Clinica Chimica Acta 516 (2021) 8–14

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Leptin in skin disease modulation

Xin Su, Guoming Zhang, Ye Cheng *, Bin Wang *

Department of Cardiology, the Xiamen Cardiovascular Hospital of Xiamen University, Xiamen, Fujian, China

ARTICLE INFO

Keywords:
Leptin
Obesity
Psoriasis
Skin disease
Immune system

ABSTRACT

In obesity, adipocytes are dysfunctional with excessive production and secretion of pro-inflammatory hormones and cytokines, ie, adipokines, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and leptin. Accumulating evidence has shown that leptin possesses pleiotropic functions including stimulation of angiogenesis and production of pro-inflammatory cytokines. Furthermore, various leptin associated activities involve a wide distribution of leptin receptors. For example, increased serum leptin was associated with tissue receptor resistance in metabolic syndrome. Although increased serum leptin, receptor and signaling impairment are involved in wound healing, hair cycle and the pathogenesis of many skin diseases such as psoriasis and lupus erythematosus as well as skin cancer, its exact role remains unclear. In the present article, we discuss the biochemistry of leptin action and its potential role in the pathophysiology of diverse skin diseases.

1. Introduction

It is an indisputable fact that under obese status, adipocytes are dysfunctional with excessive production and secretion of pro-inflammatory hormones and cytokines which are currently named adipokines, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and leptin [1,2]. Accumulating evidence has shown the role of these adipokines in energy homeostasis and immunological activity. Recently, several eye-catching findings have put forward the functions of diverse adipokines in modulating the pathogenic development of different skin diseases.

Leptin, a 16-kDa protein encoded by the obese gene on chromosome 7q31.3, is verified to be mainly synthesized and secreted by subcutaneous adipose tissue [3]. As shown in previous studies, the circulating levels of leptin are strongly associated with total body weight and BMI, suggesting a modulatory effect of leptin on food intake, body mass, and energy metabolism [4]. On the other hand, due to a wide distribution of leptin receptors, leptin possesses pleiotropic functions, such as stimulation of angiogenesis, modulation of the hormonal system, and augmentation of pro-inflammatory cytokines production [5].

Recently, it has been well-established about one-third of patients with dermatological diseases were also evidenced to have subclinical metabolic syndrome or cardiovascular diseases, it is widely accepted that many skin diseases, such as psoriasis, lichen planus, connective tissue diseases, bullous diseases, vitiligo, and chronic urticarial, are strongly associated with cardio-metabolic disorders [6]. However, as being eight-fold more common than in the normal population after correction for the traditional Framingham risk factors, the increased incidence of skin diseases cannot be simply explained by traditional dermatological risk factors. Concerning on this notion, present focus is shifting towards elucidating the potential mechanisms of adipokine-mediated dermatologic diseases [7]. Consistently, the vital role of leptin in the pathogenesis of skin diseases has begun to gain appreciation, but the function is still undefined. According to recent studies, leptin may influence dermatologic pathophysiology and resultantly might have an impact on skin diseases and systemic autoimmune disorders. Therefore, in the present article, we discuss the mechanisms of leptin action within the skin and skin appendages. Furthermore, we also aim to provide the knowledge concerning on the role of increased leptin levels in the patho-mechanisms of diverse dermatologic diseases.

2. Dermatologic diseases are closely correlated with cardio-metabolic disorders diseases

As shown in previous studies, since there is several unquestionable participation of adiposity in diverse pathological processes, such as cardiovascular diseases and inflammatory diseases, it is reasonable to presume that the increased body fat mass could induce the disruption of normal processes in the skin, among the majority of patients. Indeed, it has been shown that the obese condition presents a significant

* Corresponding authors at: Department of Cardiology, the Xiamen Cardiovascular Hospital of Xiamen University, No. 2999 Jinshan Road, 361000 Xiamen, Fujian, China.

E-mail addresses: chengyeheart@163.com (Y. Cheng), wangbinheart@163.com (B. Wang).

https://doi.org/10.1016/j.cca.2021.01.013
Received 10 August 2020; Received in revised form 17 January 2021; Accepted 18 January 2021
Available online 21 January 2021

metabolic-regulatory effect which is currently identified to be a status of chronic, low-grade inflammation. In addition, obesity could significantly lead to the disturbed secretion of multiple hormones and cytokines, such as leptin, adiponectin, and chemokines that regulate inflammation [8]. Adiposity leads to dysfunction of adipocyte, manifested by increased production of pro-inflammatory adipokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, leptin, visfatin, resistin, angiotensin II, and plasminogen activator inhibitor 1 (PAI-1). Among these adipokines, leptin is being regarded as the most important pro-inflammatory adipokine since it stimulates the production of IL-1, IL-6, and IL-12 by innate immune cells and enhances reactive oxygen species (ROS) release [9,10].

The systemic consequences of excessive adiposity also affect the skin and result in alterations in dermatologic physiology. Therefore, it could be proposed that obesity is a risk factor for the development of many dermatological diseases [11]. Indeed, obesity is shown to be closely associated with venous stasis, lymphedema, and the increased rate of infection diseases including candidiasis, intertrigo, candida folliculitis, furunculosis, erysipelas, cellulitis, erythrasma, tinea cruris, folliculitis, and necrotizing fasciitis. Moreover, it also increases the risk of selected inflammatory dermatoses, in particular psoriasis, hidradenitis suppurativa, and atopic dermatitis [12]. Some skin abnormalities such as acanthosis nigricans, keratosis pilaris, striae diseases, skin tags, and palmoplantar keratodermas are more commonly observed in obese patients than in those with normal body weight. The increased amount of androgens, insulin, growth hormone, and insulin-like growth factor in a course of obesity leads to the escalation of sebum production, which could exacerbate acne [6]. Therefore, immune dysregulation and elevated levels of pro-inflammatory adipokines, in particular leptin, have a significant influence on the skin and dermatological diseases [13].

3. The potential mechanism of leptin in system metabolism

Leptin acts as a pleiotropic hormone. Besides, it could also activate the cascade of other adipokine production. It is mainly secreted by the white adipose tissue. However, a fraction of leptin is also produced by the hypothalamus, pituitary, gastric mucosa, bone marrow, mammary epithelium, skeletal muscle, and placenta [5]. Its secretion is increased in under obese condition. In addition, insulin, glucose, estrogens, and multiple cytokines, such as TNF-α and IL-6, might also enhance leptin secretion [14]. Interestingly, the peripheral leptin level follows a circadian rhythm with a peak level seen at night. Furthermore, the serum leptin concentration is strongly correlated with fat tissue amount and BMI. As a consequence, obesity is also characterized by enhanced leptin levels [3]. Furthermore, high serum leptin concentrations coexist with leptin receptors resistance, and these disturbances are related to the pathological development of obesity [15].

