

Adiponectin Contributes to the Inflammatory Milieu in Hidradenitis Suppurativa

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ABSTRACT **Introduction:** Hidradenitis suppurativa (HS) is a severe chronic skin disease. Although the pathogenesis remains unclear, at the basis of HS there is an enhancement of the immune and inflammatory response together with a susceptibility to environmental factors. Cytokine dysregulation is crucial in HS severity and progression.

Objectives: The aim of this study was to analyze serum levels of different cytokines focusing on adiponectin concentration and its oligomers in HS patients compared to both obese and healthy subjects.

Methods: The concentrations of adiponectin and cytokines were measured using enzyme-linked immunosorbent assay (ELISA); the oligomeric distribution of adiponectin (low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) oligomers) was evaluated through Western Blotting analysis.

Results: Total adiponectin is statistically higher in HS patients compared to matched controls and obese subjects. Interestingly, Adiponectin oligomerization state is altered in HS, with an increase of HMW oligomers. Serum levels of PDGF-BB, IL-1 β , IL-5, IL-6, IL12, IL13, IL15, IL-17, GMCSE, INF γ , VEGF and MCP-1 are statistically higher while IL-1ra and RANTES levels are statistically lower in HS patients compared to healthy controls. Interestingly, adiponectin positively correlates with PDGF-BB, and IL-13.

Conclusions: Our data confirmed that the complex network that links metabolism to immune homeostasis is dysregulated in HS and that adiponectin and its HMW oligomers are actively involved in this disease. In addition, the correlation between adiponectin and PDGF-BB, and IL-13 extends the role of this adipokine in modulation of the immune response, in particular regulating the innate immune system rather than the adaptive one. Further researches are needed to clarify the complex inflammatory milieu that characterizes HS syndrome.

Introduction

Hidradenitis suppurativa (HS) is a complex, chronic inflammatory skin disease characterized primarily by a dysregulation of the innate immune system and by a chronic inflammation that is not only restricted to skin but, especially in severe cases, affects different tissues and organs [2,3]. In particular, the over-activated immune cell infiltration, that is at the basis of HS disease, enhances the inflammatory response through the secretion of a considerable quantity of pro-inflammatory (IL-1 β , TNF α , IL-17, INF γ) as well as anti-inflammatory cytokines (IL-10) and chemokines [4-6]. On the other hand, an immunological “priming” in HS comes also from environmental factors such as, smoking-related inflammatory mediators and obesity related pro-inflammatory signals [7]. In particular, in obesity, the increased adipose tissue determines a pro-inflammatory environment due to the imbalance in production of adipokines that contributes to severity and progression of HS disease [8,9]. Recently, it was described a functional interplay among adipose tissue and other organs and tissues whom dysregulation has a key role in inflammation. Indeed, adipose tissue is an endocrine organ that produces several adipocytokines among which adiponectin exerts multivalent beneficial functions; it is abundantly secreted in serum where it circulates as oligomers of different molecular weight: low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) [10]. The HMW are the most biologically active oligomers [11]. Adiponectin is involved in the regulation of energy homeostasis, insulin sensitivity and inflammation [12]; interestingly, adiponectin expression is up-regulated in different inflammatory diseases and in some auto-immune diseases, while is down-regulated in metabolic diseases [13]. Regarding hidradenitis, serum adiponectin concentrations were found to be significantly lower, while the levels of the other adipocytokines have been found significantly higher than in controls [14,23].

The aim of this study was to analyze the serum concentrations of 27 cytokines and the most abundant adipocytokine,

the adiponectin, in patients affected by HS to investigate the potential relationships with metabolic parameters, disease severity and the risk of HS. We examined cytokines, adiponectin as potential biomarkers of inflammation in HS.

Objectives

To better understand the nature of inflammation in HS and the potential cross link with adipose tissue (AT), the aim of our study was to analyze the expression of different cytokines focusing on adiponectin concentrations and its oligomeric distribution in serum of HS patients respect to both obese and healthy subjects.

