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Review article

The role of adipose tissue in the pathogenesis of Crohn's disease

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ABSTRACT

Crohn's disease (CD) is a chronic, immune system-mediated inflammatory disease affecting gastrointestinal (GI) tract. The pathogenesis of the intestinal lesions is not entirely explained and understood: excessive activation of the immune system may come as a result of the interaction of environmental, genetic and infectious factors and the mediation of abnormal intestinal flora. The main objective of the current study is to further identify the role of adipose tissue in the pathogenesis of CD. Alterations in body fat distribution, accumulation of intra-abdominal white adipose tissue (WAT) and mesenteric obesity are well-known features of CD. Up to date, data concerning the role of WAT in the pathogenesis of CD is limited with only a few studies on the relationship between WAT and the course of the disease, as well as pro- and anti-inflammatory cytokine profile and general immune system functioning.

In this review, we focus on the importance of physiological and pathophysiological WAT functions and secreted adipokines, which seem to have a vital role in the inflammatory and fibrotic processes in CD sufferers.

Contents

Introduction

Crohn's disease (CD) is a debilitating, systemic inflammatory disorder characterized by a chronic, segmental granulomatosus inflammation with periods of exacerbation and remission, which

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may involve any part of the gastrointestinal (GI) tract [1]. The pathogenesis of the intestinal lesions in CD is not entirely identified and understood. Excessive activation of the immune system and dysregulation of intestinal immunity come as a result of the interaction of various environmental and infectious factors, genetic predisposition, and the mediation of abnormal intestinal flora [1,2].

The pathophysiology of CD involves autoreactive Th-1 cells getting stimulated and triggering cell mediated immune response. Increased Th-1 CD4+ lymphocytes release an excess of proinflammatory cytokines: IL-12, IFNγ, tumor necrosis factor (TNF) α, IL-17, IL-22 and other mediators [1,3,4]. TNFα represents a key proinflammatory cytokine and dysregulation of its production has been implicated in immunopathogenesis of CD [5,6].

Alteration in body fat distribution, with accumulation of intra-abdominal white adipose tissue (WAT) is a well-known feature of CD. Mesenteric WAT (mWAT) or creeping fat (CF) is mainly hypertrophied around the intestine involved with inflammatory infiltration [7]. Recent studies suggest that WAT, besides its well-established functions, also produces and releases a great number of multifunctional proteins and those released exclusively by WAT are collectively named adipokines. An abnormal expression of leptin, adiponectin and resistin, all of which belong to adipokines has been recently reported in patients with CD suggesting that mesenteric adipocytes may act as immunoregulatory cells in intestinal inflammatory infiltration [8].

In this review, we focus on the significance of physiological and pathophysiological mWAT functions and secreted adipokines, which may play an important role in the inflammatory and fibrotic processes in patients with CD.

Obesity in patients with Crohn's disease

Understanding the interaction between obesity and CD, with concern of disease pathogenesis, phenotypic disease expression and response to therapy has important implications for proper disease management [9,10]. Noteworthy, reports from various inflammatory bowel disease (IBD) cohorts, in both pediatric and adult populations suggest that the current prevalence of overweight and obese IBD patients comes close to that of the general population, being approximately 20–30% [9].

General adipose tissue accumulation in obesity connects with systemically escalated proinflammatory mediators and humoral and cellular changes in this compartment. These adipose tissue-related alterations and their systemic outcomes lead to the perception of obesity as a chronic inflammatory state.

