Review

Molecular talk of adipokines in dermatological diseases

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Abstract: Adipose tissue is not a passive tissue storing triglycerides, but one that releases hormones, enzymes, growth factors, and cytokines. Currently, known to release more than 600 adipokines, the adipose is an active tissue involved in energy homeostasis and serving paracrine, autocrine and endocrinal functions. Besides, some adipokines (irisin and ghrelin, for example) are synthesized in the sebaceous glands of the skin and play important roles in certain dermatological diseases. This review will provide a systemic overview of adipokines, focusing on their tissue and organ distribution, functions in biological systems, and roles in dermatological diseases. Additionally, the areas where adipokines can be used in dermatological diseases and their possible future roles will be presented.

Key words: Adipose tissue, endocrinal function, cutaneous diseases.

Introduction

Adipose (from the Latin word *atleps*, meaning fat) tissue is an active tissue where fat formed from connective tissue cells is stored, many hormones are synthesized and released, and numerous biochemical and physiological events are kept under strict control. The functions of the adipose tissue include maintenance of heat isolation, storage and secretion of fats, provision of padding around organs, protection of the body and organs against mechanic and external impacts (impact absorption), promotion of the harmony of nervous activities, preservation of the order of cells, storage of fat-soluble vitamins, synthesis and secretion of adipokines (1,2), filling in of gaps between tissues, and forming a protective layer against external factors particularly in the sole of the foot and palm, among others.

The adipose tissue, 50% of which is composed of vascular elements, also includes fibroblasts, nerve elements, mast cells, pre-adipocytes, and mesenchymal cells, whose function is yet to be clarified. Since the fat taken into the cell pushes the nucleus to the side, the nucleus has an eccentric location. Based on the kind of fat droplets it includes, the adipose tissue is classified as white (unilocular) or brown (multilocular). As the white adipose tissue contains a single and large fat droplet, it appears as a "signet-ring". Cells forming the brown (multilocular) fat tissue, on the other hand, are composed of numerous small lipid droplets. Brown fat tissue cells also have numerous oval, global and fusiform mitochondria (Figure 1).

Although the gross anatomy of the human adipose tissue has not been shown in detail, white adipose tissue (WAT) is classified under two headings, as visceral and subcutaneous lipid stores. The adipose tissue underlying the skin or dermis is called the subcutaneous adipose tissue. In humans, subcutaneous adipose tissue is an extension of the dermal adipose tissue. In mice, dermal adipose tissue is separated by a layer of smooth muscles. The amounts of these two adipose tissues vary depending on age, sex, environmental temperature, diet, and metabolic conditions. In slender individuals, adipose tissue forms 8 to 10% of the body weight in males and 14 to 28% of the body weight in females. In obese individuals, however, the amount of adipose tissue is quadrupled, corresponding to 60 to 70% of body weight. White adipose tissue is generally found around the heart, blood vessels, eyes, mammary glands and bone marrow, while brown adipose tissue is located around the adrenal glands, kidneys, neck and mediastinum. Although these fat cells have different anatomic locations, they inevitably serve the same functions.

Over 100 skin diseases have described so far. Some skin diseases are minor, and others can be life-threatening. Unfortunately however, there are only a few studies across the world examining the relationship between cutaneous diseases and adipocytes. Therefore, this study will first present a systematic overview of the main adipokines associated with human health and then a review of the studies exploring the relation between
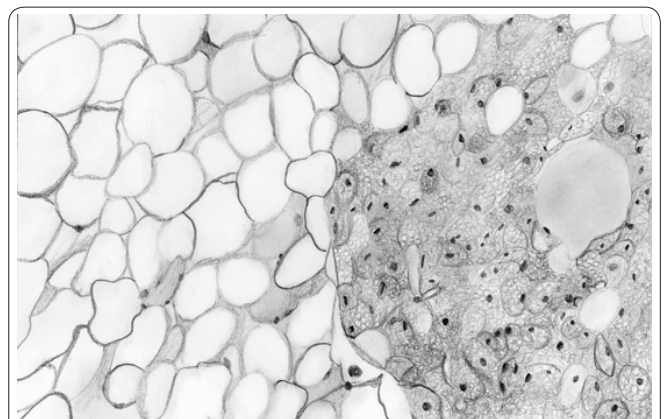

Figure 1. The general histological appearance of white and brown adipose tissue.

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dermatological diseases (except tumors) and adipokines.

Adipokines

Molecules synthesized in the fat cells (proteins / protein factors) are generally called adipokines (3). Adipokines have multiple biological functions. Table 1 presents some adipocytes and the researchers who discovered them, as well as Table 2 shows the main biochemical functions of these molecules. In 1987, Cook et al. reported a molecule released from the fat tissue and called it adipcin/complement factor D (4). However, it was not until the discovery of leptin in 1994 (5) and of adiponectin in 1995 (6) that the possibility of fat tissue being an endocrine organ was acknowledged. Following the discovery of leptin and adiponectin in fat cells, these cells came under rigorous scrutiny, which resulted in the discovery of more than 600 adipokines. Some of these peptides were already known, but their presence in the fat cell was not until today and re-consideration of metabolic events (7, 8). Thus, the focus of the later parts of this review will be adipokines which are involved in metabolic events and dermatological diseases.

