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Review

POSSIBLE ROLES OF EPIPLOIC APPENDAGES

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Summary

Historically, only the energy storage function had been attributed to adipose tissue. However, recent studies have shown that it is also able to secrete several substances which act in a paracrine or endocrine manner, contributing to the maintenance of organism's homeostasis. It has been reported that the visceral fat has distinctive secreting characteristics. Based on previous scientific observations, here we shall describe the possible functional role of epiploic appendages. The epiploic appendages may play an important role in the metabolic regulation and/or in immune defense through the secretion of specific factors, such as leptin and some inflammatory cytokines. Leptin has been seen to be involved both in the regulation of hunger signals, in coordination with the hypothalamus, and in complex immune defense processes. The exact understanding of the behavior of this hormone could play a key role in understanding the functions ascribed to the epiploic appendages.

Introduction

The epiploic appendages were described anatomically for the first time by Vesalius in 1543. They are small, physiologic peritoneal fat pouches attached to the external surface of the colon by vascular stalks.

The appendages vary considerably in size, shape, and contour. Most epiploic appendages are 1-2 cm thick and 2-5 cm long, although they can occasionally measure up to 15 cm. Each pouch is supplied by one or two small colonic end-arteries and a small draining vein[1]. Torsions or spontaneous thrombosis of the central draining vein lead to epiploic appendagitis.

On average, the adult colon has approximately 50 to 100 appendages. Epiploic appendages occur along the entire colon, but are more abundant and larger in the transverse and sigmoid colon. They are usually rudimentary at the base of the appendix and originate next to the anterior and the posterior *taenia coli* [2].

The epiploic appendages are mainly made up of adipose tissue wrapped by visceral peritoneum.

Just over a decade ago, the biological functions of the adipose tissue, which contains endothelial cells, nervous cells and immune cells in addition to mature adipocytes and

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their precursors, were reassessed

Recent studies have shown that adipose tissue is able to secrete a varied set of molecules such as hormones, growth factors, angiogenetic factors, acute phase proteins, stress response proteins of the alternative pathway of the complement system, haemostasis proteins, coagulation factors, vascular tone proteins and other molecules. All these factors secreted by adipose tissue are called "adipokines" (Table 1). This wide range of protein signals suggests that adipose tissue is a complex organ, able to establish communication links with other tissues and organs, such as the central nervous system, the liver, the skeletal muscles and the adrenal cortex. These recent observations have led to a reassessment of the adipose tissue, defining it as an endocrine organ [3].

In obesity, the increased production of most adipokines seems to led to a deregulation of multiple functions, such as appetite, energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and haemostasis [4].

Moreover, leptin, an adipokine secreted by the adipose tissue, acts in a similar fashion to inflammatory cytokines, which promote the maturation and differentiation of T helper 1 lymphocytes [5].

Recent research has also demonstrated the significant structural and functional differences between the white visceral fat and the subcutaneous one. While the subcutaneous adipose tissue affects the entire body surface, the visceral deposits consist of omental fat and a small part of mediastinal and epicardial fat.

The gene expression pattern appears very different between subcutaneous and visceral fat, with a greater influence of pro-atherogens on the second one [6].

In light of these recent discoveries, some physiological functions of the epiploic appendages, that can be included in the visceral fat category, could be proposed.

These functions could include not only the role of a soft and flexible support cushioning for the colon [7], but also a

Major adipocytokine:	Main effects:
Leptin	Satiety signal, effects on immunity, stimulates lipolysis, improves insulin sensitivity.
Adiponectin	Inhibition of the production of inflammatory cytokines, inhibition of monocyte adhesion to endothelial cells, endothelial cell activation.
Visfatin	Inhibits apoptosis of neutrophils.
Adipsin	Stimulates triglyceride storage in adipose cells and inhibits lipolysis. Possible role in immunity.
Resistin	Controversial effects on glucose metabolism.
TNF-α	Role in inflammation, reduces adiponectin synthesis
IL-6	Role in inflammation, inhibits gluconeogenesis, increases hepatic de novo synthesis of fatty acid and cholesterol.
PPAR-γ	Stimulates internalization of fatty acids and their esterification.
Angiotensinogen	Acts through vasoactive peptide angiotensin II, which seems to have pro-inflammatory effects on the adipocyte. Correlates significantly with blood pressure.
PAI-1	Anticlotting factor.
IGF-1	Role in lipid metabolism and insulin resistance.

Table 1: Adipokines effects

role in the metabolic regulation and/or in immune defense.

