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INSULIN-LIKE GROWTH FACTOR-1, PSORIASIS, AND INFLAMMATION: A MÉNAGE À TROIS?

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Psoriatic patients have an accumulation of metabolic syndrome (MS) and cardiovascular diseases (CVD), likely mediated by systemic inflammation, and exhibiting low circulating levels of insulin-like growth factor (IGF)-I, a marker of MS and CVD in the general population. The aim of this study is to determine the association of IGF-I and inflammation, and to assess the cardio-metabolic risk calculating the visceral adiposity index (VAI), in a group of psoriatic patients without MS. IGF-I, fibrinogen, C-reactive protein (CRP), and interleukin (IL)-6 levels were determined in 20 patients with moderate to severe psoriasis (age range 23-77 yrs) without MS, according to criteria of the National Cholesterol Education Program's Adult Panel III (ATP III), and 20 age- and BMI-matched controls. The standard deviation score (SDS) of IGF-I levels according to age (zSDS), the homeostasis model assessment of insulin resistance (HOMA-IR), the whole-body insulin sensitivity index (ISI), and VAI were also calculated. Psoriasis Area and Severity Index (PASI) mean value was 17.8±11. HDL cholesterol and IGF-I zSDS values were lower ($p<0.001$) and waist circumference ($p<0.001$), VAI, fibrinogen, and IL-6 ($p<0.005$) were higher compared with controls, while HOMA-IR and ISI were not statistically different. Lower IGF-I zSDS values were associated to higher values of BMI ($p=0.04$), waist circumference, VAI ($p<0.001$), PASI ($p=0.011$), or IL-6 ($p<0.001$). At the multivariate analysis PASI was the major determinant of IGF-I zSDS ($p=0.016$), accounting for 37% of its variability. In a subset of psoriatic patients without MS, chronic inflammation might be an important modulator of low IGF-I status, as a further possible mechanistic link between psoriasis and associated metabolic co-morbidities. The negative correlation between age-related IGF-I values and VAI suggest the involvement of adipocyte dysfunction in low IGF-I status more than MS *per se*. Further studies are needed to address whether these results are valid also for other psoriatic patients.

Psoriasis is a chronic immunologically-based, systemic inflammatory disease of the skin, sharing

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

with other inflammatory immune disorders similar pathogenic mechanisms involving cytokine dysregulation (1-2). In recent years, studies have demonstrated in psoriatic patients an accumulation of obesity, diabetes mellitus, and cardiovascular disease (CVD), with metabolic syndrome (MS) as the most prevalent comorbidity (3-5). Mediators and markers of inflammation, mainly tumor necrosis factor (TNF)-α, interleukin (IL)-6, fibrinogen or C-reactive protein (CRP) are involved as the possible link between psoriasis and MS (2).

It is well known that a number of inflammatory cytokines affect insulin-like growth factor (IGF)-I secretion (6), the main anabolic mediator of somatotroph axis. IGF-I has been reported to act as an autocrine/paracrine essential signal for proliferation of epidermal keratinocytes (7), and IGF-I has been found to be overproduced in psoriatic epidermis (8-9). However, despite the increase in IGF-I in psoriatic plaques, psoriatic patients exhibited low circulating levels of IGF-I, with a negative correlation to Psoriasis Area and Severity Index (PASI) (10). Low IGF-I levels have been associated with unfavourable lipid profiles, with increased cardiovascular mortality (11-13). Thus, although the possible primary or secondary effect of abnormalities in somatotroph axis activity on the psoriasis process modulation remains still unclear, the more likely association of low IGF-I with the common inflammatory pathways of both MS or psoriasis has not been considered so far.

In the present study we aimed to determine the association of IGF-I, MS, and the systemic inflammation status in the setting of psoriasis. To highlight this association, in a group of psoriatic patients without MS fibrinogen we evaluated CRP, and IL-6, as markers of inflammation, and assessed the cardio-metabolic risk calculating the visceral adiposity index (VAI), a novel sex-specific index of visceral fat function, identifying the patients with cardiometabolic risk.