Leptin

Leptin is an adipose cell hormone. It is the first adipokine discovered by Dr. Jeffrey Friedman et al. in 1994 (21). Consisting of 167 amino acids, this fat cell hormone weighs 16 kDa. It has been derived from the Greek word *leptos*, meaning *thin*. Encoded by the obese (ob) gene, it is synthesized in many tissues, including the salivary glands and lipid and subcutaneous tissue. Leptin synthesis in the subcutaneous adipokine tissue is greater than that in the visceral adipokine tissue. The location and size of fat cells affect circulating leptin concentrations (37). As the body weight drops, circulating leptin concentrations are reduced. Women have higher leptin levels than men (38). Leptin levels are elevated

Table 1. The biological tissue/cell in which molecules synthesized by some adipocytes or affecting adipocytes, and the researchers who discovered them.

| Hormones | First discovered in biological tissue/cell | | Researchers and year |
	Tissue / Cell	Method	
Fetuin-A	Serum	Centrifuging	Pederson et al. (1944) (9)
Pancreatic Polypeptide	Pancreas	Paper chromatography polyacrylamide gel electrophoresis	Kimmel et al. (1968) (10)
Motilin	Small intestines	Purification	Brown et al. (1971) (11)
FABP 4	Intestinal mucosa, liver, myocardium, adipose tissue, kidney	Protein synthesis	Ockner et al. (1972) (12)
Copeptin	Neurohypophysis	Gel filtration, chromatography, electrophoresis	Holwerda et al. (1972) (13)
Galanin	Intestinal extract	Thin layer chromatography	Tatemoto et al. (1978) (14)
Neuropeptide Y	Hypothalamus	Fragmentation analysis	Tatemoto et al. (1982) (15)
Adipsin	3T3-F442A adipocytes	Electrophoresis	Cook et al. (1987) (4)
Amylin	Pancreas islet (beta cells)	HPLC	Westermark et al. (1987) (16)
ASP	Plasma	Electrophoresis	Cianflone et al. (1989) (17)
Lipocalin 2	Neutrophil gelatinase	Immunoblotting, immune-precipitation	Kjeldsen et al. (1999) (18)
Visfatin	COS 7 and PA317 cells	cDNA library	Samal et al. (1994) (19)
Leptin	Adipose	cDNA library	Zhang et al. (1994) (5)
Adiponectin	3T3-L1 adipocytes	DNA analysis, electrophoresis	Scherer et al. (1995) (6)
Omentin	Intestinal paneth cells	İn situ hybridization, Northern blot	Komiya et al. (1998) (20)
Apelin	Stomach	RT-PCR, HPLC	Tatemoto et al. (1998) (21)
Ghrelin	X/A (ghrelin) cell	RIA, ELISA	Kojima et al. (1999) (22)
Hepcidin	Blood ultrafiltrate	Mass spectrometry	Kraus et al. (2000) (23)
Resistin	Small intestine epithelium, bronchus epithelium and white adipose tissues	Sequence analysis IHC, Electrophoresis, Western blot, Northern blot	Holcomb et al. (2000) (24)
Preptin	TC6-F7 beta-cells	RİA, İHC	Bucham et al. (2001) (25)
Salusin	cDNA library	Silico analysis	Shichiri et al. (2003) (26)
Chemerin	Dendritic cells, macrophages	Mass spectrophotometry RT-PCR	Wittamer et al. (2003) (27)
Desnutrin	3T3-L1 adipocytes	Microarray analysis	Villena et al. (2004) (28)
Obestatin	Stomach	Isolation	Zhang et al. (2005) (29)
Nesfatin-1	Hypothalamus	cDNA library	Oh-I et al. (2006) (30)
Alarin	Neuroblastic tumor	RT-PCR	Santic et al. (2006) (31)
Vaspin	Visceral white fatty tissue	PCR	Wada et al. (2008) (32)
Adropine	Liver	Microarray, In situ hybridization	Kumar et al. (2008) (33)
Irisin	Muscle cell	Western Blot	Boström et al. (2012) (34)

ASP: Acylation-stimulating protein, FABP 4: Fatty acid binding protein 4, IHC: Immunohistochemistry, RIA: Radioimmunoassay, ELISA: Enzyme-linked immunosorbent assay.

Table 2. Major biochemical functions of molecules synthesized in certain adipocytes or affecting adipocytes (7, 35 and 36).