The wide distribution of leptin receptors suggests the pleiotropic function of leptin. In detail, the expression of leptin receptor has been found in the hypothalamus, fibroblasts, endothelial cells, keratinocytes, adipocytes, and blood mononuclear cells [16]. Leptin receptor is a transmembrane receptor, which is also similar to the Class I cytokine receptors family [17]. Due to the differences in the receptor structure, several forms of leptin receptor could be distinguished, including the short isoform which contains the leptin receptor-A, the leptin receptor-C, the leptin receptor-D, and the leptin receptor-F; whereas the leptin receptor-B and leptin receptor-E are classified into the full-length isoform [18]. The latter isoform is considered to be responsible for controlling food intake and energy balance. Short isoform, such as leptin receptor-A and leptin receptor-C, are located predominantly in the central nervous system micro-vessels, where they could be responsible for adequate leptin circulation in the cerebrospinal fluid as well as the receptor-mediated transport of leptin through the blood–brain barrier [19]. Leptin receptor-A isoform and leptin receptor-C isoform in the extra-neural tissues determine the functional pleiotropy of leptin, whereas the soluble form leptin receptor-E receptor provides binding variety and the bioavailability of leptin [20].

Leptin stimulates multiple signaling pathways, including the Janus kinase/signal transducer and activator of tran-ions signaling pathway (JAK/STAT), phosphoinositide 3-kinase signaling pathway (PI3K), mitogen-activated protein kinase signaling pathway (MAPK), extracellular signaling-regulated kinase 1/2 signaling pathway (ERK1/2), adenosine monophosphate kinase (AMPK) signaling pathway and PPAR gamma coactivator/peroxisome proliferator-activated receptor signaling pathway (PGC/PPAR) [21]. Among these multiple signaling pathway, the JAK/STAT signaling transduction cascade is the main signaling pathway activated by leptin. After binding of leptin to the long isoform receptor, phosphorylation of Janus kinase (JAK2) is activated, subsequently prompting phosphorylation and activation of signal transducers as well as an activator of transcription (STAT3). Activation of STAT3 results in dimerization, followed by migration to the nucleus, where STAT3 influences the expression of target genes such as the suppressor of cytokine signaling 3 (SOCS3) [22]. Furthermore, leptin impacts mitochondrial metabolism as it increases electrons flow, the efficiency of an oxidation–reduction reaction, and energy utilization [23]. Summary of leptin and leptin receptor signal transduction pathways is shown in Fig. 1.

4. Basic biological functions of leptin

Under physiological conditions, leptin is secreted to limit food intake, control body mass, and stimulate energy expenditure by negative feedback at the hypothalamic nuclei [24]. However, adiposity leads to an irrepressible increased circulating leptin. Furthermore, obesity is not related to the suppression of appetite nor body mass reduction, due to leptin receptor resistance [25]. This phenomenon might be a consequence of the dysfunction of leptin signaling pathways, which is limited access to the receptors and followed by changes in leptin receptor expression or signal transduction [26].

Besides, leptin also affects the immune system by mainly acting as a pro-inflammatory factor. Indeed, leptin could activate the production and secretion of pro-inflammatory cytokines, as well as increases nitric oxide (NO) release and stimulates phagocytosis on monocytes/macrophages [27]. In neutrophils, this adipokine induces the synthesis of oxygen free radicals. Moreover, leptin enhances cytotoxicity and proliferation of natural killer (NK) cells. Recently, leptin has been confirmed to activate chemotaxis of eosinophils, basophils, and neutrophils [28]. Besides, this adipokine increases IL-8, IL-12, IL-6, and TNF-α release from the dendritic cells. By influencing lymphocyte receptors, leptin affects Th1/Th2 balance towards Th1 lymphocyte response and leads to an aggravation of pro-inflammatory processes. The wide impact of leptin on the immune system could imply the important role of this adipokine in the pathogenesis of autoimmune diseases [29]. The effects of leptin on different immune cells of innate immune system and adaptive immune system is shown in Fig. 2.

5. Leptin in modulating hair growth and the risk of diverse dermatologic diseases

Although the adipocyte is considered as a prevalent site of leptin synthesis, it has been reported that fibroblasts and keratinocytes also possess the ability to facilitate the production of leptin and its receptors [30]. The expression of leptin receptors has been detected in the epidermis, predominantly in the basal layer, and in the hair follicle papilla cells [31]. Interestingly, leptin possesses the ability to stimulate the proliferation of keratinocytes and fibroblasts, epithelialization, and collagen synthesis. These mechanisms lead to an improvement in skin regeneration [32]. Moreover, local synthesis and secretion of leptin increase after skin injury which result in shortening the period of wound healing [33]. Additionally, leptin also supports skin microorganism defense by activation of the expression of human defensine 2 [34].

