Original Article

Abnormal Variations in the Facial Soft Tissues of Adult Uremic Patients on Chronic Dialysis

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Abstract: Renal osteodystrophy is a common complication of uremic patients, mainly when they are in long-term regular dialysis treatment. The craniofacial skeleton is one of the peculiar targets of renal osteodystrophy, the more dramatic pattern of which is a form of leontiasis. To assess facial deformities in uremic conditions and to understand the possible relation with hyperparathyroidism, the three-dimensional coordinates of 50 soft tissue facial landmarks were obtained by an electromagnetic digitizer in 10 male and 10 female patients (aged 53–81 years) with chronic renal insufficiency and regular dialysis treatment. Similar three-dimensional coordinates were also collected for 34 healthy individuals of the same age, ethnicity, and sex. From the landmarks, facial distances, angles, and volumes were calculated according to a geometrical model of the face. Data were compared with those collected in the normal subjects by computing z-scores. Facial volumes of the chronic renal insufficiency patients were significantly larger than those of the control subjects. The increment was particularly evident in the facial middle third (maxilla), leading to a significant inversion of the mandibular-to-maxillary ratio. The lips tended to be more prominent (reduced interlabial angle). Some of these facial modifications (facial and nose height, maxillary dimensions, mandibular shape) were significantly related to the clinical characteristics of the patients (duration of renal insufficiency, duration of dialysis, parathormone (PTH) plasma levels). In regular dialysis treatment, some of the facial modifications are related to hyperparathyroidism, which supports the need for a strict metabolic control also in the early phase of uremia. (*Angle Orthod* 2005;75:320–325.)

Key Words: Face; Anthropometry; Soft tissues; Renal osteodystrophy; PTH; Uremia

INTRODUCTION

Renal osteodystrophy is a condition affecting patients with a chronically impaired renal function.[1–3] In these patients, regular dialysis treatment can only partly compensate for the lost physiological function, and several biochemical and hormonal modifications occur. Among them, hyperphosphatemia, hypocalcemia, and low plasma levels of calcitriol play a key role in conditioning renal osteodystrophy.[1–3] High bone turnover, due to elevated parathormone (PTH) plasma levels (a condition known as secondary hyperparathyroidism), and osteomalacia, due to a mineralization defect, can often be present. These modifications in bone metabolism provoke morphological changes in the skeleton, leading even to macroscopic bone deformities.[1–3]

Osteodystrophy involves numerous body districts, and it can also be observed in the craniofacial skeleton. Several reports underlined the relevant clinical signs, radiological appearances, and pathological features.[1–4] One of the extreme manifestations of this condition involves the progressive hypertrophy of the craniofacial bones, leading to a form of leontiasis ossea.[2] Literature reports on uremic leontiasis ossea are scanty, but maxillary and mandibular hypertrophy with increased palatal dimensions, a flattening of the nasal bridge together with a widening of the nares, and prominent cheek bones have all been described in these patients.[2] Recently, Schmidt et al[3] reported that neither the incidence of uremic leontiasis ossea nor subclinical craniofacial hypertrophy in uremic patients is established. The modifications of the facial skeleton will involve also its soft tissue covering, with an alteration in the appearance of the patient.

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TABLE 1. Analyzed Patients[a]

Patient	Age, y	Weight, kg	Height, cm	RI, y	Dialysis, mo	Δkg, kg	PTH, pg/mL
Women							
F01	53.4	60	165	15	48	2.0	787
F02	53.5	52	160	13	120	4.0	559
F03	61.0	82	158	4	16	3.5	277
F04	63.4	47	153	6	60	1.5	805
F05	65.1	48	149	9	108	4.0	799
F06	65.6	66	142	4	24	3.5	41
F07	68.0	52	148	24	264	3.0	502
F08	69.9	63	163	10	84	5.0	300
F09	77.7	58	153	29	144	3.0	256
F10	81.0	48	161	7	84	2.7	507
Mean	65.9	57.6	155.2	12.1	95.2	3.2	483.3
SD	9.0	10.9	7.4	8.5	72.0	1.0	263.6
Men							
M01	64.3	70	172	9	7	3.0	111
M02	66.3	66	184	20	156	4.5	500
M03	66.3	55	164	12	144	4.0	652
M04	66.4	67	168	5	60	3.0	560
M05	67.6	73	174	28	120	3.5	263
M06	68.4	74	171	10	6	2.0	71
M07	71.9	65	165	3	24	3.0	143
M08	71.9	80	155	1	11	4.0	87
M09	74.6	70	162	6	14	3.3	844
M10	80.3	60	158	6	14	2.0	205
Mean	69.8	68.0	167.3	10.0	55.6	3.2	343.6
SD	4.9	7.2	8.5	8.3	60.9	0.8	274.3