Molecules	Major Functions
Adiponectin	Anti-diabetic, anti-atherogenic, anti-inflammatory, increases insulin tolerance
Adipsin	Activation of alternative complement pathway
Amylin	Regulation of insulin secretion and glucose metabolism
Apelin	Inhibition of insulin secretion
Desnutrin	Burning fat
Chemerin	Chemoreactant and regulator of adipogenesis
FAB4	Impairment of myocardial contractility
Fetuin-A	Indicator of hepatosteatosis, inflammation and insulin resistance
Galanin	Cellular communication in central and peripheral nervous system, anti-microbial
Ghrelin	Starts feeding, regulates glucose metabolism
Hepcidin	Regulator of iron metabolism, anti-microbial
Cathepsins S, L, K	Regulation of adipose tissue mass and glucose metabolism
Leptin	Satiety signal, regulator of fertility, appetite and food intake
Lipocalin 2	Indicator of inflammation and insulin resistance
Neuropeptide Y	Regulation of food intake
Irisin	Regulation of fat and glucose metabolism
Omentin	Increases insulin sensitivity and anti-inflammatory
Plasminogen activator inhibitor	Regulation of coagulation
Preptin	Regulation of insulin secretion and glucose metabolism
Resistin	Insulin resistance, inflammation and obesity
Salusin	Hypotensive, anti-microbial
Vaspin	Serine protease inhibitor, inhibition of food intake, improves hyperglycemia
Visfatin	Regulation of pancreatic beta cell functions

FAB4: Fatty acid binding protein 4.

by proinflammatory cytokines (TNF), insulin, cortisol, overeating, glucose level, glucocorticoids and estrogen, and reduced by hunger, testosterone, growth hormone, cold, β-adrenergic agonists, epinephrine and free fatty acids.

Leptin regulates a number of biochemical and physiological systems and events, including the sympathetic nervous system, reproduction, bone metabolism, wound recovery, energy homeostasis, hematopoiesis, angiogenesis, immune and inflammatory response, and regulation of the gastrointestinal functions. Defects in the leptin gene or receptor results in the loss of control over eating and appetite. Besides, sympathetic activity and insulin resistance are reduced. Fulfilling all these functions by inhibiting the orexigenic (appetite-stimulating) signals and activating anorexigenic (appetite-inhibiting) signals in the hypothalamus, leptin keeps body weight under control.

Adiponectin

Adiponectin (GBP28, adipoQ, ACRP30) is a collagen-like plasma protein composed of 248 amino acids and weighing 30 kDa (6). With a plasma concentration ranging between 5 and 30 µg/mL, this protein of adipose origin has the highest circulating concentration among the known adipokines. Adiponectin affects estrogen, testosterone, fasting plasma insulin level, and diet concentrations. It has two primary receptors, one in the skeletal muscle (Adipo R1) and the other in the hepatic tissue (Adipo R2) (39). This adipokine regulating the energy balance and glucose and lipid metabolisms is correlated with insulin sensitivity and is elevated in response to insulin. It regulates the energy balance through muscle and liver tissues by increasing insulin sensitivity. Although it inhibits the gluconeoge-

netic enzymes and glucose production, it does not have any impact on glucose intake, glycolysis and glycogen synthesis. Adiponectin also exercises anti-diabetic, anti-apoptotic, anti-inflammatory (TNF-α), anti-atherogenic (suppressing the foam cells of macrophages), and anti-oxidative effects.

Ghrelin

Discovered in 1999, this hormone is also known as the appetite hormone (22). The key feature of ghrelin is that, although it has a peptide structure, it does not contain amino acids. This feature is not found in any other peptide hormone. After ghrelin is synthesized in the ribosomes as a peptide hormone, either an eight-carbon (octanoic acid) fatty acid or a ten-carbon saturated fatty acid or a ten-carbon unsaturated fatty acid (with a double bond) is bound to its third amino acid serine (threonine in frogs (40) at the N terminal through post-translational modification. Ghrelins with bound fatty acids are called acylated ghrelins. The bonding of these fatty acids to ghrelins was reported to be directly related to the amounts of dietary fat intake. The fatty acids in the ghrelins are severed by proteases. Ghrelins without fatty acids are called desacyl ghrelins.

Although the primary site of synthesis of this hormone was reported to be the X/A cells in the fundus part of the stomach, it is also synthesized in many other peripheral tissues including the adipose and cutaneous tissues (41). The main function of the hormone is to stimulate hunger. Therefore, its levels reach a peak immediately before meals. It has lower circulating levels in overweight individuals and higher levels in thin ones (42). It has been claimed that the main the reason why it has higher levels in the circulation of slim individuals is to lead the individual to eat so that s/he can reach a nor-

mal weight. Besides regulating appetite, ghrelin is also responsible for the release of the growth hormone. Additionally, it serves anti-inflammatory, anti-microbial, and anti-oxidant functions.

Plasminogen activator inhibitor-1

This molecule, which is a serine protease inhibitor, is found in the adipose tissue of rodents (43). Later studies showed its presence in human adipose tissue (including the pre-adipose tissue). Omental fatty tissue contains more plasminogen activator inhibitor-1 than the subcutaneous fat tissue. Plasminogen activator inhibitor-1 in the omental fat tissue is induced by cytokines and angiotensin II. Currently, it is not known why omental adipose tissue has more plasminogen activator inhibitor-1 than the subcutaneous fat tissue.