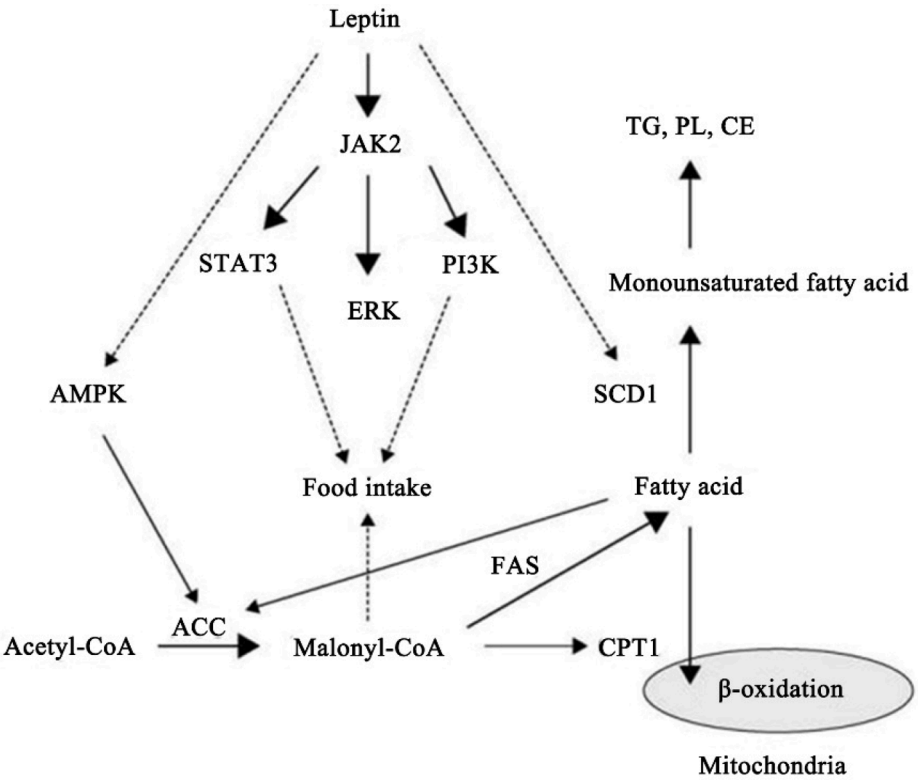

Fig. 1. Schematic representation of leptin and leptin receptor signal transduction pathways. Stimulation of leptin receptor by leptin could activate JAK2 kinase, resulting in tyrosine phosphorylation of the receptor and downstream proteins, including STAT3, SHP2, IRS2, and PI3K, that play an important role in regulating transcription of genes essential for energy intake and lipid metabolism.

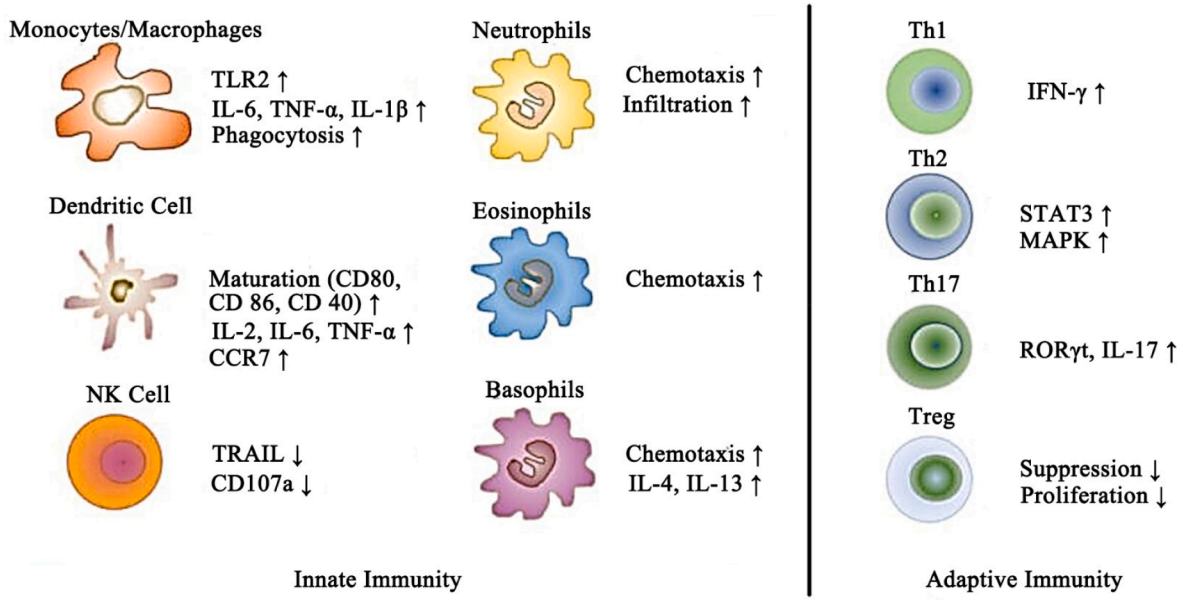

Fig. 2. Schematic representation of the effects of leptin on different immune cells of innate immune system and adaptive immune system.

However, by activation of the STAT3 signaling pathway, leptin can trigger proliferation, differentiation, migration, and stabilization of cells in the skin as well as it may modulate angiogenesis [35]. Lee et al. investigated the molecular mechanism of leptin impact on keratinocytes by observation genome-wide transcriptional responses of normal human keratinocytes (NHKs) [30]. Leptin enhanced intracellular signaling and induced pro-inflammatory reaction in keratinocytes by up-regulating the production of interleukins with a similar mechanism as observed in immune cells. Above mentioned leptin action might have a significant impact on the risk and development of skin diseases connected with obesity [36,37]. The potential role of leptin in selected skin diseases is summarized and presented in Table 1.

5.1. *Leptin in modulating the physical development of hair*

Due to the technological advances, major breakthroughs have been

Table 1
The potential role of leptin in diverse skin diseases.

Skin diseases	Serum level of leptin	Potential effect	References
Psoriasis	Elevated	Pro-inflammatory: promotion of Th1/Th17 lymphocyte axis (IL-1↑, IL-6↑, IL-17/23↑, CXCL8↑, TNF-α↑); Angiogenesis: activating the JAK/STAT3 signaling pathway; Keratinocyte-genesis: amphiregulin↑, CXCL8↑	[47–65]
Systemic sclerosis	Reduced	Anti-fibrotic: inhibiting the JAK/STAT3 signaling pathway	[66–69]
Systemic lupus erythematosus	Elevated	Pro-inflammatory: promotion of the Th1/Th17 lymphocyte axis, inhibition of Treg lymphocyte; Aging of mesenchymal stem cells (via the NAP-2 and PI3K-Akt pathway)	[70–78]
Melanoma and non-pigment tumors	Elevated	Angiogenesis: JAK/STAT3 pathway↑, VEGF↑; Mitogenic	[79–83]
Skin tags	Elevated	Promotion of keratinocyte and fibroblast growth	[84,85]
Hidradenitis suppurativa	Elevated	Pro-inflammatory: promotion of Th1 lymphocyte	[86,87]

made to explain the association between leptin and hair growth. According to the published results, immuno-histochemical analyses revealed the presence of leptin protein and leptin mRNA in the hair structures including matrix, inner root sheath, and the follicular dermal papilla [38]. Noticeably, in transgenic mice with leptin receptor deficiency (db/db), anagen was found to be delayed. The group of Sumikawa et al. suggested that leptin could be considered as an essential anagen activator in the second hair cycle and might prompt hair growth [38]. Besides, the injection of exogenous leptin stimulated anagen conversion in resting hair follicles [39]. Nevertheless, the exact mechanism of the influence of leptin on the hair cycle and hair growth is still not fully elucidated [40]. We still need more investigations to further explore the relationship between leptin and hair growth.