Methods

Participants

Fifty-three patients (31 females, 22 males), aged 30.0 ± 13.0 years, were recruited from the Dermatology Unit of the Università degli Studi della Campania “Luigi Vanvitelli”. Subjects were excluded from our study if they met any of the following criteria: age < 18 years, body mass index (BMI) < 17 or > 35, major metabolic disorders (type 2 diabetes, cardiovascular disorders, metabolic syndrome), the presence of concomitant inflammatory cutaneous or systemic disorders and the presence of cancer; were excluded also the patients receiving any systemic treatment which could interfere with the studied parameters. Disease staging was based on the three-degree scale proposed by Hurley. The mean BMI of 29.67 ± 6.1 kg/m² qualified our patients as overweight. The smoker rate amounted to 62.3%. Forty-two healthy volunteers were recruited from the CEINGE staff, they aged 33 ± 12.0 years old and constituted the control group (BMI = 23.3 ± 3.0); 53 obese subjects, aged 33 ± 12 years old (BMI = 48.4 ± 9.4), were recruited from the Foundation “Salvatore Maugeri” Telesse, Italy [15]. All HS patients fulfilled the established HS diagnostic criteria. All subjects signed an informed consent form. The study was approved

by the Ethic Committee of the Università degli Studi della Campania “Luigi Vanvitelli” (Prot. 12478/20).

Anthropometric and Biochemical Measurements

Blood samples from 53 HS patients, 42 healthy subjects and 53 obese subjects were collected after a 12-hours overnight fasting period and centrifuged to collect serum. Serum aliquots were immediately frozen in liquid nitrogen and stored at -80°C. For all participants total cholesterol, triglycerides, glycemia, C-Reactive Protein were measured (Table 1). The concentration of total adiponectin was measured in triplicate by an enzyme-linked immunosorbent assay (ELISA) as previously described [16].

The levels of 27 cytokine species (PDGF-BB, IL1 β , IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, Eotaxin, FGF, GCSF, GMCSF, INF γ , IP10, MCP-1, IP1 α , IP1 β , RANTES, TNFa, VEGF) were measured in 30 HS patients and in 39 healthy controls using a commercially available kit (Bio-Plex Pro™ Human Cytokine 8-plex Assay). The assay was performed according to the manufacturer’s instructions and the concentrations of cytokines were calculated by comparing reads with a 5-parameter logistic standard curve using a Bioplex-200 instrument (Bio-Rad).

Western Blotting Analysis of Serum Adiponectin

Five micrograms of total serum proteins were treated and subjects to electrophoresis as previously described [17]. The blots were developed by ECL (Amersham Biosciences) with the use of Kodak BioMax Light film and digitalized with a scanner (1.200 dpi) and analyzed by densitometry with the ImageJ software. Each serum sample was tested 2 times in duplicate.

Statistical Analysis

Data is expressed as average \pm standard deviation (SD) and median. The meanings of the differences in biochemical parameters between the groups were determined using the Mann-Whitney test and the Chi-square test. To evaluate the relationship with median adiponectin levels, multiple logistic regression was performed. A P value <0.05 was considered to indicate statistically significant results.

Results

Baseline Features and Serum Levels of Adiponectin in HS Patients

The anthropometric and biochemical characteristics of HS patients, sex and age-matched obese and healthy subjects are shown in Table 1. We found statistically significant difference in BMI between HS patients and controls (29.67 ± 6.12 versus 23.3 ± 3.04 , $P < 0.00$) as well as for total adiponectin serum levels ($28.25 \mu\text{g/ml} \pm 4.49$ versus $24.67 \mu\text{g/ml} \pm 3.35$, $P < 0.01$); both parameters result significantly higher in HS patients compared to controls. The statistical analysis indicated that the increase of adiponectin levels in HS is independent from BMI and sex, 2 potential confounding factors. Statistical analysis did not reveal significant difference in adiponectin concentrations among the HS groups based on the three Hurley degrees of disease severity. HS Hurley degree of HS patients are reported in Table 1: 30.2% of the patients have a Hurley I, 52.8% Hurley II and 17.0% Hurley III degree of disease severity.

