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ANTHROPOMETRIC CHARACTERIZATION OF PATIENTS WITH ACROMEGALY IN CROATIA – ESTIMATING STATURE FROM HAND LENGTH

ABSTRACT: Acromegaly is a rare disfiguring disease caused by hypersecretion of the growth hormone from the pituitary adenomas. Body proportions, including bones of the hand, have been widely used to estimate anthropometric measures, such as stature.
The main aim of this study was to compare stature, hand length, and stature/hand length ratio in healthy and patients with acromegaly and evaluate the accuracy of using hand length for the estimation of stature in patients with acromegaly.
A total of 44 patients with acromegaly were analyzed in comparison to the control group of 8944 phenotypically healthy individuals. Measurement data were analyzed using parametric and nonparametric tests, linear categorical regression (in healthy populations, and ordinal regression (in patients with acromegaly).
The results show that the criterion stature could be predicted with hand length in both male and female individuals with acromegaly, while the amount of variance explained is something higher in males. Both in males and females, the stature/hand length ratio is higher in healthy individuals-compared to acromegalic ones.
This information might be of use to endocrinologists, rheumatologists, forensic scientist as well as in research where anthropometric characterization is performed. Namely, stature estimation could be assessed inaccurately if acromegalic patients are included in the sample.

KEY WORDS: Anthropometric measurements – Acromegaly – Hand length – Estimation of stature

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INTRODUCTION

Word "*acromegaly*" is derived from the Greek words "*akros*", extremities, and "*megas*", big (Chanson, Salenave 2008). This name was suggested by Pierre Marie who published the first description of the disease and its pathology in 1886. Acromegaly is a rare disease caused by hypersecretion of the growth hormone from the pituitary adenomas resulting in somatic overgrowth, multiple comorbidities, physical disfigurement, and increased mortality (Vilar *et al.* 2017). The incidence of acromegaly is approximately 3 cases per 1 million persons per year, and the prevalence is 40 to 70 cases per million inhabitants (Chanson, Salenave 2008). Acromegaly can affect patients of both sexes equally and the average age at diagnosis ranges from 40 to 50 years, with only rare cases (up to 5%) of onset under the age 20 (Holdaway, Rajasoory 1999).

Clinical presentation of acromegaly ranges from subtle signs of acral overgrowth, soft-tissue swelling, arthralgias, jaw prognathism, mild hyperglycemia, hyperhidrosis to facial and skeletal disfigurement, florid osteoarthritis, severe headache, sleep apnea, severe hypertension, diabetic ketoacidosis, and respiratory and cardiac failure (Vilar *et al.* 2017). Earlier reports showed that growth hormone (GH) has a major position in remodeling of the skeleton through metabolic functions (Ohlsson *et al.* 1998, Ueland 2005). Its main influence on bone is based on stimulation of osteoblasts (Mohan, Baylink 1999). Earlier reports (Florini *et al.* 1996, Ohlsson *et al.* 1998) reveal the anabolic effects of the growth hormone on different tissues including muscles and bone. Analysis by Kamenicky (2011) reported that the excess of the growth hormone is associated with increased activity of the epithelial sodium channel, and this could contribute to the volume expansion and soft tissue manifestations seen in acromegaly. Ohlsson *et al.* (1998) suggested that patients with growth hormone deficiency are great models to show how growth hormone is important in longitudinal bone growth. Changes in bone of acromegalic patients include increased bone formation at periostal and endocortical surfaces, increased width of both the outer and inner cortical lamellae confirmed by iliac crest bone biopsies (Halse *et al.* 1981). Consequences of high serum concentration of GH and insulin like growth factor-1 (IGF-1) are somatic disfigurement and striking changes are observed in the enlargement of hands, feet, and fingers that are thickened, widened and stubby (Molitch, 1992, Melmed, 2002, Chanson, Salenave, 2008, Matovinović, Vrkljan, 2004).

It is not always possible to obtain stature measurement for patients and alternative anthropometric indicators have been developed to draw inferences about patient stature. The method for calculating the stature through the mathematical regression coefficients were obtained from the measurements of different bones following the criterion of Karaman (2008). Studies from Bhatnagar *et al.* (1984), Abdel-Malek *et al.* (1990), and Jindal *et al.* (1992) revealed that body proportions and the dimensions of different body segments, including the bones of the hand have been widely used to estimate stature. Hand length is easier to measure than ulna length or knee stature, it is more accessible, its measurement requires a minimum of motion and cooperation by the individual and can be obtained without the necessity of mobilizing the patient (Guerra *et al.* 2014). It has also been studied and used in forensic and legal medicine (Agnihotri *et al.* 2008).