MATERIALS AND METHODS

All patients were recruited at the Department of Systematic Pathology, Division of Clinical Dermatology, University "Federico II" of Naples, Italy. Twenty patients with moderate to severe psoriasis and without MS, were enrolled in this observational study from January to December 2010. They had not taken any medication known to affect carbohydrate or lipid metabolism for the prior 6 months. Data collected included age, sex, weight, height, body mass index (BMI), waist circumference, blood pressure, age at onset of psoriasis, severity of psoriasis, presence of any concomitant diseases or medications. Body mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference (WC) was measured at the mid-point between the umbilicus and the xiphoid. MS was excluded according to criteria of the National Cholesterol Education Program's Adult Panel III (ATP III) (14). Disease severity was assessed according to PASI. Patients with pustular, erythrodermic or arthropathic psoriasis or receiving any systemic treatment for psoriasis including acitretin, ciclosporin, methotrexate, phototherapy or biologics for at least 3 months before enrolment and having used topicals for at least 3 weeks were excluded. Exclusion criteria included smoking and alcohol abuse. Twenty healthy subjects among clerks, and medical and paramedical personnel of the Department of Molecular and Clinical Endocrinology and Oncology of the University "Federico II" of Naples, matched for sex, age, and BMI with the patients agreed to participate in this study and were used as controls. Exclusion criteria for controls were the same as the patients. All participants gave their informed consent before enrolment. The study was conducted after approval by the institutional review board of the University of Naples, Italy.

Blood samples were obtained between 08.00 h and 09.00 h from an antecubital vein after an overnight fast, with the patient in the resting position. The oral glucose tolerance test (OGTT) was performed using 75 g dextrose. Blood samples were obtained at 0, 30, 60, 90, 120, 150 and 180 min. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to Matthews et al. (15). Whole-body insulin sensitivity index (ISI) was calculated according to Matsuda and DeFronzo (16). Visceral adiposity index (VAI) was calculated according to Amato et al. (17). Briefly, the mathematical model underlying the calculation of VAI uses both anthropometric (BMI and WC) and metabolic (triglycerides and HDL-cholesterol) simple parameters, taking into account also BMI and gender.

Fasting glucose, total and HDL cholesterol, triglycerides, and transaminases, were measured by standard procedures in the Central Biochemistry Laboratory at our Institution (Roche/Hitachi Modular Analytics System). The white blood cell count was determined on an automated hematology analyzer (Beckman Instruments, Inc). Glucose was measured by an oxidase-based technique. Fasting insulin was measured by a solid-phase chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic

Products Co, Los Angeles, CA, USA). The sensitivity of the assay was 2 μIU/mL and intra-assay coefficients of variations (CV) were between 3.8-5.5%. Serum IGF-I levels were measured by IRMA after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, Texas, USA). The sensitivity of the assay was 0.8 μg/L; the normal ranges in adults aged 20–40 and 41–60 years were 110–494 and 100–300 μg/l, respectively. The intra-assay CVs were between 1.5-3.4%. The standard deviation score (SDS) of IGF-I levels according to age (zSDS) was calculated, as previously reported (13). Fibrinogen and CRP were determined with a modified Clauss method with Multifibren U and a nephelomteric assay with CardioPhase, respectively, both from Siemens Healthcare Diagnostics (Marburg, Germany). IL-6 was measured by an enzyme-linked immunosorbent assay kit (Biosurce, Camarillo, California, USA). Its sensitivity was < 2 pg/ml, and the range 7.8–500 pg/ml. The intra-assay CV for low concentration was < 5%.

Statistical analysis

All data were analyzed using the statistical package for social science (SPSS) 10.0 for Windows. All data were given as median plus (range). The Wilcoxon matched pairs signed-rank test was used to evaluate differences between groups. Bivariate correlations between variables were examined using Spearman's rhoMultiple linear regression analysis and were calculated with IGF-I SDS score as dependent variable, and waist circumference, PASI, and IL-6 as independent variables, with the stepwise selection method (p= to enter <0.05, p= to remove > 0.1, maxstep =10). The statistical significance was accepted as p value < 0.05.