Elevated serum levels of proinflammatory cytokines, C-reactive protein, and leptin and their systemic consequences may result in inflammatory state in CD and affect its progression [11]. It remains controversial whether the intestinal inflammation is a reason of fat hypertrophy as a defensive reaction or the mWAT producing proinflammatory mediators leading to inflammatory intestinal lesions [12]. Interestingly, intra-abdominal fat accumulation can be identified from the onset of the disease and is not affected by its duration or activity thus defining mesenteric obesity as a specific feature of CD [13]. CF is also positively correlated with, inter alia, fibrosis, transmural inflammation, macrophage and lymphocyte perivascular infiltration and stricture formation [14]. Stricture formation is a repercussion of mucosal ulceration, as it is followed by proliferation of fibroblasts- one of the cell types that produce collagen. Collagen abnormalities are one of CD's hallmarks; what is more, fibroblasts derived from CD patient's tissue proliferate faster and have higher ability to cause scarring of the tissue [15,16]. Collagen is a vital ingredient of extracellular matrix (ECM) and whether fibrosis occurs or not is dependent on the equilibrium of degradation and production of ECM proteins. When deposition is greater than degradation- fibrosis is promoted. This balance is regulated by the same proteins that are involved in intestinal inflammation [16,17]. Inflammation causes fibrosis, but is not vital for its progression- excessive ECM deposition may not be prevented even by anti- inflammatory treatment [16,17].

Adipose tissue is commonly divided into subcutaneous and visceral fat tissue [11]. The macroscopic features of the visceral adipose tissue adjacent to the intestinal segments involved in CD are often characterized by hypertrophied adipose tissue and mesenteric thickening considered as an important indicator of regional disease activity [6]. Histological analysis revealed a significant difference in the visceral adipose tissue observed in CD patients compared to the one found in obese individuals [18]. CF is characterized by small, increased in number adipocytes, rather than hypertrophied ones, with a distinct gene expression profile [19] [Fig. 1].

In obesity, proinflammatory genes are up-regulated, whereas CD patients show patterns of increased pro- and anti-inflammatory gene expression. Smaller visceral adipocytes produce fewer proinflammatory mediators and are less responsive to further stimulation, once being activated. During acute colitis, mononuclear cells infiltrate the mesenteric fat tissue, adipocyte size decreases, and fibrotic structures appear adjacent to the inflamed murine intestine. Furthermore, mRNA expression of TNFα, IL-1b, and IL-6 are up-regulated [11]. The proinflammatory cytokines secreted in inflammatory response promote T- and B- cell activation and acute-phase proteins. Their prolonged activation results in tissue destruction, repair and fibrosis [16].

In both obesity and in CD, macrophages accumulate in adipose tissue. They are a major source of proinflammatory mediators and contribute significantly to the systemic inflammatory response. Also, a systemic impact can be equally suggested, since C-reactive

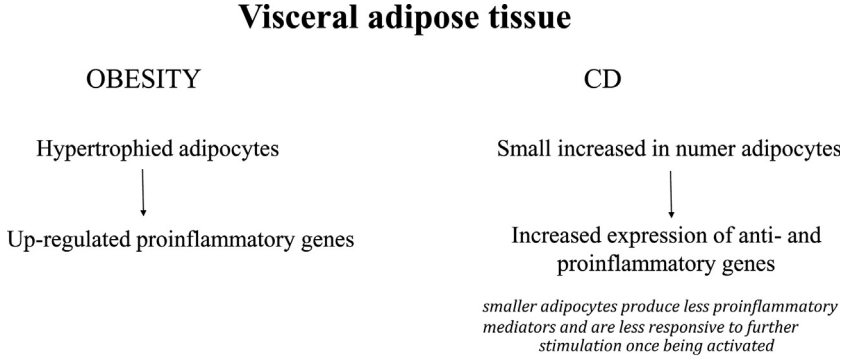

Fig. 1. Differences between visceral adipose tissue in obesity and Crohn's disease.

protein, which is found increased in active disease, can be produced by the mesenteric fat tissue [11].