As in literature was reported an opposite trend and to further validate the findings on concentration of adiponectin, we measured the levels of this adipokine in a cohort of 53 obese patients; as shown in Table 1, the comparison of

Table 1. Clinical, biochemical and anthropometrical characteristics of HS, obese patients and healthy subjects.

	HS patients (N 53)	Obese subjects (N. 53)	Controls (N 42)	P
Sex (F), N (%)	31 (53.8)	33 (62.3)	20 (47.6)	0.38
Age mean (\pm SD), years	30 \pm 13	33 \pm 12	33 \pm 12	0.37
BMI mean (\pm SD)	29.67 \pm 6.12	48.4 \pm 9.4	23.3 \pm 3.04	0.00
Cholesterol mean (\pm SD) (mg/dL)	203.54 \pm 44.16	169.94 \pm 37.21	191.48 \pm 35.22	0.00
Triglycerides mean (\pm SD) (mg/dL)	103.62 \pm 36.97	146.81 \pm 102.54	82.86 \pm 50.31	0.00
Glycemia mean (\pm SD) (mg/dL)	94 \pm 19	87 \pm 28	86 \pm 17	0.17
C-Reactive Protein mean (\pm SD) (mg/L)	6.87 \pm 8.36	8.23 \pm 8.48	-	0.41
Hurley IN (%)	16 (30.2)	-	-	-
Hurley II N (%)	28 (52.8)	-	-	-
Hurley III N (%)	9 (17.0)	-	-	-
Adiponectin mean (\pm SD) ($\mu\text{g/ml}$)	28.54 \pm 4.49	20.06 \pm 4.71	24.67 \pm 3.35	0.00

BMI = body mass index; HS = hidradenitis suppurativa; SD = standard deviation.

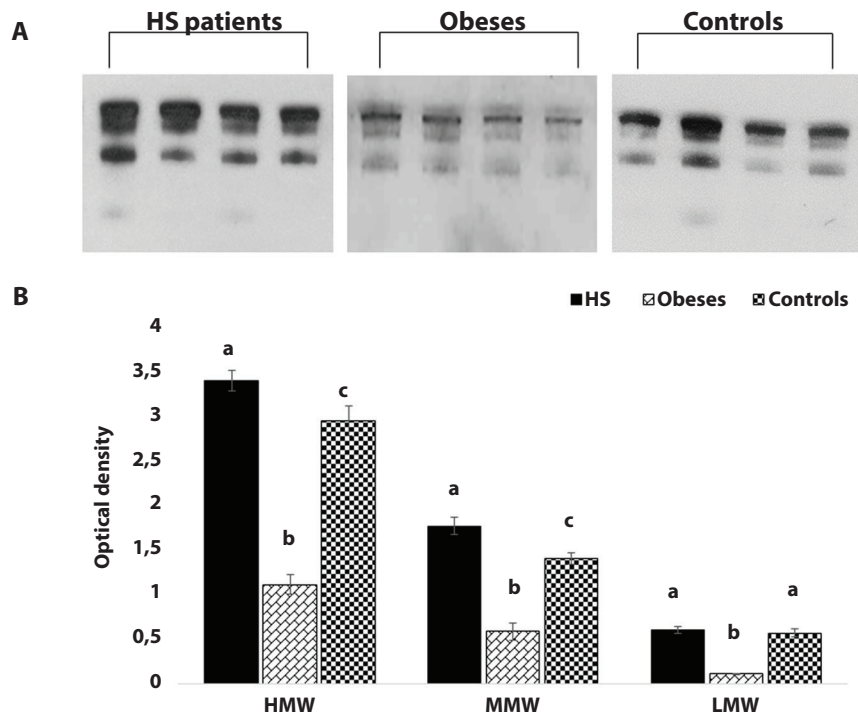


Figure 1. Western blotting analysis shows that adiponectin HMW and MMW oligomers are statistically higher in serum from HS patients compared to obese and healthy subjects. (A) Representative WB image of adiponectin different oligomers (HMW, MMW, LMW) from four HS patients, four obese subjects and four controls. (B) Graphical representation of pixel quantization of adiponectin oligomers analysed in 53 HS patients, 53 obese subjects and 42 controls. For other details see materials and methods. $P < 0.05$.