[a] RI: duration of renal insufficiency; dialysis: duration of hemodialysis; Δkg: average variation of body weight between dialyses; PTH: mean parathormone levels in the previous 12 months.

analysis systems for indirect computerized facial anthropometry including stereophotogrammetry, laser scanning, range cameras, optoelectronic instruments, and electromagnetic digitizers.[5–12] In addition, ultrasonography allows facial anthropometry to be performed even during intrauterine life.[13,14] These instruments provide the three-dimensional coordinates of selected landmarks, and euclidean geometric calculations can be used to obtain three-dimensional linear distances of selected facial structures, as well as facial areas and volumes.[5–10,12,15]

The quantitative assessment of craniofacial variations is commonly used for the characterization of diseased subjects.[6,7,9–11,16,17] To the best of our knowledge, no previous study quantitatively assessed the soft tissue facial structure of uremic patients without or with leontiasis ossea.

In the present study, the facial soft tissues of a group of patients with chronic renal insufficiency with regular dialysis treatment were measured in three-dimensional space with a computerized digitizer, and their facial dimensions (linear distances, ratios, angles, volumes) calculated and compared with a reference normal population by using z-scores.

MATERIALS AND METHODS

Patients

Data on 20 patients with chronic renal insufficiency (10 males, 10 females; aged 53–81 years) were collected in the present study (Table 1). All patients were Caucasian (northern Italians) and were under treatment at the Dialysis Unit of San Paolo Hospital (Milan). All were in a clinical stable condition during at least the last two years before evaluation, and no patient had received craniofacial surgical procedures. Patients were selected for enrollment according to the degree of hyperparathyroidism. Ten of them had serum intact parathormone (iPTH) lower than 300 pg/mL (mean 175.4, SD 96.0), whereas the remaining had serum iPTH higher than 500 pg/mL (mean 651.5, SD 142.9) (mean of the last one year of observation). Plasma iPTH levels were measured with the IRMA assay (Nichols Institute Diagnostic, San Juan Capistrano, Calif), which has a reference range of 15–65 pg/mL. Normal parathyroid status, for the uremic population, was considered for PTH <300 pg/mL. Hyperparathyroidism status was considered for PTH values >500 pg/mL.

All facial measurements were collected on the patients during the day after a dialysis procedure. Reference data were collected on 34 normal subjects (12 males, 22 females) of the same ethnic group and age. The normal subjects were either staff or relatives of the laboratory staff. No subjects with a previous history of craniofacial trauma or congenital anomalies were included in the reference group. All the analyzed individuals gave their informed consent to the experiment.

