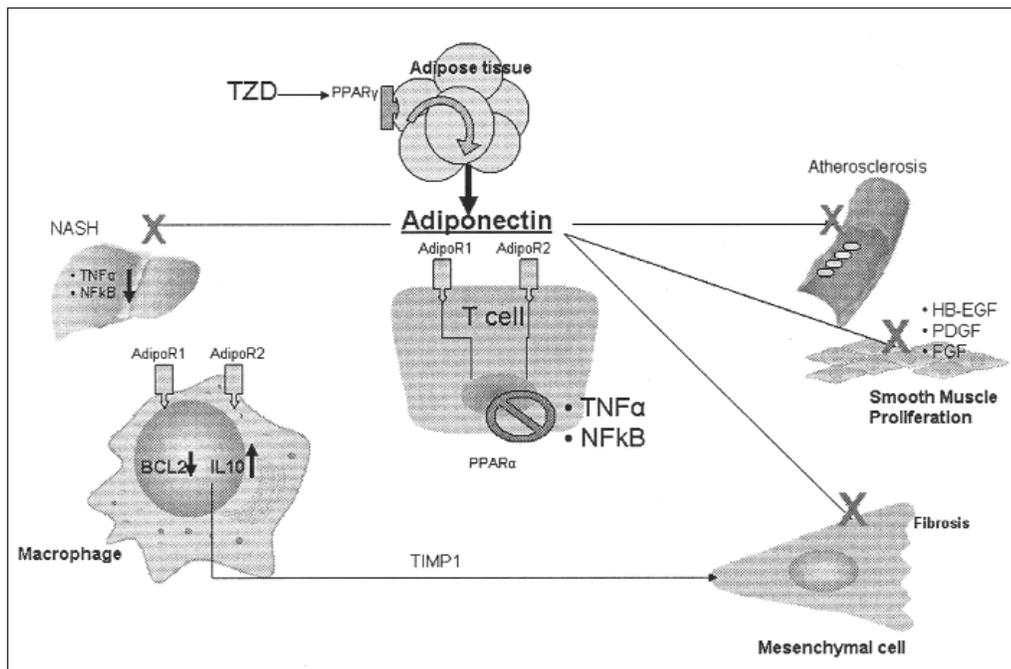
Figure 2. Anti-inflammatory role of adiponectin.
AdipoR-adiponectin receptors; BCL2: anti-apoptotic protein; HB-EGF, PDGF, FGF: growth factors that induce hyperplasia of smooth muscle; NASH: non-alcoholic steatophepatitis; NF-kB: nuclear factor implicated in regulation of cytokines; PPARγ: peroxisome proliferative activated receptor, gamma; TZD: thiazolidones, agonists of PPAR (e.g., Pioglitazone); TIMP1: regulator of enzymes involved in tissue remodeling.

vascular endothelial growth factor (VEGF) and resistin secretion is higher than in subcutaneous fat, and adiponectin expression is lower (19).

MESENTERIC ADIPOSE TISSUE AND CROHN'S DISEASE

Mesenteric fat hypertrophy is associated with Crohn's disease, and obese patients with Crohn's disease have an increased incidence of perianal disease with abscesses and fistulae (21). Although the fat wrapping may be a consequence of the intestinal inflammation, possible as a consequence of increased mesenteric PPAR-γ expression, the production of pro-inflammatory cytokines by the mesenteric adipose tissue, and infiltrating macrophages is likely to enhance the inflammatory process (22). Leptin levels have been shown to be significantly higher in mesenteric adipose tissue from patients with either Crohn' disease or ulcerative colitis, than in patients with non-inflammatory disease (23). Leptin can induce intestinal inflam-

mation, and may therefore contribute to the inflammatory process and increase TNF-α expression (23,24) TNF-α produced by both the mesenteric adipose tissue, as well as infiltrating macrophages. TNF-α is a potent pro-inflammatory agent and is likely to contribute significantly to the pathogenesis of Crohn's disease (22). Adiponectin, on the other hand, has a structure similar to TNF-α, and antagonizes the effects of TNF-α by reducing secretion and attenuating the biological actions by competing for the receptor (25). Adiponectin has also been shown to downregulate intercellular adhesion molecule-1 (ICAM-1), endothelial adhesion molecule-1 (ECAM-1) and E-selectin, thus inhibiting the migration of inflammatory cells to mesenteric tissue (26). This adipokine has emerged as a potent anti-inflammatory adipokine (Figure 2) in other conditions characterized by chronic inflammation such as NASH and atherosclerosis (27,28). Adiponectin is capable of modulating key molecules involved in pathogenesis of inflammation and repair processes (Figure 2). The very same molecules—TNFα, IL12 (inflammatory cytokines), IL10 (anti-inflammatory cytokine), and tissue growth factors are therapeutic targets in inflammatory bowel diseases (Figure 2). Therefore, this hormone is likely to play a significant role in the pathogenesis of IBD. Although mesenteric PPAR-γ expression may have a significant role in the development of mesenteric fat hypertrophy in Crohn's disease (22) it also has major anti-inflammatory effects by reducing TNF-α, and leptin expression, and increasing

adiponectin expression in adipocytes (29). A recent study by Yamamoto demonstrated that the release of adiponectin from the hypertrophied mesenteric adipose tissue in patients with Crohn's disease was significantly elevated, when compared to patients with ulcerative colitis or colon cancer, and that the secretion of adiponectin was specifically related to inflamed and hypertrophied adipose tissue and not to the normal adipose tissue in these individuals (21). An interesting observation in this study was that adiponectin concentrations were significantly lower in Crohn's disease patients with internal fistulae, than in those without internal fistulae (21).

