Skin Tensile Properties in Patients Treated for Acromegaly

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Abstract

Background : Somatotropic effects are described in the skin. Indeed, acromegaly is in part clinically recognized by cutaneous coarsening. The actual changes in tensile properties associated with the cutaneous manifestations are largely unknown. **Objectives :** To study the relationships between the skin tensile properties and the severity of acromegaly as assessed by serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). **Patients and method :** Assessments were made in 13 patients with acromegaly treated by somatostatin agonists combined or not with surgery. A total of 39 age-and sex-matched healthy subjects served as controls. Skin tensile properties were measured on the forearm and nape of the neck using a computerized suction device. **Results :** Significant differences were yielded between the skin tensile properties in patients and normal subjects. The highest IGF-1 values in the patients' medical records were positively correlated with both skin distensibility and biologic elasticity. The most recent IGF-1 serum levels were negatively correlated with the visco-elastic ratio. No correlations were yielded between any of the biomechanical parameters and GH levels, disease duration and treatment dosages, respectively. **Conclusion :** Skin in acromegaly appears to be functionally more redundant and elastic than normal skin. The biomechanical changes appear quite different from those observed in other diseases with collagen deposition such as diabetes mellitus and scleroderma.

Key Words : Acromegaly. Dermis. Mechanical properties. Growth hormone. Insulin-like growth factor-1.

The overall tensile properties of skin largely depend on the composition and architecture of the dermis [1]. As a consequence, many connective tissue disorders are in part characterized by typical changes in the tensile characteristics of the skin [1-3]. Several non-invasive methods are available to assess such features [4].

In acromegaly, skin is enlarged, acquires a doughy texture and typically presents disproportionate skinfolds [5, 6]. Skin coarsening is primarily due to an increase in the amount of collagen and glycosaminoglycans [7-9]. Objectivation of the functional consequences of this organomegaly has not yet been studied thoroughly. Reports have shown that injections of growth hormone (GH) in adults may result in increased skin thickness [10] and in unusual viscoelastic changes in the skin [11]. In fact, there is ample evidence that fibroblasts and other cells of the skin respond to GH and insulin-like growth factor 1 (IGF-1) [12-22]. These findings suggest that epidermal, adnexal and dermal cell populations can be direct and indirect tarrgets for GH [22]. Indeed, transgenic mice overexpressing GH show skin overgrowth with increased dermal thickness, significant dermal fibrosis and replacement of subcutaneous adipose tissue by fibrous tissue [23]. By contrast, GH and IGF-1 deficiencies show effects on the skin by decreasing its thickness and weakening its mechanical properties [24, 25].

The aim of the present study was to assess the in vivo tensile properties of the skin in patients treated for acromegaly, and to compare it with serum levels of GH and IGF-1.

Patients and methods

Thirteen patients with acromegaly were enrolled in the study (Table I). The M:F sex ratio was 1.6. All but one patients were treated with lanreotide (Somatuline®, Ipsen) or octreotide (Table I). Serum levels of GH (GH IRMA C.T., BC 1012, Biocode, Belgium) and IGF-1 (IGF-1 IRMA, BC 1010, Biocode, Belgium) were retrieved from the medical files. The highest GH and IGF-1 values in the medical records of each patient were considered to be representative of the climax severity of the disease. The serum levels of these biomolecules recorded at the time of the study were also retained to assess the current status of the disease. A control group was formed by 39 age- and sex-matched healthy subjects (3 normal matched volunteers for each patient with acromegaly).

The tensile properties of the skin were evaluated using a computerized suction device (Cutometer® SEM 474, C + K Electronic, Cologne, Germany) equipped with a hand-held probe having a central suction head of 4 mm in diameter. The time/strain mode was used with three cycles of 5-s traction under negative pressure of 500 mbar separated by 5-s relaxation periods (Fig. 1). The skin tensile parameters considered in this study have been previously described in detail [4, 26-30]. Each load cycle of suction to the skin results in an immediate elastic distension (ED), recorded at 0.15 s, followed by a delayed visoelastic distension, ending with the measurement of the maximum distension (MD) of the skin obtained after a 5-s traction. When the traction is discontinued, the skin tends to return to its initial position. During that phase, two parameters are recorded, namely the immediate elastic retraction (ER) after 0.1 s of relaxation and the resilient distension (RD) after a 5-s relaxation time. These measures were taken during the first and third load cycles. The differential distension (DD) was measured as the difference in MD between the third and the first cycles. In addition,, certain biologically relevant ratios of these parameters were calculated (Table II).