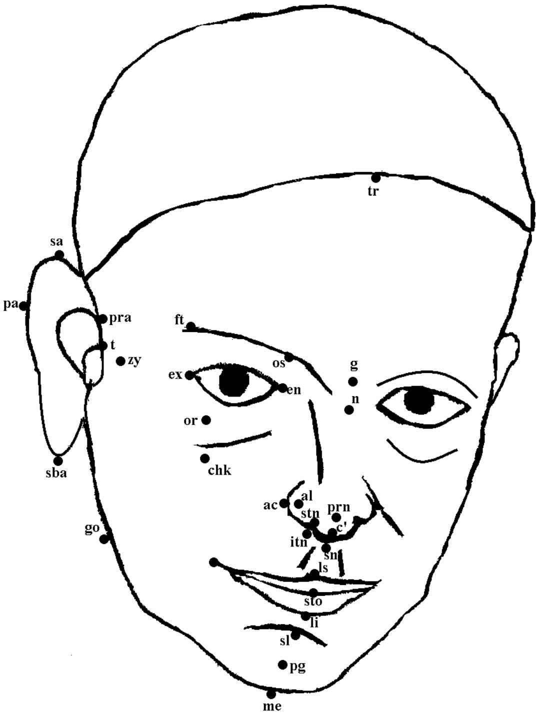

FIGURE 1. Soft tissue facial landmarks digitized on all patients. (a) Midline landmarks: tr, trichion; g, glabella; n, nasion; prn, pronasale; c′, columella; sn, subnasale; ls, labiale superius; sto, stomion; li, labiale inferius; sl, sublabiale; pg, pogonion; me, menton. (b) Paired landmarks (right and left side noted r and l): ex$_r$, ex$_l$, exocanthion; en$_r$, en$_l$, endocanthion; os$_r$, os$_l$, orbitale superius; or$_r$, or$_l$, orbitale; ft$_r$, ft$_l$, frontotemporale; chk$_r$, chk$_l$, cheek; zy$_r$, zy$_l$, zygion; t$_r$, t$_l$, tragion; al$_r$, al$_l$, alare; ac$_r$, ac$_l$, nasal alar crest; itn$_r$, itn$_l$, inferior point of the nostril axis; stn$_r$, stn$_l$, superior point of the nostril axis; cph$_r$, cph$_l$, crista philtri; ch$_r$, ch$_l$, cheilion; t$_r$, t$_l$, tragion; go$_r$, go$_l$, gonion; pra$_r$, pra$_l$, preaurale; sa$_r$, sa$_l$, superaurale; pa$_r$, pa$_l$, postaurale; sba$_r$, sba$_l$, subaurale.

Collection of three-dimensional facial landmarks

The data collection procedure was done in two separate steps and was followed by off-line calculations.[8,9,18] Initially, a single experienced operator located a set of 50 soft tissue landmarks for each subject by inspection or palpation (or both) and marked them on the cutaneous surface using an eyeliner. The subjects sat relaxed in a position suitable for a correct identification of facial features. A total of 50 soft tissue landmarks were collected, which are identified in Figure 1.[18] Midlandmarks were also mathematically derived as the midpoint between two homologous landmarks, and noted as landmark$_m$.

In the second step, the three-dimensional coordinates of the facial landmarks were obtained with a computerized electromagnetic digitizer (3Draw, Polhemus Inc, Colchester, Vt). During data collection, the subjects sat in a natural head position in a wooden chair, with the head fixed to the chair back by a wooden and foam headframe. They were asked to close their eyes, to keep their teeth in contact (centric occlusion), and to not move for the duration of the data collection.[8] Using the instrument stylus, a single operator digitized the marked landmarks according to a standardized sequence devised to reduce data collection time while the subjects sat motionless. Data collection took approximately one minute. The files of the three-dimensional (x, y, z) coordinates were obtained and stored on magnetic media. The subject was dismissed. Subsequently, computer programs devised and written by one of the authors were used for all the subsequent off-line calculations.

The reproducibility of landmark identification, marker positioning, and data collection procedure were previously reported and found to be reliable, with Dahlberg's errors on 50 landmarks of 1.20 mm (men) and 0.95 mm (women), corresponding to 1.04% and 1.05% of the relevant nasion-midtragion distances (n-t$_m$).[8]

Data analysis

The x, y, z coordinates of the landmarks obtained on each subject were used to calculate the following: facial distances (mm), angles (°), volumes (cm^3), and ratio (%) according to the geometric models of the face defined by Ferrario et al.[8,9,15,18]

- Distances: face height (n-pg), nose height (n-sn), lower face height (sn-pg), mandibular ramus height (t$_m$-go$_m$), skull base width (t$_r$-t$_l$), width of the mandible (go$_r$-go$_l$), nose width (al$_r$-al$_l$), alar base width (ac$_r$-ac$_l$), upper face depth (n-t$_m$), midface depth (sn-t$_m$), mandibular corpus length (pg-go$_m$);
- Angles: facial convexity excluding the nose (n-sn-pg), mandibular corpus convexity in the horizontal plane (go$_r$-pg-go$_l$), right and left gonial angles (t$_r$-go$_r$-pg, t$_l$-go$_l$-pg), nasolabial angle (prn-sn-ls), interlabial angle [(sn-ls)-(li-sl)];
- Volumes: total facial volume, volumes of the nose, middle (maxilla) and lower (mandible) facial thirds.[15] The volumes were computed as the sum of several tetrahedra, with the 50 landmarks serving as nodes (vertices of the tetrahedra). Total facial volume: all the facial structures from the external cutaneous surface up to a quasifrontal plane passing through the trichion, the tragi, and the gonia; nasal volume: approximated from the volumes of two tetrahedra—the first tetrahedron had the plane ac$_r$, ac$_l$, prn as its base and vertex in n, and the second had the same base and vertex in sn; maxillary volume: comprised between a quasihorizontal plane passing through the tragi and the exocanthia and a plane connecting the cheilion landmarks and the tragi, approximately corresponding to the maxilla, cheek, and nose; mandibular volume: extending up to the plane connecting the gonia and the gnation, and corresponding to the mandible; ratio of mandibular to maxillary volume.

