Insulin Growth Factor-1 Status in Hidradenitis Suppurativa: A French Institutional Pilot Study

Perrine Rousseau[1,2], Alexandra Poinas[2], Damien Masson[3], Kalyane Bach-Ngohou[3], Jean-Michel Nguyen[4], Marie Le Moigne[1,2], Barbara Bregeon[1,2], Florence Vrignaud[2], Amir Khammari[1,2], Brigitte Dréno[1,2]

[1]Nantes University, CHU Nantes, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy, INCIT, UMR 1302/EMR6001, Nantes, France; [2]Nantes University, CHU Nantes, INSERM, CIC1413, Nantes, France; [3]Nantes University, CHU Nantes Clinical Biochemistry Laboratory and INSERM U1235 TENS, Nantes, France; [4]Nantes University, CHU Nantes Epidemiology and Biostatistics Department, CRCINA, INSERM1232, University Nantes, Nantes, France

Corresponding author:
Alexandra Poinas, MD, PhD
Nantes University
CHU Nantes
INSERM, CIC1413
F-44000 Nantes, France
alexandra.poinas@chu-nantes.fr

Received: December 24, 2021
Accepted: June 1, 2023

ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease of the follicles in the apocrine glands and is associated with a deficiency in the innate immunity of the skin. It is characterized by the occurrence of nodules, abscesses, fistulas, scars.

Objective: Although a relationship has already been demonstrated between HS and innate immunity, IGF-1 status in patients with HS is still unknown. The objective of this pilot study was to determine IGF-1 status in patients with HS as well as its potential relationship with the clinical profile of the disease.

Methods: This monocentric and cross-sectional study involved 39 patients hospitalized at the Dermatology Department of CHU Nantes between November 2014 and January 2018. Clinical data and IGF1 status were collected during the follow-up consultation.

Results: Forty-nine percent of the patients had very low levels of IGF-1. At the clinical level, these patients were young and with a short duration of disease. The major difference was that IGF1-deficient patients had a higher BMI than others. The others factors differing between the two patient groups did not reach statistical significance.

Conclusion: This exploratory pilot study indicates that HS with a low level of IGF-1 could represent a specific phenotype of patients with HS. These preliminary results have to be confirmed with a larger cohort, as they could have practical consequences in the therapeutic care of these patients.

KEY WORDS: hidradenitis suppurativa, patient phenotype, insulin growth factor-1

INTRODUCTION

Hidradenitis suppurativa (HS) is an inflammatory, recurring, and debilitating skin disease of the pilosebaceous follicle that forms painful, deep-seated, inflamed nodules in the axillae, inguinal, sub-mammary, and anogenital regions (1). HS primarily affects young adult women, with a frequency ranging from 1% to 4% in Europe and North America (2). It often begins after puberty and can last for many years, with

numerous associated comorbidities, including inflammatory bowel disease, metabolic syndrome, and inflammatory arthritis.

The pathogenesis of HS is unknown, and numerous therapy alternatives are now being employed to minimize the frequency and severity of relapses, but they do not cure the condition (3,4). Some studies have found a lack of cutaneous innate immunity, including markers of local inflammation such as toll-like receptors (TLRs), cytokines such as interleukin (IL) 6, tumor necrosis factor-alpha (TNF-α), alpha-melanocyte stimulating hormone (α-MSH), and insulin growth factor 1 (IGF-1) (5). Proinflammatory cytokines (IL-36, TNF-α, IL-12, and IL-17) have been identified as potential targets in HS, and certain biologics, such as anti-TNF drugs, have been developed (6,7).

As one of these molecular and inflammatory indicators, IGF-1 is a systemic and endocrine growth factor. Although IGF-1 is produced by various organs, hepatocytes are recognized to be the principal source of circulating IGF-1. Nutrient intake and growth hormone (GH) levels are crucial factors that influence IGF-1 production not just in the liver but also in other organs. IGF-1 affects human cell development, metabolism, and differentiation via the IGF-1 receptor (IGF-1 R), which is found in nearly all organs. Indeed, it stimulates wound healing through a variety of mechanisms, including fibroblast and keratinocyte proliferation and endothelial cell chemotactic activity (8). IGF-1 insufficiency has been discovered in chronic non-healing ulcers such as diabetic sores, according to these studies (9).