Hormone theory

Leptin was identified in 1994 as a hormone produced mainly by adipose tissue [8], whose structural similarity to the class I cytokine is remarkable. It is synthesized and released by fat cells in response to changes in body fat.

It is encoded by a gene called "OB", and has been named leptin, from the Greek word "λεπτὸς", which means thin. Leptin circulates partly free and partly bound to plasma proteins, and penetrates the central nervous system by diffusion through capillary junctures in the median eminence, and by saturable receptor transport in the choroid plexus. In the hypothalamus, leptin binds to receptors that stimulate anorexigenic peptides and inhibits orexigenic peptides [9].

In the hypothalamus, there are two areas that regulate caloric intake: the hunger center, located in the lateral hypothalamus, and the satiety center in the ventral medial nucleus. Lateral hypothalamic stimulation induces a need for food, whereas stimulation of the ventral medial nucleus leads the individual to not feel the need to eat.

Leptin crosses the blood-brain barrier and activates the hypothalamus arcate nucleus neurons that produce beta-endorphin and melanocortin, while inhibiting the neurons that secrete peptide Y and AgRP protein (Agouti Related Peptide). Beta-endorphin and melanocortin have effects on appetite stimulants and inhibitors on energy consumption, while the neuropeptide Y and AgRP protein stimulate the appetite and reduce energy consumption.

Therefore, the main function of leptin appears to be to provide a signal of sufficient energy supply, since its final effect is appetite inhibition, also promoting energy consumption. It has been noticed that the amount of leptin produced is proportional to white adipose tissue accumulation.

Leptin decreases rapidly during fasting, and triggers an increase of glucocorticoids, as well as a reduction of thyroxine (T4), sex hormones and growth hormones [10].

Leptin deficiency is perceived as an absolute hunger state that leads to compensatory responses, such as hyperphagia, decreased metabolic rate and hormone

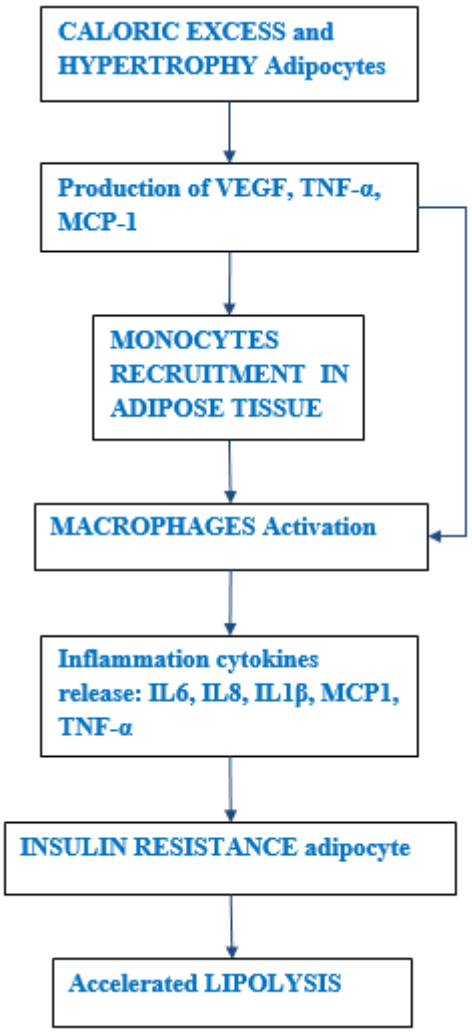

Figure 2: Pathophysiology and production of adipokines in fatty adipose tissue. The adipocyte hypertrophy triggers an inflammatory cascade with an amplification of the synthesis of vascular endothelial growth factor (VEGF) and the production of the chemoattractant for monocytes (MCP-1). The consequences are an increased vascularization of the adipose tissue with macrophage infiltration, a massive inflammation cytokine release, a local insulin resistance, an accelerated lipolysis with the release of free fatty acids (FFA) and an increased adipocyte production of leptin.