biochemical parameters between HS patients and obese subjects showed a statistically differences in BMI (29.67 ± 6.12 versus 48.4 ± 9.4 , $P < 0.00$) as well as in adiponectin levels; these latter are higher in HS than in obese patients ($28.25 \mu\text{g/ml} \pm 4.49$ versus $20.06 \mu\text{g/ml} \pm 4.71$, $P < 0.00$).

Oligomeric Distribution of Adiponectin in HS Patients

To better investigate the involvement of adiponectin in HS patients, we examined the oligomeric profile of this adipokine through the visualization of HMW; MMW and LMW oligomers. Western blot evidenced that the HMW and MMW adiponectin oligomers are increased in serum of HS patients if compared to obese and healthy subjects (Figure 1, $P < 0.05$).

Cytokine Concentration in HS Patients and Healthy Controls

To better explore the inflammatory milieu in serum from HS patients, we analyzed a panel of 27 different cytokines (PDGF-BB, IL1 β , IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, Eotaxin, FGF, GCSF, GM-CSF, INF γ , IP10, MCP-1, IP1 α , IP1 β , RANTES, TNF α , VEGF). We tested 30 HS patients and 39 controls. The results demonstrated that, among the others, PDGF-BB, IL-1 β , IL-5, IL-6,

IL12, IL13, IL15, IL-17, GM-CSF, INF γ , VEGF and MCP-1 levels were statistically higher while IL-1ra and RANTES levels were statistically lower in the serum of HS patients compared to healthy controls (Table 2).

Next, to investigate whether adiponectin is functionally related with any tested cytokines, we divided the HS patients in two subgroups using the median value of adiponectin concentration ($27.8 \mu\text{g/mL}$) as an arbitrary cut-off. According to adiponectin concentrations, patients with higher adiponectin concentrations (ie with values above the median) represented subgroup 1 and patients with lower adiponectin concentrations (ie with values under the median) represented subgroup 2. Statistical analysis performed using the univariate model showed that the patients with higher levels of adiponectin (subgroup 1) have also significantly higher PDGF-BB and a similar trend versus IL-13 (Table 3).

Conclusions

Hidradenitis (HS) is a severe chronic inflammatory skin disease primarily due to the alteration of immunity and to chronic inflammation [2,18]. A functional interconnection between immune system and adipose tissue, link observed in patients affected by metabolic disorders in which the dysregulation of energy metabolism negatively affects the immune

Table 2. Cytokine levels (pg/ml) in HS patients and healthy subjects.

Parameters		Controls (N 39)	HS patients (N 30)	P
Sex N (%)	F	17 (44%)	19 (63%)	0.10
	M	22 (56%)	11 (37%)	
Age, mean (\pm SD)		33.8 (6.8)	29.6 (13.5)	0.096
BMI, mean (\pm SD)		25.5 (3.7)	26.6 (3.8)	0.23
IL-1 β , mean (\pm SD)		2.0 (0.5)	2.3 (0.5)	0.014
IL-12, mean (\pm SD)		11.3 (1.3)	13.5 (3.9)	0.002
IL-13, mean (\pm SD)		5.5 (1.1)	8.4 (4.1)	<0.001
IL-15, mean (\pm SD)		347.2 (25.0)	390.3 (38.4)	<0.001
IL-17, mean (\pm SD)		25.0 (3.9)	27.2 (5.2)	0.048
GM-CSF, mean (\pm SD))		12.8 (0.7)	14.5 (1.5)	<0.001
IFN γ , mean (\pm SD)		13.3 (3.1)	18.6 (4.7)	<0.001
MCP-1 (MCAF), mean (\pm SD)		36.9 (15.0)	56.1 (31.7)	0.001
RANTES, median (IQR)		6833.4 (5469.2, 8214.1)	45145.1 (20829.6, 93670.0)	<0.001
PDGF-BB, median (IQR)		1638.5 (1180.5, 1991.2)	2306.6 (1701.6, 3208.0)	<0.001
IL-1ra, median (IQR)		371.5 (333.0, 446.4)	333.0 (257.0, 400.0)	0.036
IL-5, median (IQR)		52.3 (49.0, 55.5)	58.5 (52.3, 67.1)	0.002
IL-6, median (IQR)		7.6 (7.0, 8.1)	9.0 (7.8, 10.2)	<0.001
VEGF, mean (SD)		417.6 (40.2)	452.3 (52.7)	0.003