Recent studies have shown that obesity impacts the CD development, poorer prognosis, early need for surgery, the risk for active disease and earlier loss of response to therapy [9,19]. Obese individuals with CD were suggested to have a higher rate of perianal disease, and a more frequent need for hospitalization [9]. Obesity is also associated with postoperative complications, including wound infection and dehiscence of surgical anastomoses [Fig. 2]. CD patients classified as overweight or obese (BMI > 25 kg/m^2) require often surgical procedure in earlier stage, as a result of developed complications, when compared to patients with low weight (BMI < 18.5 kg/m^2) [20]. Increased body fat content impairs the efficiency of the treatment due to changed drugs pharmacokinetics. Additionally, high concentrations of circulating proinflammatory molecules also alter the therapeutic effect, what leads to the conclusion that weight-adjusted anti-TNFα therapy should be favored in obese CD patients [11]. What is more, dietary products are common luminal antigens that may influence intestinal inflammation through a number of mechanisms, inter alia alteration of gene expression, enteric flora composition changes and effects on gut permeability. High consumption of dietary fat, omega-6 fatty acids and meat is known to be associated with increased risk of developing CD [10]. The long chain dietary n-3 polyunsaturated fatty acids (PUFAs), namely docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may also be involved in the etiology of CD: PUFAs hold a role in regulation of immunological and inflammatory responses. They suppress genes activating inflammatory process, and DHA and EPA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, which prevent gastrointestinal inflammation [21].

Microbiota in Crohn's disease and obesity

CD patients demonstrate diminished mucin production and leaky intracellular tight junctions allowing for increased permeability and excess of antigens to the lamina propria. Physiological tolerance to commensal bacteria within the intestine is attributed to a down-regulation of toll-like receptors. In CD, the ability to regulate tolerance is lost, leading to persistent, unregulated response to colonic bacteria [1].

Considering fecal microbiome, biodiversity is significantly reduced in CD patients. What is more, microbiota in IBD patients is unstable- there is a relative lack of *Firmicutes*, *Bacteroides* and *Faecalibacterium prausnitzii*, and an over-representation of enterobacteria. The human commensal *F. prausnitzii* and *Bacteroides fragilis* have been shown to possess anti-inflammatory properties in cell systems and animal models [9,21]. A consistent increase in mucosa-associated *E. coli* in both ileum and colon, and their presence within the granulomas in CD implicates a primary pathogenic role [3,22].

There is a growing number of evidence underlining a role for the intestinal microbiota in the development of both obesity and CD, representing another potential association between the two conditions [9]. Bacteria can trigger adipocytes and preadipocytes proliferation *in vitro*. Therefore, a concept emerged that a boost in bacterial translocation leads to hyperplasia of adipose tissue in CD. Bacteria penetrating the intestinal barrier are likely to locate in the mesenteric fat close by, where they might provoke CF development [11].

On the other hand, impaired intestinal barrier affected by genetic, nutritional risk factors and changed microbiota influences the development of adipose-tissue inflammation in obesity. While in obesity the mucosal barrier is only mildly affected, one has to bear in mind that CD is characterized by a transmural inflammation with subsequent destruction of the intestinal barrier [11].

The mucosal barrier in healthy individuals is composed of different cells within the epithelia layer and lamina propria, including resident immune cells. It permits absorption of nutritional factors but prevents from increased translocation of bacteria and viruses. In obesity, this barrier function is undermined, what provokes intestinal inflammation in rodent models. High fat diet (HFD) promotes translocation of intestinal bacteria, thereby triggering inflammation in obesity [11]. What is more, HFD provokes intestinal permeability due to alterations in tight junctions and a low transepithelial resistance- a marker proving a defect in intestinal barrier. In consequence, the mesenteric fat is infiltrated by excessive numbers of macrophages and associated up-regulation of pro-inflammatory molecules like IL-6 and TNFα [11].

Adipose tissue as an endocrine organ

WAT is no longer considered to be an isolated tissue storing fatty acids serving as passive energy reservoir. Compelling evidence remodeled our perception of adipose tissue to a complex and highly active metabolic and endocrine organ, specific signaling center responsible for body's energy equilibrium. [23,24].