Hepcidin

Hepcidin is synthesized in the ribosomes as a pre-pro-hormone. Consequently, this hormone is found in biological fluids as a pre-pro-hormone (with 84 amino acids), pro-hormone (with 60 amino acids) and hormone (with 25 amino acids). Urine was reported to contain hepcidin molecules with 20 and 22 amino acids. Saliva and milk also have hepcidin in them. A pro-hormone convertase molecule called "furin" mediates the conversion of pro-hormone hepcidin to hepcidin (44). Hepcidin was originally named LEAP-1 (23), but later renamed as hepcidin upon the discovery of its association with inflammation (45). The hepcidin gene located on the chromosome 19 is called HAMP. The principal site of hepcidin synthesis is the liver. However, recent studies have shown that it is also synthesized in the salivary gland, fat tissue, mammary tissue, and myeloid cells (against bacterial pathogens). This peptide hormone is removed from the cell through urine. Its major function is to reduce iron absorption in the small intestines (46). Additionally, Sow et al. have reported that it prevents the reproduction of the micro-organism by causing structural damage in *M. tuberculosis* and thus has an anti-microbial character (47). Later studies have shown that it not only prevents the reproduction of a number of bacteria including *E. coli*, but also has anti-fungal effects. Hepcidin synthesis in the liver is reduced in cases of hypoxia, increased erythropoietic activity and decreased ferritin amounts. Hepcidin receptor is called ferroportin. A basolateral transmembrane protein, ferroportin is found mainly in the reticuloendothelial macrophages, liver, placenta and intestinal tissues. When ferroportin on the cell surface is reduced, iron passage to the plasma is curtailed.

Resistin

This hormone released from the adipose tissue was discovered in 2000 by two independent research teams (Steppan and colleagues, 1998; Holcomb and colleagues) (24) while researching the thiazolidinedione class of medications. The hormone was called FIZZ1 by Holcomb and colleagues and FIZZ2 by Steppan and colleagues (48). Consisting of 108 amino acids, resistin has a molecular weight of 12.5 kDa and is rich in cyste-

ine. The hormone was named by an international committee as resistin from among the alternative names of FIZZ1, FIZZ3, ADSF, RELM, adipophilin and RETN1, due to its *resistance* against insulin. As the adipose mass increases in the organism, so do the resistin amounts. Females have higher levels of resistin in circulation than males. The circulating levels of resistin are reduced by anti-diabetic drug use.

Visfatin

Visfatin is composed of 491 amino acids and weighs 52 kDa. Studies have reported abundant synthesis of visfatin in the visceral fat tissue. When the adipose mass of the organism increases, visfatin levels show a parallel increase (49). In humans visfatin amounts are directly correlated with visceral fat mass, type 2 diabetes and metabolic syndrome (50). This hormone exercises insulin-like effects on glucose and lipid homeostasis. It speeds up triglyceride synthesis from glucose, and thus triggers adipogenesis. It has been suggested that use of visfatin at pharmacological doses can benefit the potential treatment of diabetes patients. Inflammation, hypoxia and hyperglycemia elevate visfatin levels, while reducing the levels of somatostatin and insulin (51).

Omentin

It has two main forms in the circulation as omentin-1 and omentin-2. Omentin-1 and Omentin-2 are 83% homologous. Although its presence was first identified in the Paneth cells of the liver (20), it was discovered in the omental fat tissue in 2003, using the C DNA library (52). Consisting of 313 amino acids, it weighs 35 kDa. Visceral fat tissue contains more omentin than subcutaneous and mature adipose tissues. Omentins are expressed in a variety of tissues, among which are epicardial adipose tissue, thymus, ovaries, lungs, colon, small intestines, placenta, reticulocytes, and endothelial cells. It has been claimed to protect the intestines against pathogenic bacteria and to be involved in the regulation of glucose (53). Omentin also functions as a vasoconstrictor, but its role in obesity is yet to be clarified.

Chemerin

Described in 2003, chemerin is composed of 131-137 amino acids (27). Having an anti-microbial character, chemerin serves in glucose regulation, as well as the regulation of vascular inflammation response. However, its biological functions have not been fully recognized yet. Although it is synthesized abundantly in the keratinocyte cells of healthy skin, its synthesis is reduced in psoriasis (54). Being synthesized in the epidermis layer of the skin as well, chemerin has been suggested to be a critical peptide protecting the skin against pathogenic micro-organisms due to its anti-microbial effects (55).

Vaspin

Vaspin, composed of 392-395 amino acids, was identified in 2008 (32). Belonging to the family of serine protease inhibitors, vaspin regulates glucose by increasing insulin sensitivity. It inhibits the expression of

pro-inflammatory adipocytes. Although it also has a part in controlling food intake, the mechanisms by which it does so are not certain yet.