In patients with HS, IGF-1 status is still unknown. Furthermore, as previously stated, the majority of patients with HS are overweight or obese, implying that nutritional deficiencies may be linked to the disease. Consequently, we were curious about the probable association between HS and IGF-1 as well as its relationship with the clinical profile of patients with HS.

PATIENTS AND METHODS

This monocentric cross-sectional pilot study was carried out at the CHU Nantes Dermatology Department. The clinical trial was carried out in conformity with the applicable versions of the French Public Health Code, national and international good clinical practice recommendations, and the Declaration of Helsinki. Patients could sign the biocollection informed consent form during their follow-up in the Dermatology Department, allowing the Department's researchers to work on the samples and clinical data collected during the patient care. The French Ethics Committee, CPP Ouest IV, approved this biocollection and informed consent procedure, which was recorded under the number DC-2011-1399.

The inclusion criteria for this study were: male or female patients, aged 18 years or older, with a confirmed diagnosis of HS (with recurrent characteristic lesions such as deep-seated painful nodules, abscesses, draining sinuses, or bridged scars; with a typical topography such as the axillae, groin, genital or perineal region, buttocks, or intermammary folds), admitted to the Dermatology Department for HS evaluation. Patients with an eating disorder (mental anorexia), patients with acromegalia, and pregnant women were excluded, as were patients under guardianship or trusteeship.

Between November 2014 and January 2018, 41 patients with HS were hospitalized and clinically examined in the department, with 39 matching the study criteria. Patients are admitted to the hospital every year or every two years for a check-up as part of their pathological follow-up. Blood samples were obtained when patients arrived at the department at about 9 AM. Data on weight, height, body mass index (BMI), abdominal perimeter, smoking status, number of packs-years, cannabis usage, hypertension status, and low-density lipoprotein (LDL) cholesterol aim were all collected as part of routine care. The LDL target was determined using the European recommendations for cardiovascular disease prevention in clinical practice (10). Hurley status, the amount of inflammatory lesions, the number of afflicted areas based on the Sartorius score, and the number of days with discomfort per month were also evaluated.

The remaining blood sample collected for routine care was used for IGF-1 biochemical assays. They were carried out in the same local laboratory (Clinical Biochemistry laboratory, CHU Nantes) according to the manufacturer's instructions, using the IRMA IGF-1 Immunotech Beckman CoulterTM method (Prague, Czech Republic). Within 1 hour of venipuncture, blood was collected in normal serum vials and centrifuged at 2000 g for 10 minutes at 4 °C before being deep-frozen at -20 °C until analysis. Prior to commencement of the experiment, each run was validated by measuring three levels of quality control material. Up to 1600 ng/mL, the IGF-1 calibration curve was linear. The assay's lowest detection limit was 4.6 ng/mL. The repeatability (intra-assay precision) and reproducibility (inter-assay precision) coefficients for this assay were less than or equal to 5.6% and 8.3%, respectively.

The reference values were obtained using data obtained by Granada *et al.* (11) from a large cohort of healthy participants. Because reference values

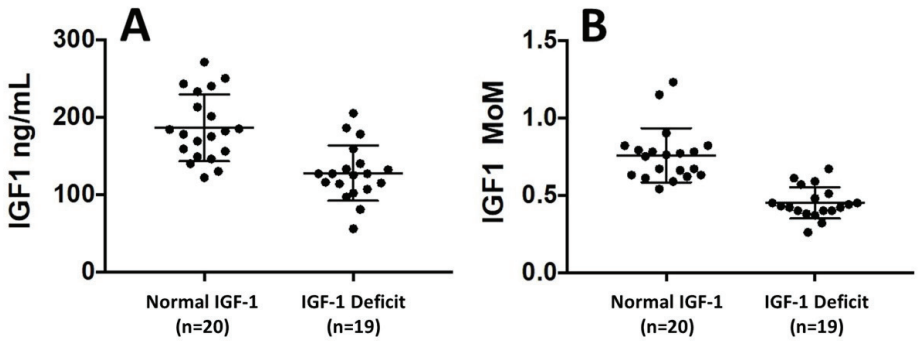

Figure 1. IGF-1 value in ng/mL (A) and MoM (B), depending on the patient group.

differ by age and gender, the measured serum concentrations of biomarkers (ng/mL) were translated into multiples of median (MoM) and then adjusted for age and gender to simplify comparison and analysis. Low IGF-1 status was defined as having an IGF-1 level that was lower than the reference values adjusted for age and gender determined by Bidlingmaier *et al.* (12).