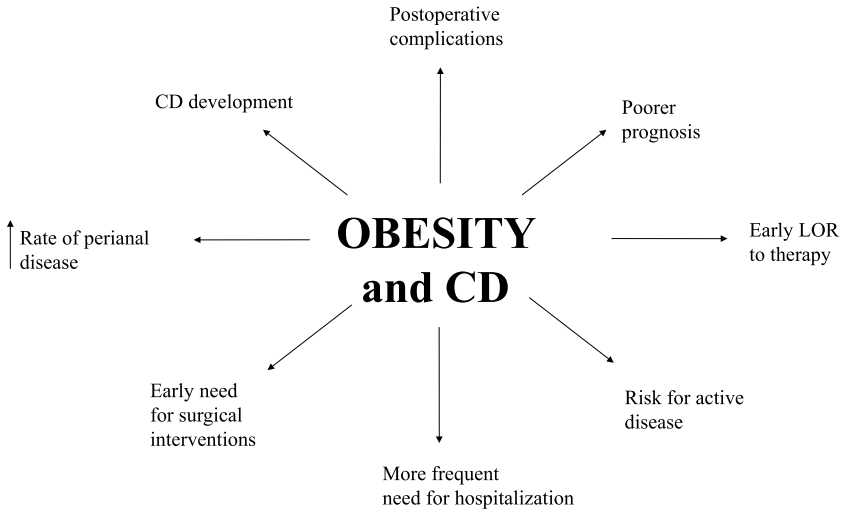

Fig. 2. Impact of obesity on course of disease in CD patients.

The structural design of adipose tissue appears to be much more complex than previously expected. Apart from adipocytes, WAT contains connective tissue matrix, nerve tissue, stromovascular cells, and immune cells [25]. Acting as an integrated unit, adipose tissue besides its ability to respond to afferent signals from traditional hormone systems and the central nervous system can also express and secrete hormones and mediators referred to as adipokines [Fig. 3]. Accumulating evidence suggest those proteins to present substantial involvement in inflammatory and metabolic pathways in human organism [26]. Among these leptin, adiponectin and resistin appear to present a promising perspective in CD [8]. Studies on WAT have revealed adipocytes can synthesise and release several important cytokines and growth factors including TNFα, considered one of the major proinflammatory molecule involved in immunopathogenesis of CD [27]. Its transcription depends on the activation of the transcription factor known as nuclear factor kB (NF-kB) and is also associated with the activity of the signal transducer and activator of transcription (STAT) family [28].

The transcription factors translocate into the nucleus and merge with regulatory DNA sequences inducing the transcription in immunoregulatory molecules' genes. The predominance of NF-kB and STAT1 activation in inflammatory bowel diseases has been previously reported in the literature [29,30].

Most recent study performed by Coope et al, aimed at evaluation of the transcription signalling pathways and cytokines expression in intestinal mucosa and mWAT of active CD patients, has revealed for the first time that the inflammatory status of mWAT in CD is mediated by STAT1 activation [31]. However, a possibility of increase of anti-inflammatory cytokines, such as IL10, due to this activation, is still a subject for further analysis. These findings reinforce the predominance of the proinflammatory NF-kB pathway in CD intestinal mucosa. Additional research in this area may help not only to understand the exact pathophysiology of CD, but also lead to developing potential pharmacologic targets to treat CD.

An example of such targeted therapy might in fact be based on a novel cellular axis involving intestinal epithelial cells (IECs) and adipocytes, recently demonstrated in a research by Takahashi et al. [32]. The study revealed that the production of MMP-9 mRNA was elevated in IECs when cultured in adipocyte conditioned medium. Interestingly, lack of increase in MMP-9 mRNA expression was noted when adipocytes were cultured in epithelial conditioned medium. Additionally, the study also showed that the epithelial response to culture in adipocyte conditioned medium can be impaired by targeting NF-κB and STAT-3. These results suggest that disrupting signalling between adipocytes and intestinal epithelia might present as a promising strategy in CD treatment.