RESULTS

Our cohorts were well-matched for sex, age and BMI (Table I). PASI median value in psoriatic patients was 15.7 (3.80-40.0), while the mean duration of illness was 24.0 years (range: 4.0–54.0). Characteristics of the study population and controls are reported in Table I. There were no significant

Table I. *Characteristics of the study population and controls.*

	Psoriatic Patients (20)		Controls (20)		p
Female to male ratio	7/10		7/10		
	median	range	median	range	
Age (yrs)	44.0	23.0-77.0	44.0	23.0-76.0	ns
BMI (kg/m^2)	26.7	19.8-44.0	23.8	19.0-46.5	ns
Waist circumference (cm)	98.0	70.0-132	75.0	56.0-115	0.008
Plasma glucose (mg/dl)	77.5	50.0-97.0	93.5	73.0-130	0.001
Insulin (μUI/ml)	8.00	2.00-27.4	6.50	3.60-23.3	ns
HOMA-IR	1.33	0.47-4.76	1.35	0.83-5.82	ns
ISI	34.6	9.63-80.5	31.9	8.04-56.1	ns
Total cholesterol (mg/dl)	196	148-267	184	155-280	ns
HDL cholesterol (mg/dl)	42.0	14.0-61.0	60.5	48.0-79.0	0.001
Triglycerides (mg/dl)	106	87.0-221	105	76.0-188	ns
VAI	2.05	0.84-8.92	1.14	0.51-2.23	0.001
SBP (mmHg)	125	120-150	123	100-140	ns
DBP (mmHg)	80.0	70.0-90.0	80.0	60.0-85.0	ns
ALT (U/l)	22.5	11.0-46.0	21.0	16.0-33.0	ns
AST (U/l)	19.0	13.0-29.0	21.0	16.0-34.0	ns
IGF-I (ng/ml)	172	89.0-227	209	131-300	0.015
IGF-I zSDS	-1.12	-3.20;-0.89	0.20	-0.43;-1.65	0.001
WBC (x 10^3/ml)	7.00	4.70-11.72	6.78	5.30-9.56	ns
Fibrinogen (mg/dl)	338	180-648	269	208-400	0.017
CRP (mg/l)	0.33	0.29-1.40	0.35	0.29-1.00	ns
IL-6 (pg/ml)	12.9	1.30-65.0	0.80	0.10-7.60	0.001

Values are reported as median and range intervals. BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; ISI: whole-body insulin sensitivity index; VAI: Visceral adiposity index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; IGF-I: insulin-like growth factor-I; IGF-I zSDS: standard deviation of IGF-I levels according to age; WBC: White blood cell counts; CRP: C-reactive protein (CRP); IL-6: interleukin (IL)-6. HOMA-IR was calculated according to Matthews et al. (15). ISI was calculated according to Matsuda and DeFronzo (16). VAI was calculated according to Amato et al. (17). The age-related IGF-I zSDS were calculated according to Colao et al. (13).