Mesenteric fat hypertrophy may therefore be considered as both a consequence, as well as a cause of inflammation in Crohn's disease. Inflammation with the secretion of cytokines, particularly of PPAR-γ inducing hyperplasia of the mesenteric fat indicates a secondary role, whereas the presence of mesenteric fat hypertrophy at the onset of disease, the relationship of the fat to areas of inflammation, and the release of pro-inflammatory cytokines, including TNF-α, and leptin, with the protective effects of adiponectin suggest a more active role of adipose tissue in Crohn's disease (22). ■

References

1. Crohn BB, Ginsburg GL, Oppenheimer GD. Regional ileitis, a pathological and clinical entity. *J Am Med Assoc*, 1932; 99:1323.
2. Desreumaux P, Ernst O, Geboes K, Gambiez L, Berrebi D, Muller-Alouf H, Hafraoui S, Emilie D, Ectors N, Peuchmaur M, Cortot A, Capron M, Auwerx J, Colombel JF. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology*, 1999; 117:73.
3. Sheehan AL, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *Br J Surg*, 1992; 79:955.
4. Smedh K, Olaison G, Nystrom PO, Sjodahl R. Intraoperative enteroscopy in Crohn's disease. *Br J Surg*, 1993; 80:897.
5. Borley NR, Mortensen NJ, Jewell DP, Warren BF. The relationship between inflammatory and serosal connective tissue changes in ileal Crohn's disease: evidence for a possible causative link. *J Pathol*, 2000;190:196.
6. Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. *Inflamm Res*, 2000; 49:497.
7. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, Yamashita S, Miura M, Fukuda Y, Takemura K, Tokunaga K, Matsuzawa Y. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med*, 1996; 2:800.
8. Fortuno A, Rodriguez A, Gomez-Ambrosi J, Fruhbeck G, Diez J. Adipose tissue as an endocrine organ: role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. *J Physiol Biochem*, 2003; 59:51.
9. Grimble RF. Inflammatory status and insulin resistance. *Curr Opin Clin Nutr Metab Care*, 2002;5:551.
10. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*, 2003;112: 1796.
11. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*, 2003; 112:1821.
12. Levine JA, Jensen MD, Eberhardt NL, O'Brien T. Adipocyte macrophage colony-stimulating factor is a mediator of adipose tissue growth. *J Clin Invest*, 1998; 101:1557.
13. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology*, 2003; 144:2195.
14. Lehrke M, Lazar MA. Inflamed about obesity. *Nat Med*, 2004; 10:126.
15. Matsuzawa Y. Adipocytokines and metabolic syndrome. *Semin Vasc Med*, 2005; 5:34.
16. Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev*, 2005; 6:13.
17. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol*, 2004; 24:29.
18. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab*, 1998; 83:847.
19. Arner P. Regional differences in protein production by human adipose tissue. *Biochem Soc Trans*, 2001; 29:72.
20. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. *J Clin Invest*, 2004;113:1582.
21. Yamamoto K, Kiyohara T, Murayama Y, Kihara S, Okamoto Y, Funahashi T, Ito R, Nezu S, Tsutsui S, Miyagawa JI, Tamura S, Matsuzawa Y, Shimomura I, Shinomura Y. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. *Gut*, 2005; 54:789.
22. Schaffler A, Scholmerich J, Buchler C. Mechanisms of disease: adipocytokines and visceral adipose tissue—emerging role in intestinal and mesenteric diseases. *Nat Clin Pract Gastroenterol Hepatol*, 2005; 2:103.
23. Barbier M, Vidal H, Desreumaux P, Dubuquoy L, Bourreille A, Colombel JF, Cherbut C, Galmiche JP. Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. *Gastroenterol Clin Biol*, 2003; 27:987.
24. Sitaraman S, Liu X, Charrier L, Gu LH, Ziegler TR, Gewirtz A, Merlin D. Colonic leptin: source of a novel proinflammatory cytokine involved in IBD. *Faseb J*, 2004; 18:696.
25. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol*, 2003; 14:561.
26. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation*, 2000; 102:1296.
27. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF- or adiponectin? *Hepatology*, 2004; 40:46.
28. Kaser S, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F, Ebenbichler CF, Patsch JR, Tilg H. Adiponectin and its receptors in non-alcoholic steatohepatitis. *Gut*, 2005; 54:117.
29. Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, Iwamoto K, Umesono K, Akanuma Y, Fujiwara T, Horikoshi H, Yazaki Y, Kadowaki T. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest*, 1998; 101:1354.