Adipose tissue-secreted proteins

Leptin

Leptin is a16-kDa non-glycosylated protein, which belongs to the type I cytokine superfamily and is characterized by a long chain four-helical bundle structure [33]. Leptin was initially known to function mainly as an anti-obesity hormone. The new data however, apart from serving as a metabolic signal of satiety, assign it numerous biological effects distinct from those expected of an adipostatic, anti-obesity hormone [34]. Leptin possesses pro-inflammatory properties. It can influence CD4+/ CD8+ lymphocyte proliferation, monocytes activation, stimulate phagocytosis and above all, enhance TNFα production- a major cytokine involved in intestinal inflammation in CD [35]. Bruun et al. reported TNFα to have a biphasic effect on leptin release. Initially it induces acute release of leptin from pre-formed pools, followed by a long-term decrement in both leptin release and leptin gene expression [36].

Additionally, Franchimont et al have found CD patients treated with Infliximab, an anti- TNFα agent, to present with notable increase in leptin levels, implying that TNFα significantly reduces leptin expression and secretion during chronic inflammatory diseases such as CD [37].

Produced predominantly by adipose tissue, leptin secretion is directly proportionate to WAT mass [38]. In a study by Barbier *et al*, increased leptin levels were observed in mesenteric fat of IBD patients compared to healthy controls. Together with previously proven leptin contribution to increased expression of TNFα in the mesentery, these facts may suggest that leptin plays an active role in the inflammatory process [39].

Leptin expression and secretion are controlled by a variety of factors. An increase is observed in response to insulin, glucocorticoids, acute infection and secretion of inflammatory mediators like TNFα, IL-1, IL-6, estrogens and CCAAT/enhancer-binding protein-α, androgens, free fatty acids, growth hormone and peroxisome proliferator-activated receptor-γ agonists [40].

Moreover, a study analyzing biopsy specimen revealed inflamed colonic epithelial cells to express and release leptin into the intestinal lumen resulting in epithelial wall damage and neutrophil infiltration, a characteristic histological finding in CD intestinal inflammatory lesions [41]. Additionally, another research confirmed CD subjects to be characterized by overexpression of

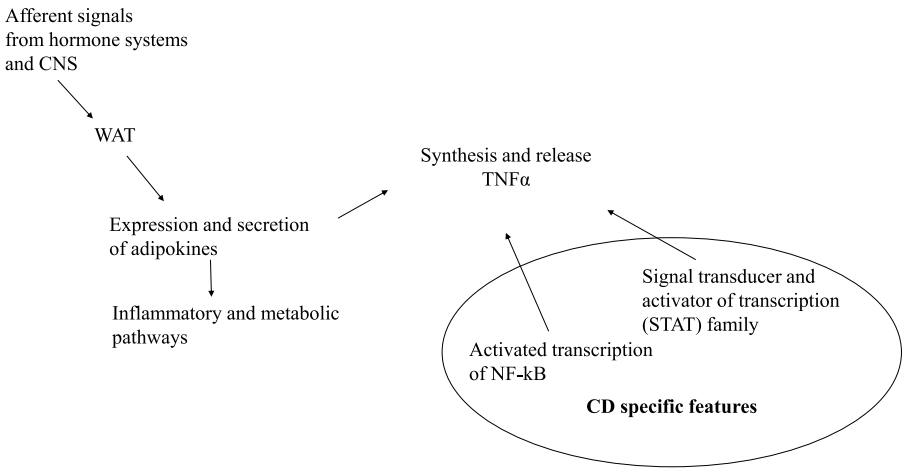

Fig. 3. The role of intra-abdominal white adipose tissue in inflammatory process in CD patients.

leptin mRNA in mesenteric visceral adipose tissue, possibly contributing to inflammatory process [39]. Together, these results bind leptin with chronic intestinal inflammation observed typically in CD.

Leptin presents additional perspectives as a marker for inflammation in CD patients. Recently, Kim et al. in a multicenter study analyzed serum adipokines levels and their correlation with clinical features and other serological markers of inflammation in CD patients. Among other findings, the study revealed that serum leptin levels were significantly correlated with C- reactive protein (CRP) levels, suggesting that serum leptin might be another potential surrogate marker for inflammation in CD patients. This study expands the concept of leptin participation in the inflammatory pathways of CD and if substantiated by additional research, leptin may serve in clinical practice as useful tool in estimating disease activity [42].