According to De-Mendonca (2000), each population group needs a population-specific formula for deriving information on stature from bone length, due to inherent variations that may be ascribed to genetic and environmental factors such as climate, lifestyle and nutrition. Different studies demonstrated the ability to assess stature from hand dimensions in healthy populations in different countries (Ishak *et al.* 2012, Numan *et al.* 2013, Sanli *et al.* 2005, Krishan, Sharma 2007, Habib, Kamal 2010). However, in previous studies on acromegalic patients a quantitative confirmation of changes in proportions of hand to stature has not been found in Croatia.

The aim of this study was to evaluate the accuracy of using hand length for the estimation of stature in patients with acromegaly. More precisely, the goal of this study was (a) to compare stature, hand length and stature/hand length ratio in healthy and in patients with acromegaly for males, (b) to examine the correlations between stature and hand length between patients with acromegaly and healthy patients, for both males and females, (c) to forecast the results in the criterion stature, with hand length as a predictor, between patients with acromegaly and healthy patients, for both males and females separately.

SAMPLE AND METHODS

The database of the Croatian Center for Clinical Neuroendocrinology and Pituitary Diseases at the "Sestre milosrdnice" University Hospital Centre,

University of Zagreb was analyzed. In total, 44 patients (23 female and 21 male), aged 23 to 77 with acromegaly in the period from 2004 to 2007 were collected as a part of the Ph.D. thesis "Biomechanics of hand in patients with acromegaly" during the project "Replacement therapy in patients with pituitary tumor" (Osvatić Matovinović 2010) which was supported by the Ministry of science, education and sports in Croatia, number 0134008. The group with acromegaly and the control group did not differ significantly with regard to age. The mean age of the patients with acromegaly was 47,98 years and the mean age of the control group was 48,37 years.

They represent 6.3% of the estimated total number of acromegalic patients in Croatia (693) taking into account the incidence rate of three acromegalic patients per year per million people according to Holdaway and Rajasoorya (1999).

The patients' age (years) and stature (cm) were recorded. The stature of the patient was measured in a standing anatomical position between the vertex and the floor, using a standing stature measuring instrument.

According to Giustina *et al.* (2011), the diagnoses were based on typical clinical acromegalic features and were confirmed by the elevation of plasma IGF-1 in combination with a failure to suppress GH on oral glucose tolerance test, and/or an elevated basal GH level and the identification of a pituitary mass on magnetic resonance imaging or computed tomography.

The reference range for GH was 0.0–5.0 ng/mL and for IGF-1 115–420 ng/mL. Electrochemiluminescence immunoassay was used for the measurement of GH, and IGF-1.

The method according to Visnapuu and Jürimäe (2007) was used for the measurement of hand length.

The patients were asked to be seated and to spread and stretch out their right hand onto a paper on the table. The contour of the hand was drawn on the paper by one examiner. The hand length is measured from the mid-point below the radial and ulnar tuberosity to the tip of the middle finger.

This study was approved by the Ethics Board of the School of Medicine, Zagreb, Croatia. Written informed consent was obtained from the patients.

The results from the national 'Croatian Anthropometric System Study' were used as a comparison (4854 females and 4090 males), aged 18 to 96, which was conducted as a technological project entitled "Garment production process improvement" at the Faculty of Textile Technology, and was supported by the Croatian Ministry of Science, Education and Sports which results are published by Ujević (2006a), Ujević (2006b), and Ujević (2006c).

STATISTICAL ANALYSES

In data analysis, both parametric and nonparametric tests were used. In spite of the small sample size, the distribution of acromegalic males and females followed a normal distribution (hand length, stature/hand length ratio and stature, Kolmogorov-Smirnov test). Hence, the t-test with consideration regarding differences in sample size was used in analyzing the differences among healthy males and females in those three variables. Spearman's rank correlation coefficient was used in analyzing acromegalic samples, while Pearson's rank correlation coefficient was used for the analyses of the healthy population. Fisher Z was used in the comparison among the values of correlation coefficients. Finally, linear categorical regression (CATREG) was used when predicting body stature in healthy individuals, while the ordinal regression was used for the same analysis for acromegalic individuals. All data were analyzed using IBM SPSS 20.0 statistical software, with significance level of $p<0.05$ and $p<0.01$.