5.2. Leptin in modulating the risk of psoriasis

Psoriasis is one of the most common skin diseases with a multifactorial pathogenesis. The dermatologic inflammation process is underlying dermatologic changes and usually has three features: erythema, thickening, and scale. The typical psoriatic skin lesions present as silver-whitish scales with sharply demarcated, red and thickened areas [41]. According to the results of epidemiological investigation, the prevalence is various in different regions, but overall it reaches approximately 2% of the world population [42]. The difference in incidence rate is strongly linked to the development status with a higher number in high-developed countries.

Psoriasis is recently considered to be a kind of genetic-, autoimmune-, and metabolic-derived disease. It has been speculated that when the genetically predisposed individual is exposed to specific environmental factors (EFs) that act along with epigenetic alternations, this individual may develop psoriatic dermatologic alterations [43,44]. The well-known EFs that are strongly linked to psoriasis include dietary habits along with obesity, microbiota, infections, alcohol intake, tobacco smoking, and psychological factors [45,46].

There are numerous studies concerning on the adipokine levels in a course of psoriasis, and these observations comprised not only leptin but also resistin, adiponectin, and others [47]. Higher levels of leptin in sera of psoriatic patients in comparison with the controls were observed [48,49]. Besides, a marked increase of leptin was found in obese individuals, particularly in those with the coexistence of psoriasis and obesity [50,51]. Moreover, Mitsuyama et al. indicated that leptin mRNA expression was significantly enhanced in obese psoriatic individuals as compared to the results of non-obese counterparts. Furthermore, both leptin levels and leptin mRNA expression in non-obese psoriatic patients did not differ significantly from non-obese non-psoriatic controls [52]. Of note, some studies indicated a decrease in peripheral levels of leptin after systemic therapy of psoriasis [53]. A positive correlation between serum leptin concentration and the severity of psoriasis lesions, evaluated with the Psoriasis Area and Severity Index (PASI), was also found [54]. Moreover, immunological changes were seen in psoriasis including that levels of pro-inflammatory cytokines produced by the Th1 subtype lymphocyte were greater than the concentration of compounds secreted by the Th2 subtype lymphocyte [55]. Due to its pro-inflammatory activity, leptin promoted IL-1, IL-6, chemokine 8 (CXCL8), and TNF-α production, which also impacts psoriasis [56]. All the above-mentioned processes stimulate the Th1/Th17 axis and result in a higher concentration of IL-17/IL-23 [57]. Besides, activation of this axis being previously enhanced by the JAK/STAT3 pathway, in which leptin is involved, can also exaggerate angiogenesis seen in psoriatic lesions [58].

It is of high importance that the analysis of the skin within psoriatic patient showed a high expression of leptin in cell plasma within all layers of the epidermis, and the presence of many inflammatory cells in contrast to the healthy skin, where leptin is present strictly in the basal layer cells of the epidermis [54]. Up-regulated expression of leptin and leptin receptor expression were observed in the epidermis of individuals with a severe form of psoriasis in comparison to the patients with mild to moderate form of the disease [59]. It has been suggested that enhanced levels of leptin in the patient's skin may induce the production of amphiregulin, which is the epidermal growth factor protein with a probable role in keratinocyte proliferation [60]. Furthermore, the concentration of chemokine inducing the keratinocyte proliferation, named C-X-C motif ligand 8 (CXCL8), was also higher in the skin of psoriatic patients [61]. It is also worth noting that leptin may stimulate CXCL8 production by monocytes [62]. Thus, we could make a reasonable speculation that leptin link obesity and psoriasis potentially via, at least partly, modulating the chemokines within circulation.

Finally, there is still little attention paid to the leptin gene polymorphism in a course of psoriasis. The group of Torres et al. did not reveal any significant differences in leptin gene polymorphism of *rs2167270* (19 G/A), *rs1137100* (326 A/G) and adiponectin gene polymorphism *rs1501299* (276 G/T), as well as any differences in leptin levels, development of arteriosclerosis and adiposity in their cohort of psoriatic patients [63]. Karpouzis et al. who examined leptin gene polymorphism *rs2060713* did not establish any link between obesity with psoriasis [64]. In contrast, Abdel Hay et al. suggested that the G2548A polymorphism of leptin gene could be identified as a predictor of higher plasma leptin levels and the increased risk of psoriasis [65]. Taken together, the relationship between polymorphism of leptin gene and the pathological development of psoriasis seems to be elucidated, however, we still need more large-scale clinical investigations.

5.3. Leptin in modulating the risk of systemic sclerosis

Apart from the dysfunction of anagen activation, the lack of activation of the STAT3 pathway leads to fibrosis of the dermis, atrophy of the subcutaneous tissue, and the higher concentration of inflammatory cells in the subcutaneous tissue [66]. Therefore, the question could be raised whether there is a link between insufficient leptin signaling pathways and dermatologic fibrosis diseases. Several meta-analyses showed that in patients suffering from systemic sclerosis, the serum leptin levels were comparable to those of the healthy population [67]. However, decreased leptin concentrations within circulation were observed in patients with active systemic sclerosis when compared to the results of individuals with inactive systemic sclerosis [68]. Consequently, these findings strongly suggest that leptin might be a potential activity marker of

disease's severity [69]. Nevertheless, the role of adipokines under systemic sclerotic condition requires intensive further research.

5.4. Leptin in modulating the risk of systemic lupus erythematosus

Recently, a possible role of leptin in systemic lupus erythematosus (SLE) pathogenesis has been emphasized. In mouse models, it was shown that leptin promoted differentiation of lymphocyte Th17 subtype and enhanced synthesis of IL-17 via the RAR-related orphan receptor gamma (RORγ) [70]. Leptin, together with another pro-inflammatory factor named neutrophil-activating protein (NAP-2), activated the PI3k/Akt signaling pathway in SLE patients, causing aging of the mesenchymal stem cells [71]. Moreover, leptin promoted survival and proliferation of auto-reactive T lymphocytes in mice with SLE-like mutation [72]. The inhibiting effect of leptin on the T regulatory subtype (Treg) was also suggested [73]. Leptin may influence the population of immune cell subsets, as well as cytokine secretion, and anti-apoptotic protein expression, but the interaction between leptin and SLE is not fully understood currently [74]. Besides, the results of studies regarding serum levels of leptin in patients with SLE in comparison with the controls are inconsistent. Additionally, no significant differences were observed between patients with active and inactive disease [75–77]. Nevertheless, a lower leptin concentration was found in the concomitance of joint inflammation and neurological symptoms in a course of SLE [78].

