Influence of disease activity and body composition parameters on cross-sectional area of the median nerve in acromegalic patients

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Short tittle: Value of cross- sectional area of the median nerve in acromegalic patients

Abstract

Introduction: Carpal tunnel syndrome (CTS) is neuropathy that occurs due to compression of the median nerve in the carpal tunnel. Acromegaly is one of the important causes of CTS.

Objective: The aim of this study was to examine median nerve with ultrasound in acromegalic patients and assess the relationship with activity, duration of disease and body composition parameters.

Patients and methods: We prospectively examined the cross sectional area (CSA) of the median nerve with high-resolution ultrasound in 107 acromegalic patients - study group (70 females and 37 males) and in 107 healthy controls (70 females and 37 males) matched for age, gender, BMI. Body composition parameters were assessed by dual - energy X- ray absorptiometry (DXA). The t-student tests and Pearson correlation were used for data analysis.

Results: The cross sectional area of the median nerve was increased in acromegalic patients compared with controls (11.9 ± 4.8 mm^2 vs. 7.7 ± 2.4 mm^2, $P < 0.001$). Positive correlation was found between the levels of IGF-1 and CSA in the study group ($R = 0.400$, $P < 0.001$). Relationship between CSA and duration of acromegaly was not confirmed. In acromegalic patients, BMI correlated with the CSA ($R = 0.294$, $P = 0.002$). There was no statistically significant difference in BMI, fat mass between the study and the control group, but lean mass was higher in acromegalic patients compared with controls (54.8 ± 13.3 vs. 51 ± 11.6, $P = 0.047$). Lean mass and LMI (total body lean mass/ height) positively correlated with CSA in acromegalic patients ($R = 0.340$, $P < 0.001$; $R = 0.424$, $P < 0.001$). No correlation was observed between fat mass and CSA of median nerve in whole groups.

Conclusion: We confirmed the enlargement of the median nerve in acromegalic patients. This enlargement is proportional to the degree of IGF-1 levels and is not dependent on the duration of the disease. The enlargement of the median nerve in acromegalic patients also depends on lean body mass, and is not dependent on fat body mass.

Keywords: acromegaly, body composition parameters, cross sectional area of median nerve, fat body mass, lean body mass, ultrasonography

Introduction

Acromegaly is a chronic progressive multisystem disorder seen in adults which is mainly caused by anterior pituitary tumours that secretes excessive amount of growth hormone (GH), resulting in insulin like growth factor 1 (IGF-1) overproduction. Hormonal effect of GH and IGF-1 include overgrowth or edema of the parts of skeleton and other tissues such as cartilage, periosteum ligaments, synovial membrane and connective tissue. Peripheral neuropathy develops due to the compression of peripheral nerve around the growing muscle and skeletal system or due to edema (Milner 2018). The most common form of peripheral entrapment neuropathy in acromegaly is carpal tunnel syndrome (CTS). Generalised neuropathy is a much less recognised complication and only occasional reports have appeared (Milner 2018). The carpal tunnel syndrome occurs in approximately 20% to 64% of acromegalic patients at the time of diagnosis (Colao et al. 2004, Jenkins et al. 2000, Sasagawa et al. 2015). Median neuropathy in acromegaly have proposed various pathogenic mechanisms, including an increase in the amount of connective tissue in the carpal tunnel, demyelination of Schwann cells, bone or synovial overgrowth of the carpal bones, or an increase in the amount of extracellular fluid in the tunnel (Sasagawa et al. 2015). Several studies reported the predominant pathology of median neuropathy in acromegaly consisting of increased edema of the median nerve in the carpal tunnel, rather than extrinsic compression due to increased volume of the carpal tunnel contents (Killinger et al. 2010, Resmini et al. 2009, Kocak et al. 2015). The exact role of growth hormone and IGF-1 in the development of CTS in acromegaly is still unknown, however improvement in CTS occurs immediately after surgery or radiotherapy (Resmini et al. 2009, Kocak et al. 2015). Diagnosis of CTS is mostly based on clinical findings (Payam et al. 2014). Nerve Conduction Studies (NCS) are still the standard for CTS diagnosis, its sensitivity ranged from 49% to 86% and false negativity ranged between 16 and 34% (Jablecki et al. 1993, Azami et al. 2014). Other more recent reviews put the sensitivity at 85-90 % and the specificity at 82-85 % and recognize that electrophysiology studies alone should not be used as the standard for diagnosis (Werner 2013). Ultrasonography (US) is now well established as a alternative tool in the diagnosis of CTS (Azami et al. 2014, Beekman et al. 2003). US is a non-invasive, cost effective, available clinical method, which can be used to assess a number of parameters of the median nerve as size, vascularity and mobility (Mc Donagh et al. 2015). The use of US in the diagnosis of CTS has been demonostrated in number of studies showing that sensitivity and specificity are approaching that of electrophysiology studies (Mc Donagh et al. 2015, Ghasemi et al. 2011,