RESULTS

When stature was compared between healthy and patients with acromegaly of males (with Wald's 95% confidence level, confidence interval (CI) of difference was -6.71 <-6.22< -5.73), the value of the t-test (24.812; df=37.2; $p<0.01$) indicated that males patients with acromegaly had higher average stature. When hand length was compared between healthy males and in patients with acromegaly (with Wald's confidence level 95%, CI of difference was –3.49 <-3.07< -2.65) the value of the t-test (14.299; df=19.8; $p<0.01$) indicated that males with acromegaly had higher average hand length. When the stature/hand length ratio between healthy and males with acromegaly was compared (with Wald's 95% confidence level, CI of difference was 0.77 <0.95< 1.13) the value of the t-test (10.228; df=19.8; $p<0.01$) indicated the stature/hand length ratio was higher in healthy individuals (*Table 1*).

When stature was compared between healthy and females with acromegaly (with Wald's 95% confidence level, confidence interval (CI) of difference was -6.51 <-3.62< -0.73) the value of the t-test (2.458; df=21.7; $p<0.05$) indicated that females with acromegaly had

higher average stature. When hand length was compared between healthy and females with acromegaly (with Wald's 95% confidence level, CI of difference was -3.07 <-2.61< -2.15) the value of the t-test (11.108; df=21.7; p<0.01) indicated that females with acromegaly had higher average hand length. When the stature/hand length ratio between healthy and females with acromegaly was compared (with Wald's 95% confidence level, CI of difference was 0.80 <0.96< 1.12) the value of the t-test (11.58; df=21.9; p<0.01) indicated the stature/hand length ratio was higher in healthy individuals (*Table 1*).

Thereafter, the correlations between stature and hand length were examined, separately for acromegalic and healthy samples, and for males and females. In males with acromegaly, the correlation between stature and hand length was not statistically significant (Rho=0.378; p>0.05), but in healthy males the same correlation was significant (r=0.467; p<0.01). Due to different sample sizes, the difference between correlation coefficients was calculated, but it was not statistically significant (Fisher Z=-0.46; p>0.05). In acromegalic females, the correlation between stature and hand length was statistically significant (Rho=0.525; p<0.01), and in healthy females the same correlation was significant as well (r=0.463; p<0.01). Due to different sample sizes, the difference between correlation coefficients was calculated, but it was not statistically significant (Fisher Z=-0.37; p>0.05).

In both female and male patients with acromegaly, the criterion stature was found to be predicted by hand length. Both regression coefficients were statistically significant at the level p<0.01, while the amount of variance explained was somewhat higher in males (*Table 2*).

In healthy males and females, the criterion stature can be predicted by hand length. Both regression coefficients are statistically significant at the level p<0.01, while the amount of variance explained is similar in males and females.

When comparing the regressions in healthy men and women (from general Croatian population) and patients with acromegaly, it's obvious that both predictions of the criterion stature based on hand length are statistically significant, but the amount of variance explained is much higher in patients with acromegaly. Hence, a much higher positive correlation between stature and hand length was found in patients with acromegaly (*Table 2*), as compared with the general population (*Table 3*).

DISCUSSION

The main goal of this research was the anthropometric characterization of patients with acromegaly in Croatia and the estimation of the accuracy of using hand length for the estimation of stature in patients with acromegaly. Anthropometric characterization is extensively being used

TABLE 1: Descriptive statistics for healthy/patients with acromegaly males and females (hand length, stature and ratio). *Samples used for this analysis were provided by Ujević (2006a), Ujević (2006b), and Ujević (2006c) from the 'Croatian Anthropometric System Study' which was part of a technological project entitled "Garment production process improvement" at the Faculty of Textile Technology, and was supported by the Croatian Ministry of Science, Education, and Sports (project number 0117013).

Acromegaly	Males (N=21)	Females (N=23)
	Mean ± Std.Dev.	Mean ± Std.Dev.
hand length	22.729±0.980	20.748±1.122
ratio stature/hand length	8.018±0.425	8.048±0.397
stature	182.048±8.896	166.696±7.048
Healthy*	Males (N=4090)	Females (N=4854)
	Mean ± Std.Dev.	Mean ± Std.Dev.
hand length	19.656±0.020	18.142±0.016
ratio stature/hand length	8.97±0.008	9.01±0.007
stature	175.829±0.131	163.073±0.107

TABLE 2: Predicting stature (criterion) on the base of hand length (predictor) in patients with acromegaly (females and males). Legend: * P< 0.01, P< 0.05. Note: Adjusted R-coefficient is showed in the table.