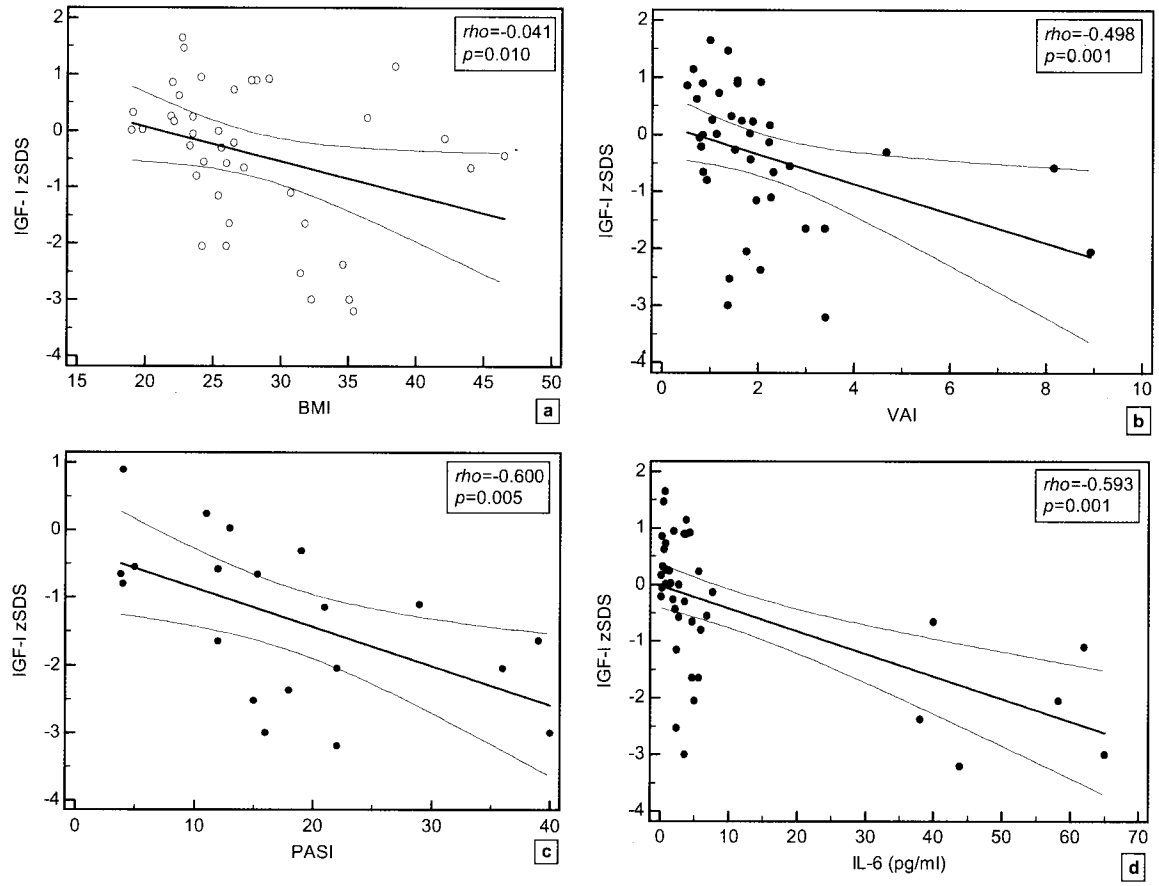

Fig. 1. *Correlations of IGF-I zSDS values with BMI (**a**), VAI (**b**), PASI (**c**), and IL-6 (**d**) in the study group. IGF-I: insulin-like growth factor-I; IGF-I zSDS: standard deviation of IGF-I levels according to age; BMI: body mass index; PASI: Psoriasis Area and Severity Index; VAI: Visceral adiposity index; IL-6: interleukin-6. The age-related IGF-I zSDS were calculated according to Colao et al. (13). VAI was calculated according to Amato et al. (17).*

differences in age and male/female ratio between the patients and controls Neither patients nor controls had a history or laboratory findings consistent with impaired hepatic or renal function, nor parasitic or any other infection. As expected, fibrinogen and IL-6 were higher in psoriatic patients than in controls. Otherwise, the main finding was that, although the absence of MS diagnosis has been considered an exclusion criteria, psoriatic patients showed high VAI values and low IGF-I levels, also measured as IGF-I zSDS values. As a matter of fact, HDL cholesterol was lower and WC was higher than controls. HOMA-IR and ISI were not statistically different between patients and controls. White blood cell counts, transaminases, and CRP levels were in normal ranges for all subjects.

Correlations between variables are reported in Fig. 1. Apart from waist circumference (rho= -0.564; p<0.001), in psoriatic patients IGF-I zSDS values showed significant inverse correlations with BMI (Fig. 1a), VAI (Fig. 1b), PASI (Fig. 1c) and IL-6 (Fig. 1d). At the multiple linear regression, PASI was the major determinant of IGF-I zSDS values (β= -0.606; t=-3.145; p=0.006).

DISCUSSION

This study showed that a subset of psoriatic

patients without MS had lower age-related IGF-I levels as compared with BMI and age-matched controls. Accordingly, VAI, fibrinogen and IL-6 levels were increased. We also detected a significant negative correlation between age-related IGF-I levels, BMI, VAI, PASI, and IL-6, with PASI as best determinant of age-related IGF-I levels, accounting for 37% of its variability. Of interest, the calculation of VAI, a novel sex-specific index indirectly expressing visceral fat dysfunction and insulin sensitivity, allowed us to highlight the increased cardiometabolic risk in psoriatic patients with higher sensitivity and specificity than classical parameters of ATP III criteria for MS.