5.5. Leptin in modulating the risk of skin tumors

Importantly, obesity and excess of adipose tissue result in higher leptin levels and increase the risk of many tumors including dermatologic tumors, melanoma, and non-pigment tumors [79–81]. According to the literature, increased leptin concentration may accelerate the growth of melanoma [82,83]. Recent research has shown a positive correlation between serum leptin levels and the number of dermatologic tags. Furthermore, a high level of leptin and impaired leptin receptors on keratinocytes and fibroblasts can trigger cell proliferation and differentiation into dermatologic tag lesions [84,85].

5.6. Leptin in modulating the risk of hidradenitis suppurativa

It has been found that obesity is a risk factor of hidradenitis suppurativa development, and patients with hidradenitis suppurativa suffer from obesity and metabolic syndrome more common than the controls. Malara and colleagues observed that leptin was significantly increased in patients with hidradenitis suppurativa [86]. It should be emphasized that enhanced local concentration of leptin in subcutaneous adipose tissue caused an intensification of inflammatory processes in the skin of patients with hidradenitis suppurativa and, additionally, resulted in an increase of systemic inflammation. Both phenomena might exacerbate the symptoms of hidradenitis suppurativa [87].

6. Conclusions and perspectives

Leptin is a pluripotent adipokine which has been confirmed to be correlated with the multiple pro-inflammatory immune responses in humans. The pleiotropic effects of leptin on the processes taking place in the pathogenesis of different dermatologic diseases have also been well demonstrated. As a consequence of adiposity and increased leptin levels, especially in conjunction with a reduced response of leptin receptors, several pathological processes occur in the skin and the skin appendages. Although the potential mechanisms of leptin activity have been thoroughly researched, the exact role of leptin in dermatologic disorders still needs further elucidated. However, when considering the relationship between leptin and skin, it should be taken into account that not only increased leptin levels have a negative impact but also probably a whole spectrum of adipokines related to low-grade inflammation might be responsible for the malfunction of the skin.

On the other hand, it is a challenge to find all of the potential confounding factors influencing the dermatologic pathology. Moreover, it is also important to explore the complex interrelations between those compounds as well as the exact mechanism of their actions within the skin and skin appendages. Another unsolved problem is that there is still no clear explanation of why some obese individuals present a worse course of skin diseases. Besides, it is still an open question of whether pharmacological intervention resulting in decreasing leptin secretion or breaking the leptin receptor resistance could be a target in different dermatologic disease treatment.

Taken together, taking into account that there is no leptin-oriented medication, the proper treatment of obesity might induce a better dermatologic condition. Up to date, the most important recommendation is to prevent and treat obesity.

Author contributions

X.S. and B.W. contributed to the study design; X.S., Y.C., and G.M.Z. wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Funding

This work was supported by grants from the National Key Research and Development Program of China (No. 2016YFC1301202).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] X. Su, D. Peng, New insight into sortilin in controlling lipid metabolism and the risk of atherogenesis, Biol. Rev. Camb. Philos. Soc. (2019).
[2] X. Su, D. Peng, The exchangeable apolipoproteins in lipid metabolism and obesity, Clin. Chim. Acta 503 (2020) 128–135.
[3] H. Munzberg, C.D. Morrison, Structure, production and signaling of leptin, Metabolism 64 (1) (2015) 13–23.
[4] B. Poeggeler, C. Schulz, M.A. Pappolla, E. Bodo, S. Tiede, H. Lehnert, R. Paus, Leptin and the skin: a new frontier, Exp. Dermatol. 19 (1) (2010) 12–18.
[5] R.J. Denver, R.M. Bonett, G.C. Boorse, Evolution of leptin structure and function, Neuroendocrinology 94 (1) (2011) 21–38.
[6] S. Seremet, M.S. Gurel, Miscellaneous skin disease and the metabolic syndrome, Clin. Dermatol. 36 (1) (2018) 94–100.
[7] B. Unlu, U. Tursen, Autoimmune skin diseases and the metabolic syndrome, Clin. Dermatol. 36 (1) (2018) 67–71.
[8] A.R. Saltiel, J.M. Olefsky, Inflammatory mechanisms linking obesity and metabolic disease, J Clin Invest 127 (1) (2017) 1–4.
[9] K. Makki, P. Froguel, I. Wolowczuk, Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines, ISRN Inflamm 2013 (2013), 139239.
[10] A.M. Tobin, T. Ahern, S. Rogers, P. Collins, D. O'Shea, B. Kirby, The dermatological consequences of obesity, Int. J. Dermatol. 52 (8) (2013) 927–932.
[11] M. Kuroda, H. Sakaue, Adipocyte death and chronic inflammation in obesity, J. Med. Invest. 64 (3.4) (2017) 193–196.
[12] P.A. Hirt, D.E. Castillo, G. Yosipovitch, J.E. Keri, Skin changes in the obese patient, J. Am. Acad. Dermatol. 81 (5) (2019) 1037–1057.
[13] D.R. Sessions-Bresnahan, A.L. Heuberger, E.M. Carnevale, Obesity in mares promotes uterine inflammation and alters embryo lipid fingerprints and homeostasis, Biol. Reprod. 99 (4) (2018) 761–772.
[14] C. Van Doorn, V.A. Macht, C.A. Grillo, L.P. Reagan, Leptin resistance and hippocampal behavioral deficits, Physiol. Behav. 176 (2017) 207–213.
[15] A.B. Crujeiras, M.C. Carreira, B. Cabia, S. Andrade, M. Amil, F.F. Casanueva, Leptin resistance in obesity: An epigenetic landscape, Life Sci. 140 (2015) 57–63.
[16] S.H. Bates, W.H. Stearns, T.A. Dundon, M. Schubert, A.W. Tso, Y. Wang, A. S. Banks, H.J. Lavery, A.K. Haq, E. Maratos-Flier, B.G. Neel, M.W. Schwartz, M. G. Myers Jr., STAT3 signalling is required for leptin regulation of energy balance but not reproduction, Nature 421 (6925) (2003) 856–859.
[17] M. Michalska-Jakubus, K. Sawicka, E. Potembska, M. Kowal, D. Krasowska, Clinical associations of serum leptin and leptin/adiponectin ratio in systemic sclerosis, Postepy Dermatol Alergol 36 (3) (2019) 325–338.
[18] J. Liu, X. Yang, S. Yu, R. Zheng, The leptin signaling, Adv. Exp. Med. Biol. 1090 (2018) 123–144.