level changes, in order to restore energy balance [11].
Experimental evidence have shown how leptin regulates, at least in part, the adjustment of the sense of hunger, and therefore the body weight. Mice with a leptin gene mutation (ob/ob) or with the mutation on its receptor (db/db) show massive obesity [12].
Congenital leptin deficiency causes severe obesity also in humans, with impaired thermogenesis and insulin resistance, responsive to treatment with recombinant leptin [13].
Chan et al. [14] examined the role of leptin in the neuroendocrine regulation and metabolic function during starvation. A placebo, low dose of recombinant-methionyl human leptin (r-metHuLeptin), or replacement-dose r-metHuLeptin was administered over a period of 72h. The replacement dose of leptin prevented the induction of hunger and changes in sex hormones, and partly prevented the suppression of the hypothalamic-pituitary-thyroid. However, unlike in rodents, the substitution of leptin during acute starvation did not affect the utilization levels of glucose, glucocorticoids or growth hormone in humans. In patients with lipodystrophy and leptin deficiency, leptin substitution therapy improved glycemic control and decreased levels of triglycerides.
In addition to the regulation of body weight, leptin regulates puberty and reproduction, fetal placental function, immune response and muscle and liver insulin responsiveness [15].
Recently, analysis of leptin expression suggest that may be a valuable parameter for predicting prognosis in laryngeal squamous cell carcinoma (SCC) and may have a possible role in predicting prognosis [16].
Leptin secreted by adipocytes of epiploic appendages could play a role in hormonal regulation, communicating with the central nervous system and assisting the secreting function of all the fatty tissues in the body.

Immunogenic theory

Hippocrates had foreseen the enormous importance of the intestine in the body's immune balance, stating that "All disease begins in the gut."
Intestinal and respiratory mucosa represent an important line of demarcation between the organism's internal environment and the outside world. The immune system must be able to distinguish the

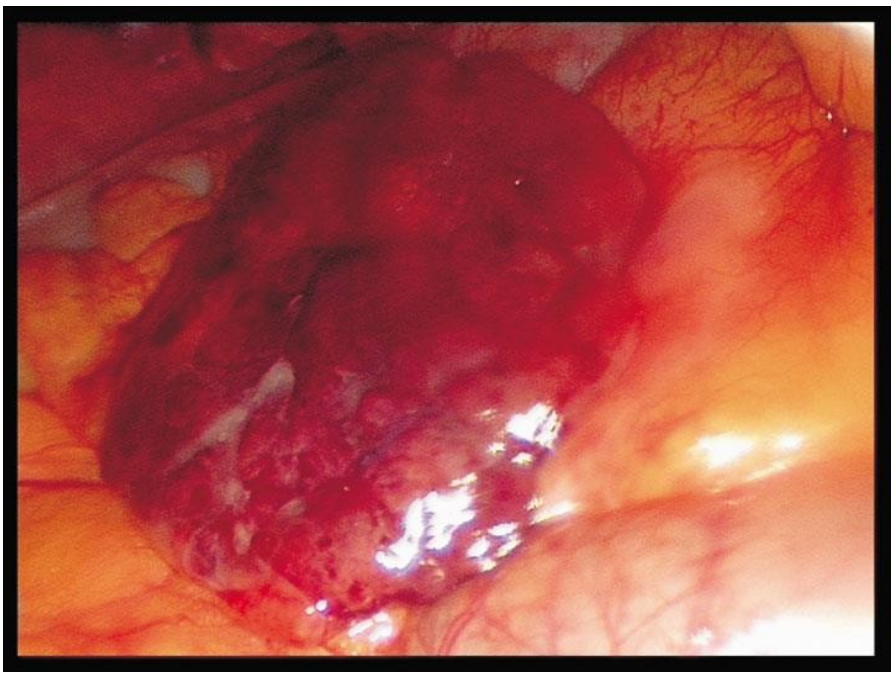

Figure 3: Laparoscopic view of a necrotic hemorrhagic epiploic appendage. (© Sand et al; licensee BioMed Central Ltd. 2007)

harmful antigens from those that are not, or it may turn non-harmful food components or "friendly" bacteria into allergic reactions or even chronic diseases.

Recently, the crucial role played by the microbiota, a collection of microbial populations that reside in the host gut in a perfectly integrated relationship, was discovered. One of the main functions of the microbiota is to protect the intestine against colonization by exogenous pathogens and potentially harmful indigenous microorganisms through several mechanisms, including direct competition for limited nutrients andmodulation of the immune response [17].

The gut hosts over a hundred trillion microorganisms and produces about 60-70% of the body's immune cells.

The most important intestinal defense is represented by the GALT (Gut-Associated Lymphoid Tissue).

The GALT is composed of different types of lymphatic tissue, situated along the intestinal walls forming clusters or isolated follicles.

Among these lymphoid structures the Peyer's patches deserve special attention.

Peyer's patches appear to consist of over 200 aggregated circular or ovoid lymphoid nodules, macroscopically appreciable on the inner wall of the small intestine, in areas with no intestinal villi. Peyer's patches are located in the lamina propria and submucosa of ileum, and extend from the pylorus to the ileocecal valve, with an increased concentration towards the end of the small intestine. Like the other aggregates of MALT (Mucosa-Associated Lymphoid Tissue), they reach their maximum development during puberty, and then diminish in number and size.