Females with acromegaly	**Beta**	**F-test**	**Std. Error**
Predictor – Hand length	0.671	5.185[1]	0.170
Criterion – Stature	R=0.671; R^2=0.450; F(3, 19)=5.185*		
Males with acromegaly	**Beta**	**F-test**	**Std. Error**
Predictor – Hand length	0.815	37.602*	0.133
Criterion – Stature	R=0.647; R^2=0.664; F(1, 19)=37.602*		

in anthropological research to infer the biological structure of populations, to examine the degree and type of morphological variations among them, and to provide information on their biological microevolution and their social and cultural features (Rudan *et al.* 1986, 1992, 1994, Smolej-Narančić *et al.* 1987, 1994, Zajc Petranović *et al.* 2014, Pribačić Ambrožić *et al.* 2015, Novokmet *et al.* 2018). More specifically, the prediction of body stature (stature) from hand length has been in the focus of numerous earlier studies (Sanli *et al.* 2005, Krishan *et al.* 2007, Habib, Kamal 2010, Ishak *et al.* 2012, Numan *et al.* 2013).

In our comparative sample of healthy individuals, males showed higher mean values in stature as well as hand length, when compared to women, which was consistent with previous publications (Agnihotri *et al.* 2008, Ilayperuma *et al.* 2009, Rastogi *et al.* 2008, Numan *et al.* 2013). When comparing stature and hand length in healthy patients with acromegaly females and males, females and males with acromegaly had a higher than average stature and hand length. These results could be expected given the fact that the hand length in patients with acromegaly was higher than in generally healthy individuals due to increased soft tissues and bone formation at periosteal and endocortical surfaces in patients with acromegaly (Kamenicky *et al.* 2011, Halse *et al.* 1981). Studies by Colao *et al.* (2003) and Wassenaar *et al.* (2011) also showed that patients with acromegaly had irreversible changes in bone, cartilage, and joints as the main feature of the disease.

In males and females, the stature/hand length ratio was higher in healthy individuals compared to acromegalic ones. If some change in the extremities occurs (as we have particularly investigated the measure of the hand), one would assume that the harmonic relationships will be changed. Therefore, we calculated the hand length and stature ratio in healthy Croatian individuals and in individuals with acromegaly. Our results revealed a difference in this ratio, which tends to be lower in individuals with acromegaly compared to healthy individuals. The lower ratio may implicate the higher level of disturbances in individuals with acromegaly.

Our results suggest that the criterion stature could be predicted with hand length both in male and female patients with acromegaly, while the amount of variance explained is something higher in males. This difference could be explained in terms of different stages in the development of acromegalia in men and women. In healthy males and females, the criterion stature could also be predicted by hand length (the amount of variance explained is similar in males and females). We ascertained that in our healthy population stature predicting is statistically significant and these results were in accordance with the studies of Ishak *et al.* (2012), Numan *et al.* (2013), Habib and Kamal (2010), Agnihotri *et al.* (2008), Ilayperuma *et al.* (2009), Rastogi *et al.* (2008), and Krishan *et al.* (2012), who showed a positive correlation between stature and hand anthropometric dimensions in different populations and offered regression equations. In both sexes, the amount of variance explained in regression equations was higher in patients with acromegaly, than in a healthy population. In other words, the (lower) ratio between body stature and hand length could be a strong indicator of acromegaly.

The difference in correlation coefficients in healthy and individuals with acromegaly between stature and hand length was not significant, both in males and females. Due to the small number of patients with acromegaly, it was expected that there were no statistically significant differences in correlation coefficients between stature and hand length, neither in healthy/females with acromegaly nor in healthy/males with acromegaly. There were tendencies of higher correlations observed both in

TABLE 3: Predicting stature (criterion) on the base of hand length (predictor) in healthy participants (females and males). Legend: * P < 0.01, P < 0.05.