The relevant biochemical markers were used to determine the systemic inflammatory and nutritional states. The Cobas® c502-module of the automated cobas®8000 system (Roche Diagnostics, Mannheim, Germany) was used to measure albumin, prealbumin, C-reactive protein (CRP), cholesterol, and triglyceride levels. The Friedewald formula was used to compute LDL cholesterol levels (13). All assays were carried out in accordance with the manufacturers' instructions.

Non-parametric tests such as the Wilcoxon and Fisher exact tests were employed to evaluate the relationship between biological parameters and IGF-1 status. R 3.6.1 statistical software was used for all statistical studies.

RESULTS

Patient clinical characteristics

There were 39 patients in this study. According to our criteria, 19 patients (49%) had low IGF-1 levels measured in ng/mL (range [56-205]; median 127) or in MoM (range [0.26-0.67]; median 0.43) (Figure 1, A and B). The remaining 20 patients had normal IGF-1 levels measured in ng/mL (range [122-2715]; median 180) or MoM (range [0.54-1.23]; median 0.76) (Figure 1, A and B).

Table 1. Patient clinical characteristics

Characteristics	Normal IGF-1 (n=20)	IGF-1 deficiency (n=19)	*P*
Median age (Year)	36 (± 10)	29 (± 11)	0.01
Gender (%)	35% male (n=7) 65% female (n=13)	42% male (n=8) 58% female (n=11)	0.74
Median BMI (kg/m²)	27 (± 6.4)	32 (± 5.4)	0.02
Overweight (%)	*65 (n=13)*	*21 (n=4)*	
Obesity (%)	*20 (n=4)*	*63 (n=12*	
Abdominal perimeter (cm)	97 (± 21)	107 (± 17)	0.12
Active smoking (%)	80 (n=16)	53 (n=10)	0.09
Disease duration (years)	11.5 (± 10)	5 (± 6.8)	0.009
Hurley's stage (%)			0.96
Stage1	*35 (n=7)*	*37 (n=7)*	
Stage 2	*50 (n=10)*	*47 (n=9)*	
Stage 3	*15 (n=3)*	*16 (n=3)*	
Stage 4	-	-	
Number of locations involved	2 (± 1)	2 (± 1)	0.28
Number of inflammatory lesions	3 (± 6)	4 (± 2)	0.18
Number of painful days per month	12.5 (± 10)	12.7 (± 10)	0.5

*The data are shown by median standard error (±) or by percentage with the number of patients in brackets

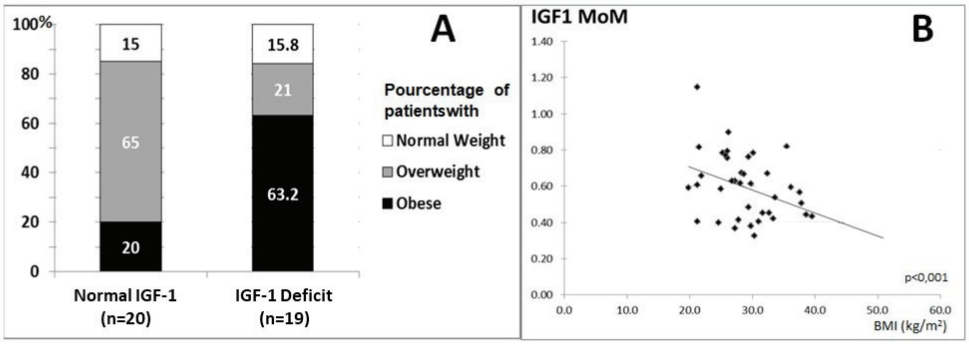

Figure 2. Patient BMIs (A) and correlation with the decrease in IGF-1 serum level (B).

Table 1 shows the clinical characteristics of patients with normal IGF-1 levels and those with IGF-1 deficit. In this study, 15/39 (38%) of the patients were men, with 7/20 having normal IGF-1 and 8/19 having IGF-1 insufficiency. Patients with IGF-1 insufficiency were significantly younger than patients with normal IGF-1 levels (median age: 29 years vs. 36 years, *P*=0.009), with a significantly shorter median disease duration (5 years vs. 11.5 years, *P*=0.009).