BMI = body mass index; HS = hidradenitis suppurativa; SD = standard deviation. Acronym list: IL (interleukin); Granulocyte-Macrophage Colony-Stimulating (GM-CSF); Interferon (INF); Monocytes Chemoattractant Protein(MCP); Platelet-Derived Growth Factor-BB (PDGF-BB); Vascular Endothelial Growth Factor (VEGF).

Table 3. Univariate analysis of anthropometric, clinical parameters and cytokines levels (pg/ml) on the basis of adiponectin levels: median value of adiponectin (27.8 μ g/ml) was used as an arbitrary cut-off.

Parameters		Adiponectin \leq 27.8	Adiponectin > 27.8	P
		N = 14	N = 16	
Sex	M, N (%)	7 (50%)	4 (25%)	0.16
	F, N (%)	7 (50%)	12 (75%)	
Age, mean (\pm SD)		30.1 (12.1)	29.3 (15.1)	0.87
BMI, mean (\pm SD)		27.3 (3.7)	26.0 (4.0)	0.36
PDGF-BB, (median) (IQR)		2984.9 (2226.8, 3463.2)	1823.9 (1306.3, 2507.5)	0.020
IL-5, median (IQR)		61.5 (55.5, 65.7)	55.5 (48.1, 68.1)	0.18
IL-13, median (IQR)		8.8 (7.3, 9.7)	5.8 (4.9, 9.6)	0.05
GM-CSF, median (IQR)		14.7 (13.9, 15.5)	13.5 (12.7, 15.8)	0.15
Hurley	I	5 (36%)	6 (38%)	0.98
	II	5 (36%)	6 (38%)	
	III	4 (29%)	4 (25%)	

system and viceversa. Indeed, in obese or overweight people there is a greater frequency of autoimmune diseases such as rheumatoid arthritis, type I diabetes and HS [24]. This functional interconnection is guaranteed by the hormonal activity of the adipose tissue through the secretion of adipokines such as adiponectin. In literature, numerous studies support the hypothesis that high levels of adiponectin represent a key

component of the body protective systemic response to the chronic inflammatory processes and immune system alterations [17,18,21].

In this study, to investigate the nature of the inflammatory milieu in HS and the potential contribute of adipose tissue, we analyzed several cytokines focusing on the most abundant adipokine, ie adiponectin and its oligomeric profile. Interestingly,

we found increased levels of adiponectin and HMW oligomers in HS patients compared to both healthy and obese subjects independently from BMI. To our knowledge, there are two studies describing adiponectin concentration in HS that found decreased serum level of adiponectin in the patients [22,23]. The discrepancy with our results may be traced back to clinical and biochemical differences of the considered patients: the study by Malara et al. analyzed patients with a very high BMI (33 versus 29.6 of our cohort), while Gonzalez-Lopez considered a cohort of patients with a more severe clinical phenotype of HS [22,23]. It is to notice, however, that we excluded that BMI might represent a confounding factor for adiponectin expression in HS patients; indeed, HS patients are more likely to have obesity and metabolic syndrome and overweight people have a greater incidence of HS [24].