Neuropeptide family

Neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PPs) resemble each other structurally, and contain 36 amino acids (56). These three peptides serve many biological functions which include memory and learning operations, elevating water and food intake, inhibition of glutamatergic and noradrenergic synaptic transmission, reduced sexual action, changes in the circadian rhythm and induction of hypothermia. In addition, NPY has been reported to inhibit proliferation in keratinocytes (57). NPY expression was identified in the cutaneous lesions of atopic dermatitis patients.

Apelin

Apelin, another adipokine, was first described in 1998 by Tatemoto et al. in the bovine stomach juice (21). Apelins first develop as pro-peptides with 77 amino acids. From these pro-peptides, apeline-36, apelin-31, apelin-28, apelin-19, apelin-17, apelin-16, apelin-15, apelin-13, apelin-12 and pyroglutaminized apelin-13 are formed through posttranslational modification. Apart from the stomach, apelins were reported to be synthesized and to have receptors in many tissues such as the heart, lung, kidney, liver, adipose tissue, gastrointestinal tract, brain, adrenal gland, and endothelium (58). Plasma apelin levels are elevated in patients with obesity, insulin resistance and hyperinsulinemia. Apelin in adipose cells are inhibited by hunger and stimulated by food intake. For instance, intracerebro-ventricular administration of apelin to satiated rodents did not produce any effect on food intake, whereas it was reported to increase food intake of hungry animals in a dose-dependent manner. In other words, apelins regulate food intake. Among other physiological effects of apelins are diuresis, positive inotropic effect, fluid and glucose homeostasis, vessel formation, cell proliferation and regulation of immunity. They also decrease blood pressure. By reducing sodium and water intake, apelins inhibit the release of vasopressin (59).

Galanin peptide family

Galanin peptide family includes the galanin-message-associated-peptide, galanin-like peptide (GALP) and alarin. Galanin was first obtained from the porcine small intestine extracts in 1978 (14). It is synthesized profusely in the central nervous system and gastrointestinal system tissues. From the 123-amino-acid pre-pro-galanin, galanins with 29 (porcine) and 30 (human) amino acids are formed by post-translation. Bovine, mouse, human and porcine galanins show over 80% homology. In the gastrointestinal system, the highest amount of galanin synthesis takes place in the duodenum, which is followed by stomach, small intestines, and colon. It is directly connected with the central nervous system through cutaneous nerves (afferent and efferent nerves). Galanin is synthesized in and released from afferent nerves. There are galanin binding sites on the human skin, around dermal arteries and arterioles, and near the sweat glands. Keratinocytes synthesize small amounts of GALP and alarin adipocytes. Galanin is involved in the protection of cutaneous tissue from pathogenic bacteria (60).

Amylin

Consisting of 37 amino acids, this hormone is released from the pancreatic beta cells together with insulin at a proportion of 100:1. Amylin was discovered in 1987 by two independent groups of researchers. European researchers called the hormone islet amyloid polypeptide (IAPP), while the American researchers referred to it as amylin (16,61). The hormone has a disulfide bond between amino acids 2 and 7, which is necessary for its biological activity. Amylin gives a sense of satiety and reduces gastric emptying. It also constrains post-prandial fluctuation in the glucose level, thereby exercising glycemic control. Amylin serves in the development of bones through calcitonin. It is a promising agent in the treatment of type 1 and type 2 diabetes. Amylin increases fat intake in 3T3-L1 adipose cells and is directly involved in the insulin resistance mechanism (62).

Preptin

Just like amylin, this peptide is released from the pancreatic beta cells with insulin. Isolated from the TC6-F7 pancreatic beta cells of rats in 2001, preptin is composed of 34 amino acids (25). It increases insulin secretion through glucose (25). Preptin contributes to bone development and prevents apoptosis in osteoblasts (63).

Fatty acid binding proteins (FABPs)

Fatty acid binding proteins belong to the family of lipid binding proteins. Its various forms from FABP1 to FABP12 have been defined. FABP1 is expressed in the liver, small intestines, pancreas, kidneys, lungs and stomach; FABP2 in the liver and small intestines; FABP3 in the heart and skeletal muscle, brain, kidneys, testes, adrenal glands, mammary glands, ovaries and brown fat tissue; FABP4 in the adipose tissues, macrophages, dendritic cells and skeletal muscle fibers; FABP5 in the skin, tongue, adipose cells, macrophages, dendritic cells, mammary glands, brain, stomach, small intestines, kidney, liver, lungs, heart, skeletal muscle, testes, retina, lenses, spleen and placenta; FABP6 in the ileum, ovarium, adrenal gland and stomach; FABP7 in the brain, central nervous system, glial cells, retina and mammary glands; FABP8 in the peripheral nervous system and Schwann cells; FABP9 in the testes, salivary glands and mammary glands; and FABP 12 in the retinoblastoma cells, retina, testis cells, cerebral cortex, kidneys and epididymis. Given this variety of forms, researchers should choose the one that is appropriate for their aims. For instance, a scientist examining cutaneous diseases should study FABP4 and FABP5, as these forms are produced by fat cells, and since FABP5 is synthesized in the skin, it seems more relevant to der-

matological diseases (64).