Among those with low IGF-1 levels, ten patients (53%) were smokers, a lower percentage than among those with normal IGF-1 levels (80% active smokers), but this difference was not statistically significant. However, 4 (21%) of these patients with low IGF-1 levels were overweight (classified by WHO as a BMI between 25 and 29 kg/m^2), and 12 (63%) were obese (BMI 30 kg/m^2). For patients with normal IGF1 levels, the percentages were reversed (Figure 2, A). Patients with IGF-1 insufficiency had a significantly higher BMI (32 kg/m^2 vs. 27 kg/m^2, *P*=0.02).

Analysis of other characteristics revealed differences that were not statistically significant: patients with low IGF-1 levels had a higher abdomen circumference (107 cm vs. 97 cm, *P*=0.12). Other clinical data did not show a significant difference between the two groups.

Correlation between MoM IGF-1 levels and BMI

Figure 2, B shows the substantial inverse association between the IGF-1 level expressed in MoM and the BMI (*P*=0.001). The greater the BMI gap, the greater the IGF-1 rate deficit.

Biological data

In terms of biological data, we found no significant difference between the two groups (Table 2). There was no aberrant liver function in either group, and no inflammation was observed by CRP or fibrinogen.

DISCUSSION

According to our findings, 49% of patients with HS have very low IGF-1 serum levels. Surprisingly, this IGF-1 insufficiency is linked to a specific patient

Table 2. Biological data

Biological data	Normal IGF-1 (n=20)	IGF-1 deficiency (n=19)	*P*
Total cholesterol (mmol/L)	2.04 (± 0.54)	1.77 (± 0.54)	0.07
LDL (mmol/L)	1.35 (± 0.42)	1.11 (± 0.37)	0.27
LDL goal achieved (%)	80 (n=16)	84 (n=16)	0.23
Triglyceride (g/L)	1.06 (± 0.61)	1.15 (± 0.7)	0.15
Prealbumin (g/L)	0.27 (± 0.07)	0.26 (± 0.06)	0.34
Albumin (g/L)	41.4 (± 3.63)	42.7 (± 3.41)	0.23
Vitamin D (ng/L)	18.2 (± 10)	16 (± 6.4)	0.93
Vitamin D deficiency (%)	90 (n=18)	100 (n=19)	1
CRP	2.5 (± 10)	2.5 (±8)	0.98
Fibrinogen (g/L)	3.8 (± 1.2)	3.7 (± 0.8)	0.86

*The data are shown by median standard error (±) or by percentage with the number of patients in brackets

profile: youthful, with a shorter disease duration and a higher BMI.

IGF-1 serum levels rise throughout childhood, plateau during puberty, and then fall in adults and the elderly (14). Changes in the phase of the circadian rhythm have been found in adolescents and the elderly (15,16). In healthy people, there is no clinically meaningful diurnal variation in total IGF-1 (17). To circumvent the circadian cycle, blood samples were collected on the patient's arrival at the day hospital, which is about 9 AM.

As IGF-1 has been shown to reduce the inflammatory response (18), the lower IGF-1 levels reported may contribute to the persistence of a local inflammatory response, resulting in delayed healing of inflammatory lesions. We did find an IGF-1 deficiency in patients with a shorter disease duration, but there was no significant difference in clinical severity between the two groups (deficiency versus normal IGF-1 rate), which could be explained by the small number of patients in our pilot trial. Indeed, Dias de Souza *et al.* demonstrated that low IGF-1 serum levels can influence the inflammatory process and lesion healing in American tegumentary leishmaniasis (19). A low IGF-1 serum level causes chronic inflammation mostly by altering IFN- levels and the TNF-/IGF-1 ratio, as well as by limiting macrophage recruitment in lesions (20). A deficit of cutaneous innate immunity has already been demonstrated in HS, and decreased IGF-1 levels may play a role (5). There was no systemic inflammation in our study, implying that the inflammation was limited to the peripheral tissues. CRP and fibrinogen levels were both within acceptable limits.