Pinilla et al. 2008). Different studies demonstrated that cross – sectional area (CSA) of the median nerve at the level of inlet of the carpal tunnel (level of pisiform bone) are significantly greater in CTS patients compared with healthy population (Dalili et al. 2011, Fu T et al. 2015, Kim et al. 2013). In previous studies, cut - off point of CSA at tunnel inlet in patients with CTS ranged from 6,5 to 15 mm^2 (Pinilla et al. 2008, Fu T et al. 2015, Mohammadi et al. 2010). Median nerve enlargement CSA $\geq$ 10 mm^2 at inlet of carpal tunnel is the most commonly used parameter to diagnose CTS on US (Mc Donagh et al. 2015, Holováčová et el. 2016). The aim of present study was to determine CSA of the median nerve at the level of pisiform bone using high resolution ultrasonography in acromegalic patients and to establish whether some relationship exists with activity and duration of disease and also with body composition parameters.

Methods

Patients

We prospectively examinated 107 acromegalic patients (70 females and 37 males) and 107 healthy volunteers (70 females and 37 males) matched for sex, age and BMI, which served as a control group. The study was performed in National Institute of Endocrinology and Diabetology in Ľubochňa, between December 2017 and December 2019. The study protocol was approved by regional medical ethics committee. Every study subject voluntarily signed an informed consent on study participation. The inclusion criteria for acromegalic patients was presence of acromegaly. Diagnosis of acromegaly was based on established criteria (Giustina et al. 2000).

Exclusion criteria for all individuals were as follows: no history of familial neuropathy, no history of alcohol consumption, no history of wrist trauma or neuropathies due to chronic renal failure, liver disease, pregnancy, cervical neuropathy, polyneuropathy and paraneoplastic inflammation. We also excluded patients with levels of thyroid stimulating hormone (TSH) higher than 5.00 mIU/l and patients suffering from diabetes mellitus. In all study subjects we performed anthropometric measurements including weight (kg), height (cm), body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters. Pain, symptoms of paraesthesia, weakness and numbness were questioned in the form of present/absent.

Laboratory methods

In all study subjects, we performed the battery of standard laboratory tests measuring blood count differential, creatinine and urea concentration, serum lipid profile, CRP level, liver enzymes, serum glucose, glycated hemoglobine, TSH, free T4 and vitamin B12. Blood samples were obtained at basal conditions after night - long fasting, between 7.30 – 8.00 am. Serum IGF-1 and GH levels were assessed by chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Products Ltd., United Kingdom). Interassay co-efficient of variability (CV) is for IGF-1 between 3.0 – 7.6 % and for GH between 6.5 – 6.6%. Normal level for serum GH was 5 ng/ml. Normal range of IGF-1 was sex and age – adjusted.

Ultrasonography

Ultrasonography was performed using 12-5 MHz linear array transducer (Hitachi-Hi Preirus – ultrasound machine, Tokyo, Japan). All patients underwent ultrasonography of carpal tunnel. The patients were seated opposite to the sonographer and their wrists were placed in horizontal supine position on the examination table with fingers semiextended. The median nerve was examinated at the carpal tunnel inlet, between the pisiform bone and the scaphoid tubercle, where the distal volar crease is an external pisiform landmark. The median nerve was evaluated in the transverse plane, we also used a longitudinal view to confirm correct identification of the median nerve. The normal appearence of the median nerve is readily recognized as it consists of multiple hypoechoic bands which are separeted by hyperechoic lines corresponding to the epineurium (Watanabe et al. 2010). On transverse sonograms, the median nerve appears as an elliptic or oval outline. The CSA of the median nerve was calculated using the direct tracing method by outlining the perimeter just inside the hyperechoic epineurium, which marked the border of the median nerve, and the area within was measured as cross sectional area. Each measurement was performed 5 times and the mean value was used for analyses.