Statistical calculations

Women were divided into two age groups: younger (six patients, 15 normal women) or older (four patients, seven

TABLE 2. Descriptive Statistics of z-scores Computed in the Uremic Patients

Variable	Mean	SD	P^a
Distances			
n-pg	0.279	1.635	NS
n-sn	1.250	2.406	.035
sn-pg	−0.200	1.170	NS
t_m-go_m	0.988	1.424	.007
t_r-t_l	0.443	0.755	.019
go_r-go_l	0.458	1.490	NS
al_r-al_l	0.934	1.509	.014
ac_r-ac_l	0.843	1.511	.025
n-t_m	0.249	0.773	NS
sn-t_m	0.766	1.338	.022
pg-go_m	0.173	1.534	NS
Volumes			
Face	2.191	0.921	<.001
Nose	0.753	1.561	.049
Maxilla	4.140	1.598	<.001
Mandible	0.494	0.867	.022
Mand/Max	−1.833	1.068	<.001
Angles			
n-sn-pg	−0.339	1.766	NS
go_r-pg-go_l	0.333	1.932	NS
t_r-go_r-pg	−0.142	1.601	NS
t_l-go_l-pg	−0.177	1.339	NS
pm-sn-ls	−0.264	1.875	NS
(sn-ls)-(li-sl)	−0.649	1.545	NS

[a] *P*, probability level of paired Student's *t*-tests; NS, not significant ($P > .05$).

normal women) than 66 years of age. Men were analyzed as a single group (10 patients, 12 normal men). Individual measurements obtained in the 20 patients were transformed to z-scores by subtracting from each value its sex and age reference mean value and dividing by the relevant reference standard deviation.[9,16,17] Descriptive statistics (mean and standard deviation) were computed for the values of the z-scores.

Statistical comparisons were performed by paired Student's *t*-tests (null hypothesis: the z-scores should be zero if facial dimensions in uremic patients do not differ from the those in reference population. The alternative hypothesis: z-scores significantly different from zero). Correlation analyses were performed between individual characteristics and the z-scores of the anthropometric measurements. For all analyses, $P \leq .05$ was considered significant.

RESULTS

In the present group of uremic patients, all the mean z-scores of the linear distances (except lower face height) were larger than in the reference subjects (Table 2). The z-scores were significantly different from zero in half the measurements. Overall, facial height (nose, mandibular ramus), width (skull base, nose), and depth (midface) increased 0.44–1.25 times in comparison with healthy, normal individuals of comparable age and of the same sex.

TABLE 3. Significant Linear Correlation Analyses Between Patient Characteristics and Anthropometric Variables

	Age	RI[a]	Dialysis	PTH
Distances				
n-pg	−0.472*	0.468*		
n-sn				0.560*
sn-pg				0.447*
pg-go_m	0.512*			
Volumes				
Maxilla		0.467*	0.517*	
Mand/Max		0.490*	0.636**	
Angles				
go_r-pg-go_l		0.455*		
t_r-go_r-pg	0.607**	0.528*	0.465*	0.444*
t_l-go_l-pg	0.468*	0.471*		

[a] RI indicates renal insufficiency. PTH: parathormone levels.

* $P < .05$; ** $P < .01$.

All facial volumes were significantly larger in the patients than in the reference subjects, and the largest difference was found for the maxillary volume. The ratio of mandibular to maxillary volume was significantly reduced in all patient groups.

Five of the measured facial angles tended to be reduced (more acute) in the uremic patients, whereas the mandibular corpus convexity in the horizontal plane was increased. On no occasion were the z-scores significantly different from zero.

Some significant linear correlations were found between patient characteristics and the anthropometric variables (Table 3). In particular, a longer duration of renal insufficiency was related to a longer facial height, a larger maxillary volume, a more different mandible-to-maxilla volume ratio, and a differently shaped mandible (convexity in the horizontal plane, gonial angles). A similar trend was found for nose height, where the duration of renal insufficiency explained about 19% of its variability. A longer history of regular dialysis treatment had nearly the same correlations.

Higher iPTH levels significantly correlated with a longer nose, an increased facial lower third, and a larger right side gonial angle. In addition, calendar age was related to face height (an inverse relationship), mandibular corpus length, and both gonial angles.