Another study on dermatologic lesions in patients with diabetes found that decreased cutaneous levels of IGF-1 were associated with delayed healing of cutaneous ulcers (21). It has been demonstrated *in vitro* to that IGF-1 enhances keratinocyte proliferation (21), and that this cell expresses IGF-1 R. The next stage in our research could be to evaluate local IGF-1 cutaneous levels in HS. In fact, if the IGF-1 serum shortage shown here reflects the IGF-1 skin level, as in diabetic ulcers, a therapeutic option for patients with HS could be the topical use of an IGF-1 cream, which has been demonstrated to improve diabetic lesions (22).

We found a substantial increase in BMI in the IGF-1 defective group (P=0.02): 63% of IGF-1 deficient patients were obese, compared with just 20% in the other group (Figure 2, A). This finding calls into doubt the link between the GH/IGF-1 axis and obesity. GH stimulates the synthesis of IGF-1. Primary IGF-1 shortage causes growth retardation, whereas excessive levels of IGF-1 are associated with acromegaly. GH and IGF-1 have a profound influence on fat, protein, and glucose metabolism. During the postprandial phase, GH secretion is reduced while insulin secretion increases, allowing glucose absorption in the skeletal muscle and promoting adipogenesis and glycogenesis. In contrast, insulin concentrations are low during fasting, whereas GH stimulates lipolysis and hepatic glucose production (23,24). Pulsatile GH secretion regulates IGF-1 production. The drop in IGF-1 may be explained by a central mechanism involving a change in the GH/IGF-1 axis; however, this hypothesis has never been tested in HS. Obesity, particularly abdominal obesity, has a significant deleterious impact on this spontaneous pulsatile GH secretion, which has been linked to severe metabolic consequences. Patients with metabolic syndrome and low IGF-1 plasma levels have a poorer prognosis for cardiovascular disease than those with normal IGF-1 levels (25). The number of obese individuals in our study was three times higher in the IGF-1 deficient group than in the normal IGF-1 group, and this was associated with a larger abdominal perimeter. This discovery opens the door to a new therapeutic option, in addition to topical IGF-1, for this subset of patients with low IGF-1 levels. In fact, an isocaloric diet mixed with metformin (an insulin sensitizer) or orlistat (a gastric and pancreatic lipase inhibitor) resulted in a considerable increase in IGF-1 levels in obese women with insulin resistance (26).

In adults, there is a positive connection between IGF-1 and 25-(OH)D levels (27). Obesity is related to a higher prevalence of vitamin D deficiency, and increasing body fat is thought to retain more 25-(OH) D and its metabolites. Our team has previously observed a decrease in vitamin D in patients with HS (5), and these results were confirmed in this investigation with a vitamin D shortage in each group (Table 2).

Tobacco use and obesity are additional risk factors reported in HS (28). There was no significant difference in smoking status between the two groups, with both groups having a high incidence of active smokers. Smoking had an unfavorable relationship with circulating IGF-1 levels, implying a direct inhibitory effect (29). Smoking may be a key cause of acquired low IGF-1 levels in patients with rheumatoid arthritis (30). The molecular underpinnings of nicotine-induced IGF-1 suppression are linked to hypothalamic-pituitary axis dysfunction. The impairment of the IGF-1 system includes a decrease in IGF-1 levels as well as increased production of IGF-1 binding proteins, which reduces IGF1R bioavailability. The alteration of the IGF-1 system is the result of cytokine-driven chronic inflammation (31). Tobacco does not appear to be the cause of IGF 1 deficiency in our case.

CONCLUSION

One of the limitations of our exploratory pilot study was that we did not have data on the linked co-morbidities in our patients. Despite a limitation (low patient number) that leads to bias, this pilot study demonstrates the existence of a subset of patients with HS that have IGF-1 insufficiency, who are mostly young and fat. It should be noted that the etiology of HS is yet unknown, although it is thought to be multifactorial. This multifactorial etiology is most likely related to the variable clinical presentation of HS in terms of lesion morphology and involvement sites. Furthermore, it suggests that there may be several forms of HS. Several classification initiatives have been launched in recent years (32,33), but they have been limited to demographic and clinical criteria and have yet to result in major advances in HS care. A new retrospective cohort study appears to reveal that the inflammatory phenotype is connected with higher CRP values, implying a higher cardiovascular risk in these individuals as well as the need for a different therapeutic approach (34).