Body composition measurements

Body composition was measured by Dual – Energy X-ray Absorptiometry (DXA) (Hologic Horizon A, Bedford, MA) using whole-body software version 13.6. Coefficient of variation was 0.78 % for fat mass and 0.52 % for lean mass. We measured total body fat mass (kg),

total body lean mass (kg) and fat percentage (%). We calculated fat mass index (FMI) = total body fat mass/ height (kg/m^2) and lean mass index (LMI) = total body lean mass/height (kg/m^2).

Statistical analysis

All statistical analyses were performed using IBM SPSS version 25 (IBM SPSS Statistics, IBM Corporation, IL, USA). Statistical power was calculated using the G∗Power v. 3.0.1 software. Qualitative variables were expressed using absolute and relative abilities. Quantitative variables were expressed as number of measurements, mean and ± standard deviation (SD). The Student t-test was used to compare groups. Correlation analyses were performed using Pearson correlation coefficient and its significance was tested by the respective test. Normality test passed for all variables. In each statistical test performed, the criteria for statistical significance was $p \leq 0.05$. All tests were two-tailed.

Results

107 acromegalic patients (70 [65.42%] females and 37 [34.58%] males) were included in the study. The mean age of acromegalic patients was 56.4 years. The age-, sex-, and BMI – matched controls consisted of 107 (70 [65.42%] females and 37 [34.58%] males) healthy subjects with mean age 57.3 years. Baseline characteristics of subjects are summarised in Table 1.

Association between duration/activity of acromegaly and CSA of the median nerve

The average duration of acromegaly was ø 11 years, baseline serum level of IGF-1 was ø 249.9 ng/ml and serum level of GH was ø 2.6 ng/ml in study group. Serum levels of GH and IGF-1 were significantly higher in acromegalic patients compared with controls (Table 1). The cross sectional area of the median nerve was increased in acromegalic patients compared with controls (11.9 ± 4.8 mm^2 vs. $7.7 \pm 2.4 mm^2$, $P < 0.001$) (Table 1).
Positive correlation was found between the serum levels of IGF-1 and CSA of the median nerve in the study group ($R = 0.400$, $P < 0.001$)) (Fig.1). Relationship between CSA of the median nerve and serum levels of GH, duration of acromegaly was not confirmed (Table 2).

48 acromegalic patients had CSA of the median nerve greater than 11mm^2. In 24 acromegalic patients, clinical signs (e.g. pain, weakness, paraesthesia and numbness) of CTS were reported. 18 pacients (37,5%) with symptoms of CTS had a CSA of median nerve greater than 11mm^2. 30 acromegalic patients (62,5%) with median nerve greater than 11mm^2 were asymptomatic of CTS. The CSA of the median nerve was increased in symptomatic patients compared with asymptomatic patients (14.6 ± 2.8mm^2 vs. 12.8± 1.7mm^2, P 0.019).

Association between body composition parameters and CSA of the median nerve

BMI weakly correlated with CSA of the median nerve in the study group (R = 0.294, P = 0.002) (Fig.2). There was no statistically significant difference in BMI, fat mass between the study and the control group, but lean mass was higher in acromegaly patients compared with controls (54.8 ± 13.3 vs. 51 ± 11.6, P = 0.047) (Table 1). Lean mass and LMI (total body lean mass/ height) positively correlated with CSA in acromegalic patients (R = 0.340, P < 0.001; R = 0.424, P < 0.001) (Fig. 3). No correlation was observed between fat mass, FMI and CSA of the median nerve in all groups (Table 2).

Discussion

Carpal tunnel syndrome (CTS) is common peripheral neuropathy in acromegaly. The pathological mechanisms of peripheral nerve abnormalities in acromegaly remain unclear (Resmini et al. 2009, Oktayoglu et al. 2015). ~~whether it can be secondary caused by intristic factores, including histopathological changes and intraneural edema, or caused by extrinsic factores related to the fact that nerves cross- joints passing through narrow passageways, the osteofibrous tunnels, within which they may undergo compression~~ Ultrasonography allowed an accurate and reliable depiction of the median nerve based on the established criteria (Tagliafico et al. 2007). In present study we performed measurement of CSA of the median nerve at the level of pissiform bone using high – resolution ultrasound in acromegalic patients. Previous studies reported greater median nerve in acromegalic patients in comparison to healthy controls (Resmini et al. 2009, Kocak et al. 2015, Tagliafico et al. 2008). In our study we confirmed enlargement of the median nerve in acromegalic patients based on criterion that CSA of the median nerve over 10 mm^2 at the pisiforme axis is the most used parameter for diagnose of CTS with a sensitivity higher than 97.9% (Mc Donagh et al. 2015). 48 acromegalic patients had CSA of the median nerve greater than 11mm^2. Thirty of