In addition to the GALT, the conspicuous intestinal mucus secretion has an important role to trap a great amount of microorganisms and to eject them in collaboration with the peristaltic movements.

Other defense mechanisms include the action of the intestinal or hepatic-derived proteolytic enzymes and the production of HCl by the parietal cells of the stomach which neutralize the functionality of some potentially pathogenic microorganisms.

Finally, the Paneth cells, placed at the base of the crypts of Lieberkühn, produce and reverse into the intestinal lumen a series of peptides with bactericidal function, such as lysozyme and defensins, active against a broad spectrum of both Gram-positive and -negative bacteria.

Thus the intestine has numerous means of defense against pathogens, caused by its particular position. Therefore the presence of an additional fat coverage would not be a surprise, since epiploic appendages would assist and strengthen the immunogenic role of the digestive tract.

Numerous studies now suggest a clear link between adipose tissue and immunity.

Already in 1993, Hotamisligil et al. [18] had reported the production of the tumor necrosis factor (TNF-α), multipotent cytokine with various immunological functions, by the white adipose tissue, particularly evident in genetically obese animals. Later, other factors secreted by adipose tissue, such as interleukins (IL-1, IL-6, IL-8, IL-10), interferon-γ, growth factors, such as transforming growth factor-β and the vascular endothelial growth factor, chemotactic protein (chemoattractant factor for monocytes-1) and factors of the complement cascade were identified. The circulating levels of these factors increase with increasing fat mass, especially if abdominal.

Many phlogosis factors are produced, not only by adipocytes, but also by activated macrophages residing in adipose tissue; the presence of these inflammatory cells is most likely determined by the recruitment of circulating monocytes through chemotactic factors produced by hypertrophied adipocytes caused by caloric excess. Mmonocyte infiltration in adipose tissue amplifies the inflammatory process [19].

The visceral adipose tissue cultures produce , more prophlogistic interleukins (IL -6, IL-8), angiotensinogen, PAI-1, TNF-α and growth factors compared to subcutaneous adipose tissue. Many of these factors are produced by the stromal fraction of adipose tissue and by macrophages

that infiltrate the adipose tissue of obese subjects in much greater numbers than those with a normal weight.

Visceral adipocytes' products, unlike those of the subcutaneous adipocytes, determine a prophlogistic environment and have direct access to the liver [3].

Specific observations allow to hypothesize the relationships between adipose tissue, immune system and inflammation. Firstly, among the adipokines produced from omental fat are, as mentioned above, proteins of the alternative complement pathway system, known to be involved in immune defense processes. Secondly, two adipokines in particular, visfatin [20] and adipsin, are worthy of attention in view of the possible interpretation of the omental fat as immunogenic structure. The first inhibits apoptosis of neutrophils, while the second presents obvious structural similarities with the complement factor D [21].

The adipose tissue is also an important production area of angiotensinogen and angiotensin II. A correlation has been found between plasma levels of angiotensinogen and obesity [22].

Angiotensin II seems to have pro-inflammatory effects on adipocytes and stimulates oxidative stress, and these effects are inhibited by the angiotensin 1 receptor (AT1) blocker. These pro-inflammatory effects result in a reduction of the inflammatory tone when treated with angiotensin-converting enzyme inhibitors or AT1 receptor blockers [23].

Clinical observations seem to reinforce the evidence of the link between fat deposits and immune defenses. Aanorexic patients have a lower level of immune defense [24].

The cause may be found, at least in part, in the reduced production of these adipokines secreted by the adipose tissue and involved in defense processes, and therefore it would not be ascribed only to the general debilitation of the organism.

As mentioned earlier, leptin shows obvious similarities with cytokines. In 1998 Lord, Matarese et al. showed that *in vitro*, leptin has a significant influence on the maturation of human T lymphocytes, playing an important role in the immune system [25].

In fact, leptin can accelerate the thymic homeostasis and the secretion of inflammatory agents, such as interleukin-1 and tumor necrosis factor. Thus, it has an action similar to other inflammatory cytokines, promoting lymphocyte maturation and differentiation of T helper 1 [26-27]. Moreover, the similarity in the functions undertaken is paired with the structural similarity with the class I cytokines.

Studies conducted in mice, involving a 20% reduction of body weight, have immediately led the animals to a condition of immunosuppression. The leptin deficient mice are frailer wildtype mice, with a lower number of lymphocytes compared to normal mice, and they are more exposed to infections.