It is critical to determine whether the group we have isolated corresponds to a subtype of HS that requires specific management, including treatment. IGF-1 has been linked to the formation of chronic inflammatory nodules because it plays a crucial role in healing and inflammation regulation. These findings need to be validated in a larger study, which is one of the goals of the COVER cohort on HS (NCT04352036) that we have just established in the North-West of France in collaboration with the Institut de Dermatologie du Grand Ouest (IDGO).

Abbreviations:

α-MSH: alpha-melanocyte stimulating hormone
BMI: body mass index
CRP: C-reactive protein
GH: growth hormone
HS: Hidradenitis suppurativa
IGF-1: insulin growth factor 1
IL:interleukin
LDL: low-density lipoprotein
MoM: multiples of median
TLRs: toll-like receptors
TNF-α: tumor necrosis factor-alpha

Acknowledgements: We would like to thank the entire Clinical Research team of the dermatology department for its help in this trial.

References:

1. Jemec GBE, Kimball AB. Hidradenitis suppurativa: Epidemiology and scope of the problem. J Am Acad Dermatol. 2015;73(5 Suppl 1):S4-7.
2. Revuz JE, Canoui-Poitrine F, Wolkenstein P, Viallette C, Gabison G, Pouget F, *et al.* Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol. 2008;59:596-601.
3. van Straalen KR, Schneider-Burrus S, Prens EP. Current and future treatment of hidradenitis suppurativa. Br J Dermatol. 2020;183:e178-87.
4. Robert E, Bodin F, Paul C, Konstantinou MP, Gall Y, Grolleau JL, *et al.* Non-surgical treatments for hidradenitis suppurativa: A systematic review. Ann Chir Plast Esthet. 2017;62:274-94.
5. Guillet A, Brocard A, Bach Ngohou K, Graveline N, Leloup AG, Ali D, *et al.* Verneuil's disease, innate immunity and vitamin D: a pilot study. J Eur Acad Dermatol Venereol. 2015;29:1347-53.
6. Hessam S, Sand M, Gambichler T, Skrygan M, Rüddel I, Bechara FG. Interleukin-36 in hidradenitis suppurativa: evidence for a distinctive pro-inflammatory role and a key factor in the development of an inflammatory loop. Br J Dermatol. 2018;178:761-7.
7. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol. 2011;164:1292-8.
8. Grant M, Jerdan J, Merimee TJ. Insulin-like growth factor-I modulates endothelial cell chemotaxis. J Clin Endocrinol Metab. 1987;65:370-1.
9. Botusan IR, Zheng X, Narayanan S, Grünler J, Sunkari VG, Calissendorff FS, *et al.* Deficiency of liver-derived insulin-like growth factor-I (IGF-I) does not interfere with the skin wound healing rate. PloS One. 2018;13:e0193084.
10. Fowkes FGR, Murray GD, Butcher I, Folsom AR, Hirsch AT, Couper DJ, *et al.* Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. Eur J Prev Cardiol. 2014;21:310-20.
11. Granada ML, Ulied A, Casanueva FF, Pico A, Lucas T, Torres E, *et al.* Serum IGF-I measured by four different immunoassays in patients with adult GH deficiency or acromegaly and in a control population. Clin Endocrinol (Oxf). 2008;68:942-50.
12. Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J, *et al.* Reference intervals

for insulin-like growth factor-1 (IGF-I) from birth to senescence: Results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99:1712-21.