The negative correlation between IGF-I and PASI in our patients were similar to previously published data (10). Also the association between psoriasis and MS has been already reported (2-5), the systemic inflammation being the potential link between psoriasis and associated metabolic comorbidities (2). Recently, the association was investigated between the morbidity in the elderly and the progressive opposite changes in IGF-I and IL-6 levels with age (18). However, the possible link of low IGF-I with inflammation beyond the confounding effects of MS and age in the setting of psoriasis had not been previously demonstrated. For the first time we found that the low IGF-I status in psoriatic patients was present independently of age and classical criteria of MS. Apart from age, it is well-known that different factors, such as glucose homeostasis (19) and inflammation (6, 12), have been reported to affect IGF-I metabolism IGF-I, while up to 90% circulating IGF-I originates in the liver (19).

As basal insulin levels or the surrogate index of IR used in this study were similar to those of controls, and liver function tests were normal in all the subjects, the low age-related IGF-I levels cannot be ascribed to impaired glucose homeostasis or liver dysfunction.

The increased VAI values highlighted in our group of psoriatic patients independently of MS diagnosis is in line with a recently published study reporting the independent association of VAI with cardio- and cerebrovascular events, but not with MS (20). In particular, VAI calculation is based on simply but quantitative continuous parameters, including physical (BMI and WC) and metabolic (tryglycerides and HDL-cholesterol), and it takes into account also BMI and gender. Our data further supported the involvement of other non-classical risk factors, i.e. altered production of adipocytokine by dysfunctional adipocytes, in the chronic low-grade inflammation of psoriatic patients.

In the present study, PASI was the major determinant of IGF-I. A number of epidemiological studies have suggested that IGF-I levels in the lower normal range are associated with an increased risk of ischemic heart disease, stroke, hypertension, reduced glucose tolerance, and diabetes (11, 21-24). Although the relationship between IGF-I and cardiovascular disease is still unknown, a protective role in the development of atherosclerosis was suggested for free IGF1 levels (24). Taking into account the involvement of inflammatory cytokines in IGF-1 regulation (6, 12), particularly of visceral fat-derived adipocytokines, the results on the relationship between IGF-1, psoriasis and inflammation, the three main variables of the study, led us to hypothesize that: i) low IGF-I may represent a consequence of the psoriasis-related inflammatory state; ii) the inverse relationship between IGF-I and PASI might represent an epiphenomenon of the psoriasis-related inflammatory state; iii) the inverse correlation between IGF-1 and VAI suggests the involvement of the adipocytes dysfunction in low IGF-I status more than MS *per se*; iiii) low IGF-I, may be involved in the increased cardiometabolic risk in psoriasis, similarly to aging (22), obesity and type 2 diabetes (23), CVD (21), and cystic fibrosis (25). In particular, we previously reported that lower age normalized IGF-I levels were associated with increased prevalence of severe hypertension and diabetes mellitus in a population of healthy subjects (13).

Due to the small number of patients enrolled and the cross-sectional design of the study, these results must be regarded as preliminary data and cannot be generalized beyond the cases studied. Moreover, we cannot draw conclusions on the natural progression of these relationships over time. Nevertheless, the calculation of age-related SDS of IGF-I and VAI strengthened the evidence obtained in this study.

In conclusion, taking into account the association between IGF-I and cardiovascular mortality in the general population, our study added new

information on the relationships between IGF-I, inflammation and psoriasis, the three main variables of the study, in the setting of the cardiometabolic risk of psoriatic patients. The chronic inflammation in psoriasis might be an important modulator of the low IGF-I status, which in turn could be added as a further possible mechanistic link between psoriasis and MS components. VAI highlighted the increased cardiometabolic risk in psoriatic patients with higher sensitivity and specificity than ATP III criteria and its negative correlation with age-related IGF-I values suggested the involvement of the adipocyte dysfunction in low IGF-I status more than MS *per se*. Further studies are needed to address whether these results are also valid beyond this subset of psoriatic patients.

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