Lipocalin-2 [neutrophil gelatinase-associated lipocalin (NGAL)]

Lipocalin-2 is a member of the family of lipocalin proteins which also includes the fatty acid binding proteins. It prevents the reproduction of pathogenic bacteria and exercises growth hormone-like effects (65). It enhances the activity of MMP-9 which leads to the destruction of extracellular matrix and cell membrane. Recent studies have indicated that it can be a marker of kidney injury. Lipocalin-2 is expressed in the adipose cells, epithelium, colon, prostate, mammary glands and renal tubules. Stress, inflammation, infection, ischemia, Behcet's disease and psoriasis increase the synthesis of lipocalins (66).

Cathepsins

The term *cathepsin* is derived from the Greek word *kathepsein*, meaning *digestion*. Many cathepsins have been described, including B, C, F, H, K, L, O, S, V, X and W cathepsins. Lysosomal cathepsins are synthesized as pre-pro-enzymes in many human tissues including the adipose cells. Cathepsins regulate the glucose metabolism and adipose tissue mass (67).

Fetuin-A

Fetuin-A is an acute phase glycoprotein having a molecular weight of 60 kDa and is synthesized primarily in the liver (hepatocytes) and adipose cells. Binding to insulin receptors in the muscle and fat tissue, it inhibits the activity of insulin receptor tyrosinase activity (68). It shows the steatosis in the liver and is a marker of both inflammation and insulin resistance. It has also been associated with the progression of cancer (69).

The cutaneous structure and the adipokines synthesized in the skin

Covering the body surface and fulfilling vital functions, the skin is composed of the layers of epidermis, dermis and subcutis. Keratinocytes (squamous cells) are the basic cells of the epidermis. Besides, Merkel cells, Langerhans cells and melanocytes are reported to be found in the dermis. The general histological appearance of the skin is presented in Figure 2. Squamous cells originate from the ectoderm and synthesize keratin, which is the primary protein of stratum corneum, hair, and nails. Epidermis is formed from the basal stratum (Str. Germinativum), stratum spinosum (Malpighian or Prickle layer), granular stratum (Str. Ganulosum) and stratum corneum (keratinized layer, horny layer).

The dermis layer of the skin is composed of elastic, reticular fibrils and collagen connective tissue. Dermis papillae extend into epidermis like the fingers of a glove. The extensions of the epidermis towards the dermis, on the other hand, are called "rete ridges".

The subcutis (Panniculus) layer lies below the dermis. This layer consists of lobules formed from adipokine cells separated by fibrous septa. This stratum of the skin protects the internal organs from external trau-

mas. The subcutis stratum serves as a storage for some hormones. Hair, apocrine glands, eccrine sweat glands, nails and sebaceous glands are the other structures of the skin (70).

Studies in the last two decades have revealed that the skin is not only a cover veiling the skin, but also that the epidermis, beyond being a static barrier, is a critical endocrine organ serving endocrine and exocrine functions (71).

Epidermal cells synthesize neuropeptide Y (NPY), peptide YY (PYY), and pancreatic polypeptide, and these molecules have receptors in the skin. NPY prevents the accumulation of cAMP which increases upon induction of forskolin in keratinocytes. Put differently, NPY inhibits keratinocyte proliferation. Likewise, NPY and PYY irreversibly inhibit the reproduction of pathogenic micro-organisms in the human skin (72). Epidermis layer also synthesizes profuse amounts of galanin. Besides, FABP5 was reported to be synthesized by the skin and adipose tissue. Although this much is known about these molecules being synthesized in the skin, it is still not clear what functions they serve there.

Irisin, which converts the white adipose tissue into brown adipose tissue, was first reported to be synthesized in the skeletal muscle (34), and then in the smooth muscles, fat tissue (73) and cutaneous sebaceous glands (74). The key smooth muscle of the skin, arrector pilorum is attached to the hair follicle under the sebaceous gland. Besides, the skin synthesizes a molecule called dermcidin (75), which has an anti-microbial and endocrine character. Apart from these, ghrelin hormone was reported to be synthesized by the skin (76). Similarly, the synthesis of the chemerin molecule takes place in the epidermis layer (55). These hormones are also adipokines. As for the other adipokines, it is yet to be shown whether they are synthesized in the skin or not, and this remains a significant topic for research.
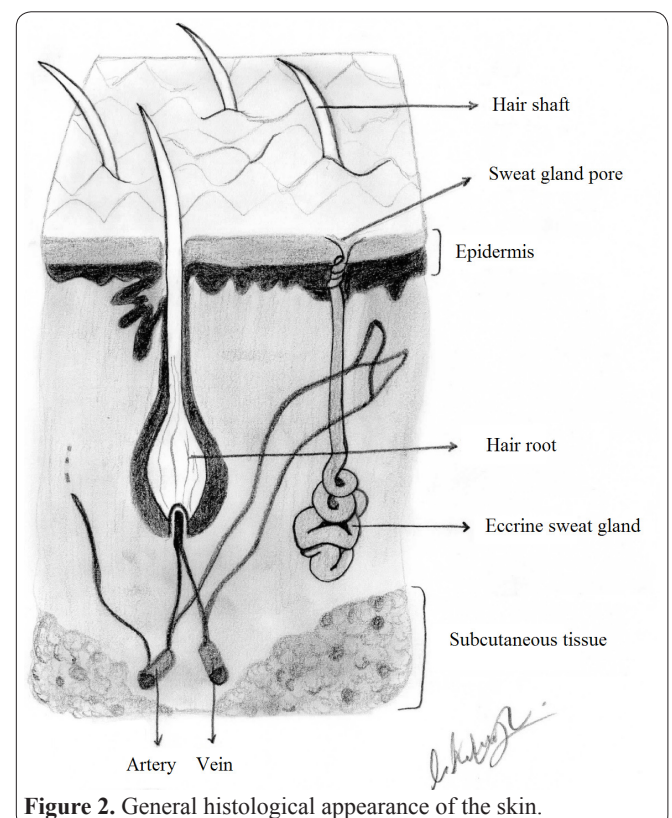
Furthermore, although there are innumerable skin