In addition, although the significance of the molecular distribution of adiponectin is still largely unknown, it has been shown that the HMW oligomers have a stronger biological meaning and is the most important contributor to adiponectin functions [10]. Our findings that HS is associated with high circulating adiponectin levels, combined with a shift towards the HMW forms reinforce the hypothesis that adiponectin has a strong functional role in regulating inflammation in HS. The specificity of adiponectin role in HS is confirmed also by the significant difference of its concentrations that we found in the two populations, HS and obese subjects.

Next, in this study, we analyzed different cytokine expression previously reported to spill-over from the skin lesions into the systemic circulation resulting in heightening risk for systemic inflammation in HS patients [1]. Among the others, we found that PDGF-BB, IL-1 β , IL-5, IL-6, IL12, IL13, IL15, IL-17, GM-CSF, INF γ , VEGF and MCP-1 levels are statistically higher in HS patients while IL-1ra and RANTES levels are statistically lower in the serum of HS patients compared to healthy controls. Serum cytokine levels are very often altered in HS patients [25,23]. In accordance with our data, the levels of the pro-inflammatory IL-17 cytokine, whose production is made by neutrophils and Th17 cells, is increased in HS patients [26,27]. IL-17 is crucial in determining the inflammatory process of HS, inducing the expression of other pro-inflammatory cytokines, such as IL1 β and TNF α and stimulating the activation of adaptive immune cells [1,28]. On the other hand, one study found no differences in IL-17 levels between patients and controls [29]. Regarding IFN- γ , no statistically decrease was found in the serum of HS patients while a significant difference was found in another study [7].

Although not significant, our data also evidenced that IL-10 is higher in HS patients than in controls suggesting that the immune system is compensating the dysregulation in Th/Treg ratio typical of HS compatible with the mild phenotype of most of our patients. In accordance with our results, increased serum IL-10 levels compared to control was

reported in one study [30]; in two other studies no statistical difference was found [31,32].

Finally, for the first time, we correlated cytokines expression level to adiponectin concentration. We found that adiponectin correlates with PDGF-BB, and IL-13 but not with IL-17, IL-1 β , and INF γ suggesting that adiponectin function might be related to the innate immune system activation rather than the adaptive one, exerting anti-inflammatory actions. Previously, adiponectin has been demonstrated to directly and specifically bind PDGF-BB in smooth muscle cells suppressing their proliferation and migration [33] suppressing the development of atherosclerosis, promoting inflammation. Arita et al. demonstrated that the inhibitory effects of adiponectin towards PDGF-BB result in suppression of vasculogenesis and inflammation [33]. The association between adiponectin and PDGF-BB in HS patients suggests that the adipokine probably counteracts the inflammatory process triggered by the disease.

As IL-13 has been described as anti-inflammatory factor in the adipose tissue, the direct correlation with adiponectin further confirms that adiponectin is acting as anti-inflammatory molecule [34]. In addition, IL-13 has been involved in the maintenance of macrophages in an anti-inflammatory state as M2 phenotype supporting the hypothesis that adiponectin might participate in the regulation of the innate immune response [35].

There are two main limitations in the present study, one is the relatively small number of patients and the other is the absence of a large cohort of severe patients. In addition, the great heterogeneity in age, gender, environmental factors and potential comorbidities among the HS analyzed patients in different studies may be at the basis of the variability found in the expression of cytokines.

In conclusion, our data confirmed that the complex network that links together metabolism to immune homeostasis is dysregulated in HS and that adiponectin and its HMW oligomers are not only actively involved in the HS but that interacts with the complex inflammatory systemic milieu made by pro-inflammatory cytokines. In addition, the correlation between adiponectin and PDGF-BB, and IL-13 extends the role of this adipokine in modulation of the immune response suggesting that adiponectin might act regulating the innate immune system rather than the adaptive one. Further researches are needed to clarify the complex inflammatory milieu that characterizes HS syndrome.

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