[19] N. Wada, S. Hirako, F. Takenoya, H. Kageyama, M. Okabe, S. Shioda, Leptin and its receptors, J. Chem. Neuroanat. 61–62 (2014) 191–199.
[20] M. Schaab, J. Kratzsch, The soluble leptin receptor, Best Pract Res Clin Endocrinol Metab 29 (5) (2015) 661–670.
[21] J. Wauman, L. Zabeau, J. Tavernier, The leptin receptor complex: heavier than expected? Front Endocrinol (Lausanne) 8 (2017) 30.
[22] Y. Zhang, S. Chua Jr., Leptin function and regulation, Compr Physiol 8 (1) (2017) 351–369.
[23] O. Kwon, K.W. Kim, M.S. Kim, Leptin signalling pathways in hypothalamic neurons, Cell. Mol. Life Sci. 73 (7) (2016) 1457–1477.
[24] A. Yadav, M.A. Kataria, V. Saini, A. Yadav, Role of leptin and adiponectin in insulin resistance, Clin. Chim. Acta 417 (2013) 80–84.
[25] G. Paz-Filho, C.A. Mastronardi, J. Licinio, Leptin treatment: facts and expectations, Metabolism 64 (1) (2015) 146–156.
[26] N.E. Gulcelik, M. Halil, S. Ariogul, A. Usman, Adipocytokines and aging: adiponectin and leptin, Minerva Endocrinol. 38 (2) (2013) 203–210.
[27] A. La Cava, Leptin in inflammation and autoimmunity, Cytokine 98 (2017) 51–58.
[28] A. Stofkova, Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity, Endocr Regul 43 (4) (2009) 157–168.
[29] V. Abella, M. Scotece, J. Conde, J. Pino, M.A. Gonzalez-Gay, J.J. Gomez-Reino, A. Mera, F. Lago, R. Gomez, O. Gualillo, Leptin in the interplay of inflammation, metabolism and immune system disorders, Nat. Rev. Rheumatol. 13 (2) (2017) 100–109.
[30] M. Lee, E. Lee, S.H. Jin, S. Ahn, S.O. Kim, J. Kim, D. Choi, K.M. Lim, S.T. Lee, M. Noh, Leptin regulates the pro-inflammatory response in human epidermal keratinocytes, Arch. Dermatol. Res. 310 (4) (2018) 351–362.
[31] A. Murad, A.K. Nath, S.T. Cha, E. Demir, J. Flores-Riveros, M.R. Sierra-Honigmann, Leptin is an autocrine/paracrine regulator of wound healing, FASEB J. 17 (13) (2003) 1895–1897.
[32] A. Glasow, W. Kiess, U. Anderegg, A. Berthold, A. Bottner, J. Kratzsch, Expression of leptin (Ob) and leptin receptor (Ob-R) in human fibroblasts: regulation of leptin secretion by insulin, J. Clin. Endocrinol. Metab. 86 (9) (2001) 4472–4479.
[33] S. Tadokoro, S. Ide, R. Tokuyama, H. Umeki, S. Tatehara, S. Kataoka, K. Satomura, Leptin promotes wound healing in the skin, PLoS ONE 10 (3) (2015) e0121242.
[34] N. Kanda, S. Watanabe, Leptin enhances human beta-defensin-2 production in human keratinocytes, Endocrinology 149 (10) (2008) 5189–5198.
[35] S. Frank, B. Stallmeyer, H. Kampfer, N. Kolb, J. Pfeilschifter, Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair, J. Clin. Invest. 106 (4) (2000) 501–509.
[36] K.M. Tong, D.C. Shieh, C.P. Chen, C.Y. Tzeng, S.P. Wang, K.C. Huang, Y.C. Chiu, Y. C. Fong, C.H. Tang, Leptin induces IL-8 expression via leptin receptor, IRS-1, PI3K, Akt cascade and promotion of NF-kappaB/p300 binding in human synovial fibroblasts, Cell. Signal. 20 (8) (2008) 1478–1488.
[37] Y.J. Kim, J.S. Kim, Y.R. Seo, J.H. Park, M.S. Choi, M.K. Sung, Carnosic acid suppresses colon tumor formation in association with antiadipogenic activity, Mol. Nutr. Food Res. 58 (12) (2014) 2274–2285.
[38] Y. Sumikawa, S. Inui, T. Nakajima, S. Itami, Hair cycle control by leptin as a new anagen inducer, Exp. Dermatol. 23 (1) (2014) 27–32.
[39] C.H. Won, H.G. Yoo, O.S. Kwon, M.Y. Sung, Y.J. Kang, J.H. Chung, B.S. Park, J. H. Sung, W.S. Kim, K.H. Kim, Hair growth promoting effects of adipose tissue-derived stem cells, J. Dermatol. Sci. 57 (2) (2010) 134–137.
[40] R. Watabe, T. Yamaguchi, R. Kabashima-Kubo, M. Yoshioka, D. Nishio, M. Nakamura, Leptin controls hair follicle cycling, Exp. Dermatol. 23 (4) (2014) 228–229.
[41] M.G. Lebwohl, H. Bachelez, J. Barker, G. Girolomoni, A. Kavanaugh, R.G. Langley, C.F. Paul, L. Puig, K. Reich, P.C. van de Kerkhof, Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey, J. Am. Acad. Dermatol. 70 (5) (2014) 871-81 e1-30.
[42] R. Parisi, D.P. Symmons, C.E. Griffiths, D.M. Ashcroft, P. Identification, Management of, t. Associated ComorbidiTy project, Global epidemiology of psoriasis: a systematic review of incidence and prevalence, J. Invest. Dermatol. 133 (2) (2013) 377–385.
[43] T.J. Russell, L.M. Schultes, D.J. Kuban, Histocompatibility (HL-A) antigens associated with psoriasis, N. Engl. J. Med. 287 (15) (1972) 738–740.
[44] L. Barrea, F. Nappi, C. Di Somma, M.C. Savanelli, A. Falco, A. Balato, N. Balato, S. Savastano, Environmental risk factors in psoriasis: the point of view of the nutritionist, Int. J. Environ. Res. Public Health 13 (5) (2016).
[45] L. Naldi, L. Chatenoud, D. Linder, A. Belloni Fortina, A. Peserico, A.R. Virgili, P. L. Bruni, V. Ingordo, G. Lo Scocco, C. Solaroli, D. Schena, A. Barba, A. Di Landro, E. Pezzarossa, F. Arcangeli, C. Gianni, R. Betti, P. Carli, A. Farris, G.F. Barabino, C. La Vecchia, Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study, J, Invest. Dermatol. 125 (1) (2005) 61–67.
[46] J. Zeng, S. Luo, Y. Huang, Q. Lu, Critical role of environmental factors in the pathogenesis of psoriasis, J. Dermatol. 44 (8) (2017) 863–872.
[47] T.D. Rachakonda, J.S. Dhillon, A.G. Florek, A.W. Armstrong, Effect of tonsillectomy on psoriasis: a systematic review, J. Am. Acad. Dermatol. 72 (2) (2015) 261–275.
[48] S. Coimbra, H. Oliveira, F. Reis, L. Belo, S. Rocha, A. Quintanilha, A. Figueiredo, F. Teixeira, E. Castro, P. Rocha-Pereira, A. Santos-Silva, Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy, J. Eur. Acad. Dermatol. Venereol. 24 (12) (2010) 1386–1394.
[49] A. Kyriakou, A. Patsatsi, D. Sotiriadis, D.G. Goulis, Serum leptin, resistin, and adiponectin concentrations in psoriasis: a meta-analysis of observational studies, Dermatology 233 (5) (2017) 378–389.