Figure 2. General histological appearance of the skin.

diseases, such as acne, skin allergies, skin cancer, stretch marks, freckles, boils, eczema, baldness, wrinkles, rash, spots, acne vulgaris marks, callus, alopecia, beard inflammation, cellulitis, psoriasis, wart, carbuncle, vitiligo, herpes, scabies, erysipelas, to name a few, studies examining how they are related to adipokines are scarce. The rest of this review addresses the studies investigating the relations between adipokines (with the exception of interleukins, which are important adipocytes) and cutaneous diseases.

Cutaneous diseases and adipokines

Acanthosis nigricans
Benign acanthosis nigricans is usually associated with obesity. In this disease, leptin and resistin adipokines are elevated, while adiponectin is reduced (77).

Psoriasis
It is not clear whether there is a relationship between psoriasis and adiponectin, although adiponectin was reported to increase in psoriasis (78,79). While serum retinol-binding protein 4 (RBP4), preptin and amylin decrease, serum leptin, visfatin, apelin, ghrelin, resistin and high-molecular-weight adiponectin and total adiponectin levels increase in this disease and these increases can be reversed by treatment (cyclosporine) (79). No consensus has been reached on the relationship between neuropeptide Y and omentin levels, and psoriasis. Although omentin amounts generally increase in psoriasis, one study reported a decrease (80). There is also no consensus the relationship between newly discovered adipokine-myokine, irisin and psoriasis (81,82).

Systemic sclerosis
Patients with systemic sclerosis have higher levels of apelin and resistin (83,84). In the early period, apelin levels were reported to be even higher. Adiponectin and leptin levels, on the other hand, were found lower in systemic sclerosis (85). Still, active systemic sclerosis patients have lower leptin levels than inactive ones (86). Additionally, it was reported that patients in the pre-menopausal period had higher leptin values than those in the post-menopausal period (87). Omentin levels are also found lower in this disease (88).

Behcet's Disease
Prohepcidin, hepcidin, salusin alpha, preptin and amylin amounts are reduced, whereas salusin-beta levels are elevated in Behcet's disease (89).

Acne vulgaris
Desnutrin, a recently discovered adipokine, was reported to be lower in this disease (90). The course of adipokines in various dermatological disease can be found in Table 3. Although there are numerous dermatological diseases, as the table shows, studies usually address the relations between adipokines and the diseases that are the most common in societies and that cause the major cosmetic problems. Given that the skin is a critical endocrine organ and certain adipokines are synthesized in the skin, it is obvious that the skin is bound to provide a prolific area of research.

What should be known when analyzing adipokines in biological fluids

MEROPS data show that the human genome contains over 700 proteases. Peptide/protein hormones are rapidly broken down by cellular proteases. Since adipokines have peptide/protein structure, when they are being studied, protease inhibitors must be used to protect them from proteases. In general, use of 500 KIU of protease inhibitor (aprotinine, for insntance) per milliliter of biological samples is recommended. Adipokines can be measured by enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) methods. If adipokines are to be studied in tissue samples, the tissue must be boiled in a water bath for 5 to 10 minutes to inactivate proteases. Thus, these samples can be kept stable at -20 or -80°C for years (115).

Conclusion and future directions
The adipose tissue, the weight of which corresponds to 20% of the body weight, secretes more than 600 adipokines (7,8). The adipokines secreted from and synthesized by adipose cells have attracted growing interest over the last two decades and it seems that they will continue to do so in the future. The patho-physiology and biochemistry of the adipose tissue is of particular concern not only to academic researchers, but also to physicians providing routine health care services, as at present, beyond being a storage for fats, the adipose tissue is an endocrinal organ where new hormones are being discovered.