Females – healthy	**Beta**	**F-test**	**Std. Error**
Predictor – Hand length	0.463	1325.704*	6.641
Criterion – Stature	R=0.463; R^2 =0.215; F(1,4852) =1325.704*		
Males – healthy	**Beta**	**F-test**	**Std. Error**
Predictor – Hand length	0.467	1138.345*	7.395
Criterion – Stature	R=0.467; R^2 =0.218; F(1, 4088)=1138.345*		

females with acromegaly and healthy males when compared with healthy females and acromegalic individuals, respectively. However, seeking potential reasons for these differences was beyond the scope of our study. The straightforward explanation might be that the observed differences in correlations reflect different tendencies in healthy/females and males with acromegaly.

The most important observation of this study is the higher length of hand and the lower stature/hand length ratio in patients with acromegaly, which could be used as an indicator of the presence of acromegaly disease in average healthy populations. This information might be of use to endocrinologists and rheumatologists in evaluating the progress of rehabilitation programs due to the knowledge of irreversible changes in bone, cartilage, and joint suggested by Colao *et al.* (2003), Wassenaar *et al.* (2011) and at least partial reversible change of soft tissue in controlled disease as presented by Ben-Shlomo and Melmed (2006). Additionally, since the estimation of stature is one of the key anthropometric measurements in general and is used in numerous anthropological, forensic, and epidemiological studies, it needs to be considered that the stature estimation could be assessed inaccurately if individuals with acromegaly are included in the sample. The estimation of stature based on hand length would in that case be overestimated. The assessment will be wrong, on the one hand, due to vertebral fractures, most often in the thoracolumbar region, on the other hand, due to the greater length of the hand due to the increase and thickening of the final phalanges of the hand, which become hypertrophied. (Melmed 2002, Molitch 1992, Chanson, Salenave 2008).Therefore, based only on the length of the hand or the length of the finger, the body height will be wrongly estimated, people with acromegaly will be shorter than it would be estimated based on the length of the hand. Observations can come in handy to forensic scientists, and anthropologists. In daily practice, increase the sensitivity of the general population and doctors to pay attention to the disease that can cause swelling and increase in the length of the hand, because the changes occur gradually.

Data on patients with acromegaly in Croatia is limited and our study provides new insight into the population specifics of patients with acromegaly in Croatia. Although our sample is relatively small, we believe it is a valuable contribution to general data on acromegaly.

This study provides valuable data for the estimation of stature in Croatian patients with acromegaly. To the best of our knowledge, this study represents the first report on body stature/hand length ratio in the Croatian population with acromegaly. Additional value is a comparison of patients with acromegaly and healthy individuals under the same conditions. However, an important restriction in the generalization of our observations is the fact that a comparison of acromegalic individuals with a healthy population can be only approximate, given the huge sample disproportion. Namely, different statistical methods were used in the analyses of the general population and for patients with acromegaly, according to the number of participants (disproportion is obvious even in overall populations). In the future, increasing the number of individuals with acromegalia included in the study and using randomized samples would help to improve the possibility of generalization, as well as cross-cultural investigations.

CONCLUSIONS

In patients with acromegaly, stature, and hand length are higher and the stature/hand length ratio is lower than in the healthy population. In males with

acromegaly, the correlation between stature and hand length is not significant, but in healthy males, the same correlation is statistically significant and positive. Due to different sample sizes, the differences between correlation coefficients between stature and hand length were calculated, but they were not statistically significant. In females with acromegaly, the correlation between stature and hand length is statistically significant, as well as in healthy females. The difference among these correlation coefficients is not significant.

When comparing the results of the regression analyses in healthy men and women (from the general Croatian population) and patients with acromegaly, it is obvious that both predictions of the criterion stature based on hand length are statistically significant. However, the amount of variance explained is much higher in patients with acromegaly. Hence, a higher positive correlation between stature and hand length is found in patients with acromegaly, as compared with the average population.

These findings may be useful in obtaining stature in adults with enlarged hands and with discordance in the estimation of stature suggestive of acromegalia, in case they got affected by accidents and mass disasters, especially if there is no possibility for direct measurement.

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AUTHOR CONTRIBUTIONS

Conceptualization, M. M., M. G., S. M.; methodology, J. S.; data analysis, M. M., J. S.; writing - original draft preparation, M. M., M. G., J. S., J. Š., D. H. A., N. N., S. M.; writing - review and editing, M. M., D. H. A., J. Š., N. N., S. M.. All authors have read and agreed to the published version of the manuscript.

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