Adiponectin

Adiponectin is an approximately 30-kDa polypeptide composed of 247 amino acids consisting of four domains [43]. Interestingly, its molecular architecture bears a striking similarity in the terminal structure of the globular domain to TNFα despite a lack of homology in primary sequence [44]. This architectural resemblance however, is hard to observe in their biological activity. Based on its antagonism towards TNFα, adiponectin presents anti-inflammatory properties. Proven by multiple studies those two molecules have been verified with the ability to suppress each other's production and antagonize each other's action in their target tissues [45].

Consecutive studies revealed adiponectin to present with a wide range of metabolic effects. In the liver adiponectin enhances insulin sensitivity, increases fatty acid oxidation, and reduces hepatic glucose output [46]. In muscle, adiponectin stimulates glucose utilization and fatty acid oxidation [47].

Most notably however, a significant anti-inflammatory impact has been reported, especially in endothelial cells and macrophages. Within the vascular wall, adiponectin inhibits monocyte adhesion on endothelial cells by decreasing the expression of adhesion molecules, inhibits macrophage transformation to foam cells by inhibiting expression of scavenger receptors, and decreases proliferation of smooth muscle cells in response to growth factors. In addition, adiponectin increases nitric oxide production in endothelial cells and stimulates angiogenesis [48,49].

The impact of adiponectin on the course of CD and its origin have been widely studied. Yamamoto et al showed that adiponectin production is enhanced in hypertrophied mWAT adjacent to intestinal lesions observed routinely in CD [6]. This up-regulation has also been proven by Paul et al and confirmed to be higher than in patients suffering from diverticulitis and colon cancer [12]. Adiponectin's overexpression combined with its' complex anti-inflammatory impact, can negatively regulate inflammatory reactions found in CD patients.

Resistin

Resistin is a 12.5 kDa peptide hormone consisting of 108 amino acids that belongs to a cysteine-rich protein family also referred to as "found in inflammatory zone" [50]. Although resistin was originally postulated to contribute to insulin resistance, recently the focus shifted to its involvement in inflammatory process [51].

In humans, resistin is expressed predominantly in peripheral mononuclear cells and, at very low levels, in endothelial-, muscle- and adipose cells [52]. Higher expression of resistin was found in the mWAT of CD patients who underwent surgery compared with individuals operated on for colon cancer [13].

Expression of resistin is influenced by numerous bioactive factors. In rodent adipose cells, resistin expression is induced by corticosteroids, prolactin, testosterone, and growth hormone, whereas insulin, epinephrine, and somatotropin have an inhibitory effect [53]. Also, some pro-inflammatory agents are claimed to regulate resistin expression. Both TNFα and IL-6 significantly up-regulated resistin mRNA expression in human peripheral blood mononuclear cells [54]. This observation confirms that resistin is involved in variety of inflammatory pathways, implying its possible role in CD pathogenesis.

There is a growing body of evidence concerning resistin's pro-inflammatory activity. This adipokine has been reported to stimulate the production and secretion of TNFα and IL-12 through the activation of NF-kB signaling pathway [55]. The pro-inflammatory action has also been supported with multiple reports of resistin increased level in conditions characterized by chronic inflammation. As an example, a positive correlation of higher synovial fluid resistin levels in both ostearthtritis and rheumatoid arthritis has been revealed, with values almost ten times higher in the latter [56].