this patients were asymptomatic of CTS. In 24 acromegalic patients, clinical signs (e.g. pain, weakness, paraesthesia and numbness) of CTS were reported. Eighteen of them had a CSA measurement greater than 11mm2, which is considered pathognomonic for CTS. CTS occurs with a prevalence of 64% in patients with sensory disturbances (Colao et al. 2004, Jenkins et al. 2000, Kaneyama et al. 1993). Even if asymptomatic, most patients with acromegaly have subclinical functional abnormalities detected on NCS (Kaneyama et al. 1993). The CSA of the median nerve in acromegalic patients positively correlated with concentration of IGF-1 in our study. Tagliafico et al. reported the same positive impact of IGF-1 on CSA of the median nerve in their study (Tagliafico et al. 2008). On the other hand Kocak et al. in their study on 38 acromegalic patients did not confirm this association (Kocak et al. 2015). The exact role of IGF-1 in pathology of CTS in acromegaly is still unknown. GH and IGF-1 interfere to the pathogenesis of CTS by several effects. GH and IGF-1 stimulates protein synthesis, differentiation and proliferation of muscle cells, chondrocytes and osteoblasts (Xiao et al. 2019). This process promotes skeletal growth and soft tissue enlargement which can cause the compression of median nerve in CTS. Another effect of GH reported in recent study is increased activity of epithelial sodium channel and this could contribute to the volume expansion and soft tissue manifestation (Lugo at el. 2012). The major pathogenetic factor for CTS of median nerve in acromegaly seems to be the increased edema of median nerve, but an increase in connective tissue, demyelination of Schwann cells, an increase in extracellular fluid of the carpal bones and bony or synovial overgrowth of carpal bones can be involved as well (Killinger et al. 2010, Resmini et al. 2009, Kocak et al. 2015, Lugo at el. 2012, Laike et al. 2020). Thes predominant pathophysiological mechanisms of the median neuropathy in acromegaly was supported by the study of Jenkins et al. who reported the occurence of increased nerve size with increased signal intensity on T-2 weighted magnetic resonance images as a sign of increased edema of the median nerve (Jenkins et al. 2000). He also described rapid reduction of nerve size after levels of circulating growth hormone and IGF-1 were decreased (Jenkins et al. 2000). This was also confirmed by ultrasonographic studies showing that acromegaly was associated with edema of not only the median nerve but also with ulnar nerve (Tagliafico et al. 2008). Patients with active acromegaly have generalised visceral edema related to the effect of GH on the distal kidney, where it increases epithelial sodium channel activity and stimulates sodium reabsorption (Kamenický et al. 2014). Additionally we examined the influence of body composition parameters on the CSA of the median nerve. We confirmed a positive correlation between CSA of the median nerve and BMI in the study group. Several studies have confirmed the same results, but these studies