[50] M.G. Myers Jr., R.L. Leibel, R.J. Seeley, M.W. Schwartz, Obesity and leptin resistance: distinguishing cause from effect, Trends Endocrinol. Metab. 21 (11) (2010) 643–651.
[51] M. Wasim, F.R. Awan, S.S. Najam, A.R. Khan, H.N. Khan, Role of leptin deficiency, inefficiency, and leptin receptors in obesity, Biochem. Genet. 54 (5) (2016) 565–572.
[52] S. Mitsuyama, F. Abe, M. Kimura, M. Yoshida, T. Higuchi, Association between leptin gene expression in subcutaneous adipose tissue and circulating leptin levels in obese patients with psoriasis, Arch. Dermatol. Res. 307 (6) (2015) 539–544.
[53] A. Campanati, G. Ganzetti, K. Giuliodori, M. Marra, A. Bonfigli, R. Testa, A. Offidani, Serum levels of adipocytokines in psoriasis patients receiving tumor necrosis factor-alpha inhibitors: results of a retrospective analysis, Int. J. Dermatol. 54 (7) (2015) 839–845.
[54] A.A. Cerman, S. Bozkurt, A. Sav, A. Tulunay, M.O. Elbasi, T. Ergun, Serum leptin levels, skin leptin and leptin receptor expression in psoriasis, Br. J. Dermatol. 159 (4) (2008) 820–826.
[55] S.R. Georgescu, M. Tampa, C. Caruntu, M.I. Sarbu, C.I. Mitran, M.I. Mitran, C. Matei, C. Constantin, M. Neagu, Advances in understanding the immunological pathways in psoriasis, Int. J. Mol. Sci. 20 (3) (2019).
[56] A. Johnston, S. Arnadottir, J.E. Gudjonsson, A. Aphale, A.A. Sigmarsdottir, S. I. Gunnarsson, J.T. Steinsson, J.T. Elder, H. Valdimarsson, Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation, Br. J. Dermatol. 159 (2) (2008) 342–350.
[57] Y. Fritz, P.A. Klenotic, W.R. Swindell, Z.Q. Yin, S.G. Groft, L. Zhang, J. Baliwag, M. I. Camhi, D. Diaconu, A.B. Young, A.M. Foster, A. Johnston, J.E. Gudjonsson, T. S. McCormick, N.L. Ward, Induction of alternative proinflammatory cytokines accounts for sustained psoriasiform skin inflammation in IL-17C+IL-6KO mice, J, Invest. Dermatol. 137 (3) (2017) 696–705.
[58] E. Calautti, L. Avalle, V. Poli, Psoriasis: A STAT3-centric view, Int. J. Mol. Sci. 19 (1) (2018).
[59] N.C. Bavoso, J.M. Pinto, M.M.S. Soares, M.D.S. Diniz, A.L. Teixeira Junior, Psoriasis in obesity: comparison of serum levels of leptin and adiponectin in obese subjects - cases and controls, An Bras Dermatol. 94 (2) (2019) 192–197.
[60] A. Markaki, K. Gkouskou, K. Stylianou, E. Dermitzaki, K. Perakis, A. Margioris, E. Daphnis, Relationship between adiposity, adipokines, inflammatory markers and lipid profile in hemodialysis patients, Eur. Rev. Med. Pharmacol. Sci. 18 (10) (2014) 1496–1498.
[61] C.R. Mauro, B.T. Nguyen, P. Yu, M. Tao, I. Gao, M.A. Seidman, L.L. Nguyen, C. K. Ozaki, Inflammatory "adiposopathy" in major amputation patients, Ann. Vasc. Surg. 27 (3) (2013) 346–352.
[62] K. Watanabe, M. Suzukawa, S. Arakawa, K. Kobayashi, S. Igarashi, H. Tashimo, H. Nagai, S. Tohma, T. Nagase, K. Ohta, Leptin enhances cytokine/chemokine production by normal lung fibroblasts by binding to leptin receptor, Allergol. Int. 68S (2019) S3–S8.
[63] T. Torres, N. Bettencourt, J. Ferreira, C. Carvalho, D. Mendonca, C. Vasconcelos, M. Selores, B. Silva, Lack of association between leptin, leptin receptor, adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat volume and atherosclerotic burden in psoriasis patients, Arch. Physiol. Biochem. 121 (3) (2015) 103–108.
[64] A. Karpouzis, G. Tripsianis, E. Gatzidou, S. Veletza, Assessment of leptin gene polymorphism rs2060713 in psoriasis vulgaris, ISRN Dermatol. 2014 (2014), 845272.
[65] R.M. Abdel Hay, L.A. Rashed, Association between the leptin gene 2548G/A polymorphism, the plasma leptin and the metabolic syndrome with psoriasis, Exp. Dermatol. 20 (9) (2011) 715–719.
[66] K. Harada, T. Maeda, J. Matsubayashi, M. Uchiyama, R. Irisawa, K. Go, R. Tsuboi, Centrifugal lipodystrophy of the scalp manifesting as centrifugal lipodystrophic alopecia, Clin. Exp. Dermatol. 43 (3) (2018) 286–290.
[67] C.C. Yang, H.M. Sheu, P.L. Chung, C.H. Chang, Y.S. Tsai, M.W. Hughes, T.L. Tuan, L.L. Huang, Leptin of dermal adipose tissue is differentially expressed during the hair cycle and contributes to adipocyte-mediated growth inhibition of anagen-phase vibrissa hair, Exp. Dermatol. 24 (1) (2015) 57–60.
[68] M. Budulgan, B. Dilek, S.B. Dag, I. Batmaz, I. Yildiz, M.A. Sariyildiz, R. Cevik, K. Nas, Relationship between serum leptin level and disease activity in patients with systemic sclerosis, Clin. Rheumatol. 33 (3) (2014) 335–339.
[69] Y.H. Lee, G.G. Song, Meta-analysis of circulating adiponectin, leptin, and resistin levels in systemic sclerosis, Z. Rheumatol. 76 (9) (2017) 789–797.
[70] Y. Yu, Y. Liu, F.D. Shi, H. Zou, G. Matarese, A. La Cava, Cutting edge: Leptin-induced RORgammat expression in CD4+ T cells promotes Th17 responses in systemic lupus erythematosus, J. Immunol. 190 (7) (2013) 3054–3058.
[71] H. Chen, B. Shi, X. Feng, W. Kong, W. Chen, L. Geng, J. Chen, R. Liu, X. Li, W. Chen, X. Gao, L. Sun, Leptin and neutrophil-activating peptide 2 promote mesenchymal stem cell senescence through activation of the phosphatidylinositol 3-Kinase/Akt pathway in patients with systemic lupus erythematosus, Arthritis Rheumatol. 67 (9) (2015) 2383–2393.
[72] G. Amarilyo, N. Iikuni, F.D. Shi, A. Liu, G. Matarese, A. La Cava, Leptin promotes lupus T-cell autoimmunity, Clin. Immunol. 149 (3) (2013) 530–533.
[73] V. De Rosa, C. Procaccini, G. Cali, G. Pirozzi, S. Fontana, S. Zappacosta, A. La Cava, G. Matarese, A key role of leptin in the control of regulatory T cell proliferation, Immunity 26 (2) (2007) 241–255.
[74] Q. Yuan, H. Chen, X. Li, J. Wei, Leptin: an unappreciated key player in SLE, Clin. Rheumatol. 39 (2) (2020) 305–317.
[75] M. Al, L. Ng, P. Tyrrell, J. Bargman, T. Bradley, E. Silverman, Adipokines as novel biomarkers in paediatric systemic lupus erythematosus, Rheumatology (Oxford) 48 (5) (2009) 497–501.

