Visceral adipocytes: old actors in obesity and new protagonists in Crohn's disease?

Zulian A, Cancello R, Micheletto G, Gentilini D, Gilardini L, Danelli P, Invitti C.

Gut. 2012 Jan; 61(1):86-94

KLÁRA FRIVOLT
Comenius University Medical School and University
Children's Hospital, 2nd Department of Pediatrics

Klára Frivolt
is a resident at the University Children´s Hospital in Bratislava. She is interested in pediatric IBD and currently she works on her PhD Thesis at the Ludwig Maximilian University in Munich.

IIntroduction

Crohn's disease (CD) is characterized by the presence of expanded adipose tissue located at the mesenteric attachment around areas of inflamed intestine [1]. The inflamed adipose tissue marked with macrophage and T cell infiltration, endothelial cell activation and fibrosis, is an active endocrine and immune organ and serves as a source of pro- and anti-inflammatory cytokines. Microscopically mesenteric adipocytes in CD were described to be small with a 4-fold increased number compared to healthy controls [2]. Adipose tissue in obesity (visceral/omental and subcutaneous) also shows inflammation and is not only characterized by increased numbers of adipocytes, but also by adipocyte enlargement [3].

What is this paper about?

Using morphological and molecular-genetic methods the authors studied the subcutaneous and intraabdominal fat tissue of morbidly obese (n=8) or stricturing CD patients (n=8) with comparison to healthy lean subjects (n=8) undergoing intraabdominal surgery.

The fat compartments were divided into the following groups:

1. Subcutaneous adipose tissue,
2. Visceral adipose tissue from the omentum,
3. Adipose tissue from the mesenteric attachment close to the
    a. healthy intestine,
    b. inflamed intestine in case of CD.

Key findings

The subcutaneous adipocytes in obese patients were significantly larger (hypertrophic) compared to CD and healthy controls. CD patients and lean controls had comparably sized subcutaneous adipocytes, without any morphological signs of inflammation. The mesenteric adipose tissue of healthy intestine in obese and lean controls showed no inflammatory cell infiltration. In CD patients there were less inflammatory and fibrotic changes of mesenteric fat tissue close to healthy sections of the CD intestine compared to the fat tissue attached to the inflamed CD intestine. However there was a clear difference in the size of adipocytes: visceral adipocytes in CD were smaller in comparison to obese individuals and to CD mesenteric adipocytes close to the inflamed intestine. In summary, the morphological analyses showed that adipocytes of CD patients had a significantly smaller diameter in all adipose tissue compartments compared to obese subjects. In comparison to lean individuals, this difference was only detectable in the intraabdominal fat compartment.

In a second step the authors studied the inflammatory changes of adipose tissue by microarray analysis. Considering the global gene expression of whole adipose tissue compartments in CD, the subcutaneous fat tissue formed an expression cluster that was independent of the other intraabdominal adipose depots. The visceral and mesenteric adipose tissue, located close to the affected intestine, showed an upregulation of inflammatory genes. Looking more closely, the global gene expression of isolated visceral adipocytes in CD formed an independent branch in clustering analysis, suggesting a distinct function of visceral and mesenteric adipocytes. Isolated visceral adipocytes in both, CD and obese patients, revealed an upregulation of genes related to inflammation/immune response and downregulation of genes required for mitochondrial function. By proper characterization of involved genes, visceral adipocytes in CD exert a greater upregulation of anti-inflammatory genes compared to obese patients. The mostly marked difference is in the expression of prokineticin 2, with a much higher expression in CD patients.

Overall Conclusion

This is the first study comparing adipose tissue in CD versus obesity, both characterized by accumulation and inflammation of the intraabdominal fat tissue. Previous studies directly examining the creeping fat in CD described morphological changes and altered expression of some pro- and anti-inflammatory cytokines/adipokines in comparison to healthy controls or patients with diverticulitis [4-6]. The authors showed a clear difference between the two diseases with respect to the morphological picture of adipose tissue compartments. In fact, the visceral adipocytes of CD and obese patients share 40% of the expressed genes. An upregulation of anti-inflammatory genes in visceral adipocytes was detected. The authors therefore suggest a protective role of visceral fat tissue in CD.

In this study the authors have not depicted the gene expression of adiponectin. Previously adiponectin was shown to be downregulated in obesity [7] but upregulated together with leptin, TNF-alpha and CRP in mesenteric adipose tissue in patients with CD [4-6, 8, 9]. Therefore it would have been interesting to study the expression of adiponectin in CD compared to obesity.

Prokineticin 2 is expressed by macrophages and neutrophils infiltrating the damaged tissue, but its expression on adipocytes has not been described yet. This finding might be explained by the changed expression pattern and function of immunologically activated preadipocytes and adipocytes under inflammatory conditions in CD [10]. Interacting with its receptors, prokineticin 2 can induce visceral pain [11]. Its markedly higher expression in CD may explain the clinical differences in pain perception in CD and obesity. The proper function of prokineticin 2 in the creeping fat however needs to be further clarified.

References

1. Crohn, B.B., L. Ginzburg, and G.D. Oppenheimer, Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. JAMA, 1984. 251(1): p. 73-9.
2. Peyrin-Biroulet, L., et al., Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? Gut, 2007. 56(4): p. 577-83.
3. Maury, E. and S.M. Brichard, Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol, 2010. 314(1): p. 1-16.
4. Paul, G., et al., Profiling adipocytokine secretion from creeping fat in Crohn's disease. Inflamm Bowel Dis, 2006. 12(6): p. 471-7.
5. Desreumaux, P., et al., Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. Gastroenterology, 1999. 117(1): p. 73-81.
6. Barbier, M., et al., Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. Gastroenterol Clin Biol, 2003. 27(11): p. 987-91.
7. Maury, E., et al., Adipokines oversecreted by omental adipose tissue in human obesity. Am J Physiol Endocrinol Metab, 2007. 293(3): p. E656-65.
8. Yamamoto, K., et al., Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. Gut, 2005. 54(6): p. 789-96.
9. Peyrin-Biroulet, L., et al., Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. Gut, 2012. 61(1): p. 78-85.
10. Cousin, B., et al., A role for preadipocytes as macrophage-like cells. FASEB J, 1999. 13(2): p. 305-12.
11. Watson, R.P., et al., Increased prokineticin 2 expression in gut inflammation: role in visceral pain and intestinal ion transport. Neurogastroenterol Motil, 2012. 24(1): p. 65-75, e12.