Concerning CD, resistin levels significantly decrease after anti-TNFα therapy and has been therefore proposed as a marker of successful therapy. Basing on its characteristics and serum level variations, resistin has been suggested as an independent predictor of disease activity in patients with CD [57,58].

mWAT expression and serum levels of adiponectin, leptin and resistin in CD patients

Relatively few studies have investigated secretion of adipokines and their implications for CD. Of those published, the results are diverse and often conflicting. According to a comprehensive study focused on mWAT, mean adiponectin concentration in hypertrophied mesenteric adipose tissue of CD patients was significantly higher than in normal mesenteric adipose tissue of controls [6]. Increased expression of adiponectin mRNA and increased release of adiponectin in mWAT were also reported by Paul et al. and Karmiris et al.; however the differences between studied groups of patients were on the margin of statistical significance [8,12]. Consecutive research provided conflicting conclusions, revealing serum adiponectin concentration in active CD as similar [58] or even lower than found in healthy controls [60]. Adiponectin concentration in hypertrophied mWAT has also been found to correlate negatively with serum CRP levels, a fact not observed in controls [6]. Although this pathway is yet to be explored, the difference between those two groups may be relevant to the CD specific involvement of mWAT.

With regard to leptin, numerous studies present conflicting results. Whereas Paul et al. [12] detected significantly higher secretion rate of leptin in relation to patients with colorectal cancer and diverticulitis, consecutive studies reported lower or similar baseline leptin serum levels in CD subjects [8,59,60].

Resistin is not exclusively produced and secreted by adipose tissue, it can also be found in mononuclear cells, macrophages and stem cells, thus making it a more complex molecule to study [52]. In mWAT of CD patients the expression of resistin is elevated compared to subjects with colorectal cancer [12]. Similarly, the circulating levels of resistin are reported higher than in healthy controls [8,59].

A big concern in the understanding of the involvement of adipokines in the pathogenesis of CD is also patient's body mass and the amount of adipose tissue. Both adiponectin and resistin production and release appear to be associated with patients' BMI. A significant positive association of leptin with high BMI has been found. Karmiris et al. have proven that patients with BMI < 25 had significantly lower serum leptin levels compared with subjects

with BMI > 25 [8]. A contrasting observation has been made in adiponectin levels. Studies on this subject revealed a negative correlation between serum adiponectin levels and BMI in obese patients [61]. Consistent with these findings is also a CD population-based study, where adiponectin concentration and release correlated inversely with BMI [6].

Adipokines levels are significantly influenced by implemented treatment. Steroid therapy has been proven to down-regulate adiponectin secretion. Glucocorticoids in human visceral adipose tissue strongly suppress its expression [62] and in the light of recent findings this data transferred on creeping fat in CD may explain decreased adiponectin expression in CD subjects [12].

Leptin presents as the only cytokine that is strongly up-regulated by steroid treatment in CD patients [12]. It has been established that a 3-month treatment period with corticosteroid alone or with azathioprine leads to elevated leptin level [59]. Moreover, a study reviewing the impact of anti-TNFα agents on serum leptin concentration revealed an increase in serum levels following received treatment, thus proving TNFα to have a substantial role in CD pathogenesis [37].

Conlusions and perspectives

In conclusion, novel understanding of WAT as an active secretory organ obliges to no longer consider mesenteric adipocytes only as simple bystander cells in CD. Extended research gives evidence of several adipose tissue-derived proteins to be involved in multiple metabolic and inflammatory pathways. With additional data on adipokines correlation with expression of pro-inflammatory cytokines such as TNFα, the potential role of adipokines in CD pathophysiology merits further discussion.

Although the exact role of visceral and mesenteric adipose tissue in modulating immunity and inflammation in the course of CD still requires further clarification, it has become conspicuous that in CD we observe a different type of adiposity, with different biochemical properties. Further studies following this observation might contribute to comprehensive explanation of adipokine role in disease pathogenesis, provide reliable markers for disease course and treatment efficacy as well as implicate novel, a more rational therapeutic approaches.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

A. Zielińska, P. Siwiński, M. Włodarczyk and A. Sobolewska-Włodarczyk were involved in the literature search, analysis and interpretation; A. Zielińska, P. Siwiński, M. Włodarczyk wrote the manuscript; M. Włodarczyk, A. Sobolewska-Włodarczyk, M. Wiśniewska-Jarosińska and J. Fichna were involved in manuscript development and its revision, all authors read and approved final manuscript.

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