Measurements were taken from the left mid volar forearm and the nape of the neck. The values were expressed as means (M) and SD with calculation of the coefficient of variation ($CV = 10^2$ SD. M^{-1}). Differences between body sites were tested for their statistical significance using the paired Student t-test. Regression analysis models were applied to evaluate the relationships between the biomechanical values and hormonal levels. The best model, i.e. linear, logarithmic, exponential or power, was chosen on the basis of the highest coefficient of correlation (r). A p value lower than 0.05 was considered significant.

Results

For each biomechanical parameter, interindividual variability was quite large among patients with acromegaly (Table III). In contrast, intraindividual differences between the two body test sites were very low. In absence of any significant regional differences (Table III), the values obtained from the volar forearm and the nape of the neck were averaged for further search of correlations with hormonal values. Compared to matched normal subjects, patients with acromegaly showed a significant increase in MD ($p < 0.01$) combined with significant reductions in VER ($p < 0.05$), EF ($p < 0.01$) and RER ($p < 0.05$).

From all the correlations tested between each of the GH and IGF-1 levels, disease duration, somatostatin agonist dosages and skin tensile parameters, only three reached significance (Fig. 2a, b, 3). MD and BE increased in parallel with the values of maximum IGF-1 (linear correlation, $r = 0.60$ and 0.64, respectively, $p < 0.01$) . In contrast, VER values were negatively correlated with the most recent IGF-1 serum levels (logarithmic correlation, $r = -0.54$, $p < 0.05$).

Discussion

There is ample evidence that skin is under the influence of many neuroendocrine influences [22]. Previous studies indicated that the precise assessments of the mechanical properties of this organ reveal quite specific changes in hormone-related connective tissue disorders including menopause, diabetes and GH deficiency [1, 11, 25, 28-33]. In addition, such assessments reveal some correlations between the severity in skin and bone alterations [30]. Thus, determining the mechanical properties of skin may also represent a non-invasive tool for predicting internal manifestations of some connective tissue disorders.

It is recognized that the suction method parameters do not lend themselves to quick simple explanation. In the present test design, the 4-mm probe aperture allowed the suction force to be transmitted to the first 1 to 1.5 mm of the dermis. This limitation permits indeed a comparison between the intrinsic properties of normal skin and those of a presumably thicker dermis in acromegaly. Hence, the well recognized effect of tissue thickness upon the biomechanical properties of skin [1, 25, 34] is minimized. Our study indicates that the skin tensile properties are markedly altered in patients treated for acromegaly. This was indeed not a surprise because there is ample clinical clue for such changes. In the overall assessment, skin in acromegaly exhibited increased distensibility with more subtle changes in its viscoelastic aspects. The interindividual variations in skin tensile properties were larger in the patients than in the healthy subjects.

The present data distinguish the most recent and the maximum GH and IGF-1 imbalances in acromegaly. No significant correlation was yielded between GH serum levels and the skin tensile properties. In contrast, distinct correlations were found between each of the IGF-1 levels and values of some biomechanical parameters.

This may be explained by the quite stable intra-individual IGF-1 values in contrast with the variable amplitude and frequency in GH pulses [12, 35]. There was evidence that both maximum skin distensibility (MD) and biologic elasticity (BE) increased with the disease severity as assessed by the highest recorded IGF-1 values. Such a finding is at variance with other skin conditions including diabetes and scleroderma which are also associated with deposits of collagen [27-29]. In these disorders, MD is typically decreased and elasticity changes are variable. Indeed, the functional consequences of increased collagen content in the dermis may be quite different according to the agencement of the fibrils and bundles. It is noteworthy that such structures are stretched and tightly bound each other in scleroderma, resulting in increased skin stiffness. Skin in acromegaly shows a different microanatomy and lacks these tensile characteristics. It appears to be more enlarged, redundant and doughy rather than tight and stretched. Hormonal changes in acromegaly induce imbalanced soft tissue enlargement with increased dermal thickness [12]. This feature cannot explain the MD increase, but rather would be suspected to be responsible for the reverse. The present data suggest that the skin envelope is more increased in area than in thickness. Thus, skin increases in size at a greater extent than needed to simply cover the volume of the underlying bones, muscles and subcutaneous tissues.