DISCUSSION

Anthropometry gives an objective aid to the qualitative appraisal of soft tissue anatomy of the head and face, supplying the clinician with useful indications about the anatomical structures and regions that differ the most from the norm.[6,7,9–11,16,17]

In the present study, a three-dimensional, noninvasive system allowed a fast (in less than one minute of data collection, one subject's complete set of data are available offline in 10 minutes), low-cost, and quantitative analysis of the soft tissue facial characteristics in a group of adult uremic patients on regular dialysis treatment. Indeed, soft tissues can be studied with noninvasive methods, and the assessments can be performed frequently without any additional biological burden to the patients.[8]

Notwithstanding the substantial skeletal modifications found in patients with an impaired renal function,[1–3] which can lead to massive modifications even in facial appearance,[2] quantitative assessments of the overlying soft tissue morphology have been sparingly performed. In particular, until now, no detailed analyses of the variations in facial dimensions and shape in adult uremic patients have been published.

The soft tissue data collected on the present group of patients were compared with the values obtained in normal subjects of the same age, sex, and ethnic group by calculating z-scores. The use of z-scores allows to standardize data collected on individuals of different sex and age and to deal with a single group of patients in the assessment of statistical significances.[9,17]

Overall, the chronic renal insufficiency patients had larger, wider, and deeper faces than their normal peers. Although the standardized differences were only partly significant when single distances (height, width, depth) were considered, the analysis of global values (volumes) reached the statistical significance on all occasions.

Probably, the three-dimensional assessment of volume magnified the tendency of larger facial dimensions, where the interindividual variability prevented the assessment of a statistical significance. The increment in facial dimensions was particularly evident in the facial middle third (maxilla), leading to a significant inversion of the mandibular-to-maxillary ratio. The larger maxilla was accompanied by a tendency to more prominent lips (reduced interlabial angle). Some of these facial modifications (facial and nose height, maxillary dimensions, mandibular shape) were significantly related to the clinical characteristics of the patients (duration of renal insufficiency, duration of dialysis, iPTH levels).

The present data are difficult to compare with previous reports because literature references on the modifications of facial structures during chronic renal insufficiency deal mainly with the radiological appearance,[1–4] and the extreme manifestation of leontiasis ossea seems to have been described in only nine patients.[2,3] Cutaneous alterations, a common problem in uremic patients,[19] have been described only on a pathological base.

Overall, the key macroscopic features of leontiasis ossea, as described by Lee et al[2] and found in the patients in the present study, include a maxillary and mandibular skeletal hypertrophy as well as prominent cheek bones, and these features are significantly related to the soft tissue appearance. Increased palatal dimensions may explain the more prominent lips. The widening of the nostrils is directly measured by the significantly increased soft tissue nose width.

Lee et al[2] reported that sex, race, age, length of dialysis treatment, or of the renal insufficiency did not seem to be predictive factors for the development of leontiasis ossea. In contrast, we did not assess patients with a fully developed alteration of the craniofacial skeleton but subjects who may be at risk of developing this further complication of their principal disease. In the patients in the present study, significant correlations were found between the anthropometric variables and the duration of the clinical history (renal insufficiency and dialysis), as well as the anthropometric variables and the mean levels of iPTH. These relationships were found in both the maxilla and the mandible (chin and gonial angle). The effect of race could not be assessed because all patients were of the same ethnic group. Age and sex were removed from the analysis by using the z-scores. Nevertheless, between 50 and 80 years of age some significant modification in mandibular morphology was found. These age-related trends were in the same direction as those apparently provoked by the clinical history of the patients and should be analyzed in detail in a future investigation.

Among the limitation of the present study, it has to be mentioned that facial volumes were obtained from a geometrical model of face where only some discrete landmarks have been sampled, and the surfaces between contiguous landmarks that are actually curved have been approximated by linear planes. Therefore, the calculations cannot provide the actual anatomical measurements but only an approximation of their values.[15] Nevertheless, the same approximation was used for both the patients and the reference subjects, and only the difference between the two values was considered. Furthermore, the method has been used in our laboratory for approximately a decade with valuable results.[15]

In addition, the patients in the study represent a convenience sample, and the results must be considered with caution. Only further investigations performed on larger groups of patients may allow a deeper insight into the facial appearance of uremic subjects.

In conclusion, the method used in the current investigation allowed a simple, low-cost, fast, and noninvasive examination of the patients and provided a quantitative assessment of the standardized deviation from the norm to be used also on a longitudinal base. We believe that the method could be profitably used to assess the modifications of the facial structures in uremic patients even before the development of manifest clinical signs of renal osteodystrophy, thus allowing a finer monitoring of the additional burdens experienced by them.

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