[76] S. Barbosa Vde, P.L. Francescantonio, N.A. Silva, Leptin and adiponectin in patients with systemic lupus erythematosus: clinical and laboratory correlations, Rev. Bras. Reumatol. 55 (2) (2015) 140–145.
[77] H.M. Li, T.P. Zhang, R.X. Leng, X.P. Li, X.M. Li, H.F. Pan, Plasma/serum leptin levels in patients with systemic lupus erythematosus: a meta-analysis, Arch. Med. Res. 46 (7) (2015) 551–556.
[78] M. Vadacca, E.M. Zardi, D. Margiotta, A. Rigon, F. Cacciapaglia, L. Arcarese, F. Buzzulini, A. Amoroso, A. Afeltra, Leptin, adiponectin and vascular stiffness parameters in women with systemic lupus erythematosus, Intern. Emerg. Med. 8 (8) (2013) 705–712.
[79] F. Amjadi, R. Mehdipoor, H. Zarkesh-Esfahani, S.H. Javanmard, Leptin serves as angiogenic/mitogenic factor in melanoma tumor growth, Adv. Biomed. Res. 5 (2016) 127.
[80] O.S. El Safoury, R.M. Abdel Hay, M.M. Fawzy, D. Kadry, I.M. Amin, O.M. Abu Zeid, L.A. Rashed, Skin tags, leptin, metabolic syndrome and change of the life style, Indian J. Dermatol. Venereol. Leprol. 77 (5) (2011) 577–580.
[81] C. Praestegaard, S.K. Kjaer, J. Christensen, A. Tjonneland, J. Halkjaer, A. Jensen, Obesity and risks for malignant melanoma and non-melanoma skin cancer: results from a large Danish prospective cohort study, J. Invest. Dermatol. 135 (3) (2015) 901–904.
[82] D.B. Rivadeneira, K. DePeaux, Y. Wang, A. Kulkarni, T. Tabib, A.V. Menk, P. Sampath, R. Lafyatis, R.L. Ferris, S.N. Sarkar, S.H. Thorne, G.M. Delgoffe, Oncolytic viruses engineered to enforce leptin expression reprogram tumor-infiltrating T cell metabolism and promote tumor clearance, Immunity 51 (3) (2019) 548–560 e4.
[83] B. Zhou, D. Wu, H. Liu, L.T. Du, Y.S. Wang, J.W. Xu, F.B. Qiu, S.Y. Hu, H.X. Zhan, Obesity and pancreatic cancer: An update of epidemiological evidence and molecular mechanisms, Pancreatology 19 (7) (2019) 941–950.
[84] I.B. Putra, R. Siregar, N.K. Jusuf, O. Ginting, R. Nurhayati, Correlation between serum leptin level with type and number of lesion skin tag, Open Access Maced. J. Med. Sci. 7 (1) (2019) 53–55.
[85] M.A. Shaheen, N.S. Abdel Fattah, Y.A. Sayed, A.A. Saad, Assessment of serum leptin, insulin resistance and metabolic syndrome in patients with skin tags, J. Eur. Acad. Dermatol. Venereol. 26 (12) (2012) 1552–1557.
[86] A. Malara, R. Hughes, L. Jennings, C.M. Sweeney, M. Lynch, F. Awdeh, I. Timoney, A.M. Tobin, K. Lynam-Loane, L. Tobin, A. Hogan, D. O'Shea, B. Kirby, Adipokines are dysregulated in patients with hidradenitis suppurativa, Br. J. Dermatol. 178 (3) (2018) 792–793.
[87] G. Shalom, T. Freud, I. Harman-Boehm, I. Polishchuk, A.D. Cohen, Hidradenitis suppurativa and metabolic syndrome: a comparative cross-sectional study of 3207 patients, Br. J. Dermatol. 173 (2) (2015) 464–470.