The short term effects of hormonal disturbance in acromegaly appear different from those related to the climax severity of the disease. Viscosity of skin (VER) decreased proportionally to the increase in the last IGF-1 recorded value. Such a negative correlation was relatively weak and the scatterplot showed considerable spread. In addition, this aspect is at variance with previous findings made in GH abusers among adult body builders [11]. In this latter group of individuals, the musculature was indeed impressive and much more developed than in patients with acromegaly. Hence, the skin tension imposed by the volume of muscles was likely different in this distinct group of individuals. In addition, fluid retention was likely present in the dermis. A direct effect of somatostatin agonists on the tensile properties of skin cannot be dismissed from the present observations. However, no correlation was found in this study between the biochemical parameters and the mean drug dosages and the total amount of lanreotide and octreotide administered to the patients.

In conclusion, IGF-1 levels appear to control, at least in part, the tensile properties of skin. The excess in IGF-1 may yield distinct short-term and long-term functional consequences on the skin physiology. The predictive value of the presently described biomechanical alterations for the severity of internal manifestations remains to be settled.

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Table I - Demographic data of the patients with acromegaly

Patient	Gender	Age (year)	Time elapsed since diagnosis (year)	Surgery	Somatostatin ag treatment Duration (year Current mean d month
1	M	54	17	+	none
2	M	65	5	0	Lanreotide 5 y, 90
3	M	65	1	+	Lanreotide 0.5 y,
4	M	38	1	+	Lanreotide 0.5 y,
5	M	34	5	+	Lanreotide 3 y, 12
6	M	49	11	+	Lanreotide 11 y, 12
7	M	73	5	0	Lanreotide 5 y, 90
8	M	51	13	+	Octreotide 11 y, 6
9	F	71	5	0	Lanreotide 5 y, 12
10	F	43	17	+	Lanreotide 3 y, 12
11	F	67	13	+	Lanreotide 13 y, 6
12	F	56	9	+	Lanreotide 4 y, 90
13	F	31	6	0	Lanreotide 6 y, 12

Table II Rheologic ratios (%) quantifying the skin tensile strength

Extension phase during skin elevation

Viscoelastic ratio, VER = 10^{2} (MD-ED)ED^{-1}

Recovery phase during skin relaxation

Biologic elasticity, BE = 10^{2} (Md-RD)MD^{-1}

Relative elastic recovery, RER = 10^{2} (MD-ER)MD^{-1}

Elastic function, EF = 10^{2} (MD-ER) ED^{-1}

Table III : Mean ± SD and coefficient of variation (CV, %) of the biomechanical parameters evaluated on the volar forearm and neck

	Acromegaly		Controls
Parameter	Volar forearm_	Neck	Volar forearm
MD (nm)	257 ± 76 (29.6 %)	255 ± 96 (37.6 %)_	161±33 (20.5 %)
BE (%)	70 ± 12 (17.1 %)_	71 ± 14 (19.7 %)	73±8 (18 %)
VER (%)	47 ± 21 (44.7 %)	48 ± 18 (37.5 %)	97±10 (10,3 %)
EF (%)	57 ± 21 (36.8 %)	52 ± 22 (42.3 %)	70±15 (21,4 %)
RER (%)	39 ± 11 (28.2 %)	35 ± 12 (34.3 %)	56±8 (14,3 %)
DD (nm)	24 ± 21 (87.5 %)	23 ± 13 (56.5 %)	31±8 (25,8 %)

Figure captions

Fig 1 Deformation of skin in response to three cycles 5s- suction separated by 5-s relaxation. See text for the definition of the biomechanical parameters.

Fig 2 Scatterplot of (a) MD values μm and (b) BE values (%) according to the maximum IGF-1 levels (ng/ml) in the patients' history. Positive linear relationships are yielded (MD : $r = 0.60$, $p < 0.01$; BE : $r = 0.64$, $p < 0.01$).

Fig 3 Scatterplot of VER values (%) according to the most recent IGF-1 levels (ng/ml) in the patient's history. A negative linear relationship is yielded ($r = -0.50$, $p < 0.05$).