Even though this endocrinal organ is explored extensively by biochemists, physiologists and endocrinologists, it has not come under the close examination of dermatologists, and consequently, there are few scientific studies about it in the field of dermatology. It is true that the real cause of many dermatological diseases is not known yet; still, some of them are recognized to be directly connected with inflammation and to involve endocrinal disorders. Considering that adipose tissue comprises 20% of body weight and a significant portion of fats accumulate in the subcutaneous tissue and many anti-inflammatory molecules and hormones are synthesized in and secreted from the adipose tissue, there is an obvious need for dermatologists to uncover the relations between dermatological diseases and adipokines. The discovery of adipokines connected with dermatological diseases will have strong implications for treatment, and thus will contribute to the elimination of many cosmetic problems.

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Table 3. How hormones synthesized in adipocytes or affecting adipocytes are altered in dermatological diseases.

Dermatosis	Hormone	Sample - method	Outcome	Researchers
Psoriasis	Adiponectin	Plasma – ELISA	↑	Kaur et al. (2008) (91)
	Adiponectin	Serum – ELISA	↑ ↓ ↓ ↓	Ozdemir et al. (2012) (79) Baran et al. (2014) (92) Xue et al. (2012) (93) Campanati et al. (2015) (94)
	Apelin		↑	Dertlioglu et al. (2013) (95)
	Leptin	Serum – ELISA	↓ ↑ ↑ ↑	Baran et al. (2014) (92) Campanati et al. (2015) (94) Xue et al. (2012) (93) Ozdemir et al. (2012) (79)
	Omentin	Skin, Serum – ELISA, IHC	↓	Zhang et al. (2015) (96)
		Serum – ELISA, RT-PCR, Electrophoresis	↓	Turan et al. (2014) (97)
		Serum – ELISA	↑ ↓ ↓	Xue et al. (2012) (54) Ismail et al. (2012) (98) Takahashi et al. (2013) (99)
	Visfatin	Serum – ELISA	↑ ↑	Campanati et al. (2015) (94) Ismail et al. (2012) (98)
	Resistin	Serum – ELISA	↑ ↑ ↑ ↑ ↔	Campanati et al. (2015) (94) Takahashi et al. (2013) (99) Gisondi et al. (2013) (100) Ozdemir et al. (2012) (79) Xue et al. (2012) (54)
	Ghrelin	Serum – ELISA	↑ ↑	Ozdemir et al. (2012) (79) Ucak et al. (2014) (76)
	Amylin	Serum – ELISA	↓	Dogan et al. (2014) (101)
	Chemerin	Serum – ELISA	↑ ↓	Gisondi et al. (2013) (100) Xue et al. (2012) (54)
	FABP 4	İHK, Northern blot	↔	Kuijpers et al. (1997) (102)
	Hepcidin	Serum – ELISA	↑	Dilek et al. (2014) (103)
	Lipocalin 2	Serum, Skin biopsy– ELISA	↔	El-Hadidi et al. (2014) (66)
	Neuropeptide Y	Plasma – RIA	↔	Reich et al. (2007) (104)
	Preptin	Serum – ELISA	↓	Dogan et al. (2014) (101)
Allergic contact dermatitis	Adiponectin	Serum – ELISA	↑	Kaur et al. (2014) (105)
Atopic dermatitis	Neuropeptide Y	Plasma – RIA	↑ ↑	Salomon et al. (2008) (106) Hodeib et al. (2010) (107)
Dermatitis	Leptin	Plasma – ELISA	↔	Kaur et al. (2014) (105)
Behçet's disease	Amylin	Serum – ELISA	↓	Dogan et al. (2014) (101)
	Hepcidin	Serum, Saliva /Salivary gland– ELISA, İHK	↓	Cicek et al. (2014) (108)
	Leptin	Leptin G2548A – ELISA	↔	Aydin et al. (2007) (109)
	Preptin	Serum – ELISA	↓	Dogan et al. (2014) (101)
	Salusin	Serum – ELISA	Sal-α ↓, Sal-β↑	Erden et al. (2014) (89)
Skin tag's	Leptin	Serum – ELISA	↔	Gorpelioglu et al. (2009) (110)
	Leptin	Plasma – ELISA	↑	El Safoury et al. (2011) (111)
Acne vulgaris	Desnutrin	Serum – ELISA	↓	Demir et al. (2014) (90)
	Ghrelin	Serum, pilosebaceous tissues – ELISA, İHK	↓	Cicek et al. (2015) (112)
Benign cutaneous tumors	Leptin	Skin biopsy – ELISA	↑	El Safoury et al. (2010) (113)
Polymyositis / dermatomyositis	Neuropeptide Y	Plasma – RIA	↑	Liu et al. (2004) (114)
Systemic sclerosis	Omentin (Intelectin-1)	Serum – ELISA	↓	Miura et al. (2015) (88)
Vitiligo	Neuropeptide Y	Plasma, Skin – RIA	↑	Tu et al. (2001) (93)

ELISA: Enzyme-linked immunosorbent assay; IHC: Immunohistochemistry; ↑: increase; ↓: decrease; ↔: constant; FABP4: Fatty acid binding protein 4; Sal-α: Salusin alpha; Sal-β: Salusin beta.

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