13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.
14. Brabant G, von zur Mühlen A, Wüster C, Ranke MB, Kratzsch J, Kiess W, *et al.* Serum insulin-like growth factor I reference values for an automated chemiluminescence immunoassay system: results from a multicenter study. Horm Res. 2003;60:53-60.
15. Duffy JF, Czeisler CA. Age-related change in the relationship between circadian period, circadian phase, and diurnal preference in humans. Neurosci Lett. 2002;318:117-20.
16. Duffy JF, Czeisler CA. Age-related change in the relationship between circadian period, circadian phase, and diurnal preference in humans. Neurosci Lett. 2002;318:117-20.
17. Skjaerbaek C, Frystyk J, Kaal A, Laursen T, Møller J, Weeke J, *et al.* Circadian variation in serum free and total insulin-like growth factor (IGF)-I and IGF-II in untreated and treated acromegaly and growth hormone deficiency. Clin Endocrinol (Oxf). 2000;52:25-33.
18. Sukhanov S, Higashi Y, Shai SY, Vaughn C, Mohler J, Li Y, *et al.* IGF-1 reduces inflammatory responses, suppresses oxidative stress, and decreases atherosclerosis progression in ApoE-deficient mice. Arterioscler Thromb Vasc Biol. 2007;27:2684-90.
19. de Souza LD, Vendrame CMV, de Jesus AR, Carvalho MDT, Magalhães AS, Schriefer A, *et al.* Insulin-like growth factor-I serum levels and their biological effects on Leishmania isolates from different clinical forms of American tegumentary leishmaniasis. Parasit Vectors. 2016;9:335.
20. Giraud E, Lestinova T, Derrick T, Martin O, Dillon RJ, Volf P, *et al.* Leishmania proteophosphoglycans regurgitated from infected sand flies accelerate dermal wound repair and exacerbate leishmaniasis via insulin-like growth factor 1-dependent signaling. PLoS Pathog. 2018;14:e1006794.
21. Blakytny R, Jude EB, Martin Gibson J, Boulton AJ, Ferguson MW. Lack of insulin-like growth factor 1 (IGF1) in the basal keratinocyte layer of diabetic skin and diabetic foot ulcers. J Pathol. 2000;190:589-94.
22. Achar RAN, Silva TC, Achar E, Martines RB, Machado JLM. Use of insulin-like growth factor in the healing of open wounds in diabetic and non-diabetic rats. Acta Cir Bras. 2014;29:125-31.
23. Berryman DE, Glad CAM, List EO, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat Rev Endocrinol. 2013;9:346-56.
24. Møller N, Jørgensen JOL. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev. 2009;30:152-77.
25. Aguirre GA, De Ita JR, de la Garza RG, Castilla-Cortazar I. Insulin-like growth factor-1 deficiency and metabolic syndrome. J Transl Med. 2016;14:3.
26. Kujawska-Luczak M, Szulinska M, Skrypnik D, Musialik K, Swora-Cwynar E, Kregielska-Narozna M, *et al.* The influence of orlistat, metformin and diet on serum levels of insulin-like growth factor-1 in obeses women with and without insulin resistance. J Physiol Pharmacol Off J Pol Physiol Soc. 2018;69(5).
27. Bogazzi F, Rossi G, Lombardi M, Tomisti L, Sardella C, Manetti L, *et al.* Vitamin D status may contribute to serum insulin-like growth factor I concentrations in healthy subjects. J Endocrinol Invest. 2011;34:e200-203.
28. Kromann CB, Deckers IE, Esmann S, Boer J, Prens EP, Jemec GBE. Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study. Br J Dermatol. 2014;171:819-24.
29. Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosén T, Lindstedt G, Lundberg PA, *et al.* Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol (Oxf). 1994;41:351-7.
30. Erlandsson MC, Doria Medina R, Töyrä Silfverswärd S, Bokarewa MI. Smoking functions as a negative regulator of IGF1 and impairs adipokine network in patients with rheumatoid arthritis. Mediators Inflamm. 2016;2016:3082820.
31. O'Connor JC, McCusker RH, Strle K, Johnson RW, Dantzer R, Kelley KW. Regulation of IGF-I function by proinflammatory cytokines: at the interface of immunology and endocrinology. Cell Immunol. 2008;252:91-110.
32. Canoui-Poitrine F, Le Thuaut A, Revuz JE, Viallette C, Gabison G, Poli F, *et al.* Identification of three

hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study. J Invest Dermatol. 2013;133:1506-11.

33. van der Zee HH, Jemec GBE. New insights into the diagnosis of hidradenitis suppurativa: Clinical presentations and phenotypes. J Am Acad Dermatol. 2015;73(5 Suppl 1):S23-26.
34. Cuenca-Barrales C, Montero-Vilchez T, Salvador-Rodríguez L, Sánchez-Díaz M, Arias-Santiago S, Molina-Leyva A. Implications of hidradenitis suppurativa phenotypes in cardiovascular risk and treatment decisions: A retrospective cohort study. Dermatol Basel Switz. 2021;1-6.