Therefore, malnutrition, with little fat and little leptin, is linked with an increase in infectious diseases.

More recently, a possible link has been shown between leptin and autoimmune diseases, such as multiple sclerosis and diabetes mellitus type I [28].

An interrupted production of leptin in mice with autoimmune encephalomyelitis, equivalent to human multiple sclerosis, stops the progression of the disease and the symptoms are considerably alleviated [29].

Guinea pigs with recessive gene encoding leptin (ob/ob) have a lower probability of manifesting the disease. However, when they receive doses of leptin, the susceptibility becomes higher [30].

Injection of leptin in mice that develop autoimmune encephalitis worsens the disease. Even the males, which have a lower encephalomyelitis susceptibility than females, have the same chance of getting the disease when leptin is induced.

These observations lead to the hypothesis that leptin can favor the cellular inflammatory response and consequently lead to the onset of autoimmune diseases.

Recently, it has been shown that leptin is also involved in spontaneous autoimmune diseases, such as type 1 diabetes (TD1) in non-obese diabetic (NOD) mice. Leptin, indeed, accelerates the disease onset and progression by stimulating

autoimmune destruction of β-cells and significantly increases IFN-γ production in peripheral T-cells [31].
In patients with multiple sclerosis, leptin levels and interferon gamma are higher in cerebrospinal fluid. In multiple sclerosis, leptin does not originate only from fat tissue, but also from the inflammatory cells of the nervous system. The proliferation of T lymphocytes against myelin basic protein, that causes demyelination, was inhibited in sick mice by anti-leptin or anti-leptin receptor (ObR) antibodies, causing a slowing down of the disease [32].
By administering the hormone once again, a rapid worsening of the disease was noticed.
In addition to clinical observations, statistical and historical data seem to confirm the link between body weight and immune system.
In countries with a better quality of life, a gradual increase in cases of obesity and a concomitant increment of autoimmune diseases such as multiple sclerosis, type I diabetes and rheumatoid arthritis can be observed. However, cases of diseases caused by infections have declined. In poor countries with a much higher rate of malnutrition, the opposite has actually occurred.
It has been said that Peyer's patches undergo a physiological progressive involution process once puberty is reached. However, that is common to other immune structures, such as the thymus and spleen.
The epiploic appendages reach the maximum size in adolescence and then regress in post-pubertal age.
Clinical cases refer to an inflammation of the epiploic appendage as epiploic appendagitis (EA) [2].
Epiploic appendagitis is a rare cause of focal abdominal pain in otherwise healthy patients with mild or absent secondary signs of abdominal pathology. It can mimic diverticulitis or appendicitis on clinical exam.
Abdominal pain is the leading symptom; the pain is usually located in the left, and sometimes in the right lower abdominal quadrant. Due to the lack of pathognomic clinical features, the diagnosis of epiploic appendagitis is difficult. It is also very infrequent [2].
A variety of complications can follow EA. [33] Accompanying surrounding inflammation can trigger adhesions with multiple secondary symptoms. Another possible complication is local abscess formation, simulating a neoplastic lesion. Intussusception, bowel obstruction, abscess formation and peritonitis are further described complications [34].
Surgical therapy is not usually necessary but the desuetude to the recognition of this pathology could induce to unnecessary surgical exploration for "acute abdomen" [35].
Inflammation of epiploic appendages could be in some way related to an immune over-activation of these appendices.

Conclusions

For a long time, epiploic appendages were thought to have only the role of providing a soft and flexible support cushioning the colon. In recent years, important discoveries have been made regarding the functions of adipose tissue. It is no longer considered merely as energy storage, but as a fully integrated organ in systemic metabolism. Based on these observations, the functions of epiploic appendages should be re-assessed. In particular, the secretion of leptin, mainly entrusted to white fat, suggests a hormonal regulation action. The communication with the hypothalamic nuclei points to a satiety signal. Leptin also suggests an immune function since recent studies have shown a direct correlation with various autoimmune diseases, such as multiple sclerosis and type I diabetes.In addition to leptin, adipose tissue also secretes complement pathway factors. The hypothesis of a possible immune function of epiploic appendages seems to be supported by clinical cases and inflammation of the epiploic appendages (EA).
Although the mechanisms through which the epiploic appendages would carry out such tasks are not currently clear, advances in the knowledge on the physiology of adipose tissue, allow us to expand the functions attributed to visceral fat in

general, thus potentially leading to a better understanding of the role the epiploic appendages.

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