were performed on the general population (Sharifi et al. 2008, Mondelli et al. 2016, Shiri et al. 2015). In acromegaly GH and IGF-1 excess is associated with alterations in body composition, including an increase in body water, lean body mass and a reduction in body fat. According to these facts we performed body composition measurement using DXA. DXA divides body composition into fat, bone mineral and lean mass. Lean mass includes mass of skeletal muscle, organs and soft tissue (including tissue water). In our study no correlation was found between CSA of the median nerve and fat mass in all groups but we found a positive correlation between CSA of the median nerve and lean mass and also with calculated LMI in acromegalic patients. GH has an anabolic effect on skeletal muscle, including suppression of locally synthesized myostatin and stimulation of protein synthesis (Moller et al. 2003, Katznelson 2009). On the other hand, GH has a lipolytic effect resulting in a reduction in adipose tissue and a sodium retention effect resulting in an increase in total body water and exracellular water. Several studies confirmed higher lean body mass in acromegalic patients compared to controls using DXA scans (Gibney et al. 2009, Kaji et al. 2001, Freda et al. 2009). Measurement of lean mass in acromegaly using DXA has limitation, because DXA can not reliably differentiate water vs. protein. Several studies have confirmed the expansion of total body water (TBW) and extracellular water (ECW) in acromegalic patients, leading authors of these studies to conclude that increased soft tissue mass hydratation and not skeletal muscle was the cause of increased lean mass in acromegaly (Gibney et al. 2009, Reid et al. 2015, Füchtbauer et al. 2017). These studies were performed by several techniques including isotopic dilution. Another studies have examined lean body mass using total body potassium for assessing body cell mass (BCM) but results have been conflicting in acromegaly (Pirlich et al. 2003, Landin et al. 1993). Studies examining effect of GH on protein synthesis confirmed anabolic effects of acromegaly on lean body mass (Gibney et al. 2009, Velloso et al. 2008, Viral et al. 2013). Despite the increase in protein synthesis in acromegaly, skleletal muscle may be functionally weaker. Examinations performed on skeletal muscle mass in acromegaly patients by biopsy confirmed hypertrophy of type 1 and atrophy of type 2 muscle fibers (Freda et al. 2009, Madsen et al. 2012, Brumback et al. 1983). These data suggest that acromegaly results in changes in skeletal muscle function that do not clearly correlate with the degree of change in lean body mass (Madsen et al. 2012, Brumback et al. 1983). Our results and also previous research suggest that edema of the median nerve could be dominant pathophysiological mechanism of CTS in acromegaly althoug other causes such as soft tissue enlargment and skeletal growth can participate as well. Futher research is necesseary to determine these relationships better. To our knowledge this is the first study

investigating the influence of body composition parameters using DXA scan on CSA of the median nerve in acromegalic patients.

Limitations

Although optimum care had been tried by the researcher in this study, still some limitations exist. The study is limited by a relatively small sample size because of low incidence of the disease and there were gender differencies in number of patients present. The study was also designed as a cross sectional therefore subject to selection bias.

Conclusion

In our study we confirmed the enlargement of median nerve in acromegalic patients. This enlargement is proportional to the degree of IGF-1 levels and is not dependent on the duration of disease. According to our findings the enlargement of median nerve in acromegaly also depends on body compostition. We confirmed positive correlation between CSA of the median nerve and BMI in acromegalic patients. CSA of the median nerve significantly correlates with lean mass but we haven´t found any correlation with fat mass.

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Conflict of interest

Authors declare, that they have no conflicts of interest concerning this article

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Table 1. Baseline characteristics of subjects

Characteristics	Study group (n=107)	Control group (n=107)	p-value
Sex (M/F)	37/70	37/70	
Age (year)	56.4±12.4	57.3±13.0	ns
M/F	51.8±11.5/58.8±12.1	52±10.5/58.9±11.5	
Duration of disease (year)	11±10.1	-	
GH (ng/ml)	2.6±5.7	0.37±0.5	< 0.001
IGF-1 (ng/ml)	249.9±173.3	134±48.6	< 0.001
M/F	288.8±202.2/229.4±154.7	138±40.7/134±47.2	
Anthropometric measurements			
Height (cm)	171±8.9	170.3±9.1	ns
M/F	179.3±7.1/166.6±6.2	176.1±7.8/165.8±6.7	
Weight (kg)	86.4±18.8	84.5±18	ns
M/F	99.4±16.0/79.6±16.4	93.6±16.7/79.8±16.9	
BMI (kg/m^2)	29.5±5.8	29.7±5.1	ns
M/F	31.0±5.1/28.7±6.0	30.2±4.2/29.7±5.8	
Ultrasonography			
CSA of n. medianus (mm^2)	11.9±4.8	7.7±2.4	< 0.001
M/F	13.2±4.7/11.2±4.7	7.9±1.4/7.5±2.4	
DXA measurements			
Total fat (%)	35.7±6.9	36.7±7.8	ns
M/F	29.6±5.6/39±5.1	28.8±4.2/40.8±5.4	
Fat mass (kg)	31.8±9.7	31.9±10.2	ns
M/F	30.6±9.3/32.5±9.9	28.6±7.8/34.4±10.5	
Lean mass (kg)	54.8±13.3	51±11.6	0.047
M/F	68.7±10.0/47.4±7.8	62.4±12/42.7±9.8	
FMI (kg/m^2)	11±3.6	11.3±4.0	ns
M/F	9.6±3.1/11.7±3.6	8.6±2.4/12.6±4.1	
LMI (kg/m^2)	18.5±3.5	16.9±2.8	0.039
M/F	21.4±3/17±2.9	19.7±2.7/15±2.4	

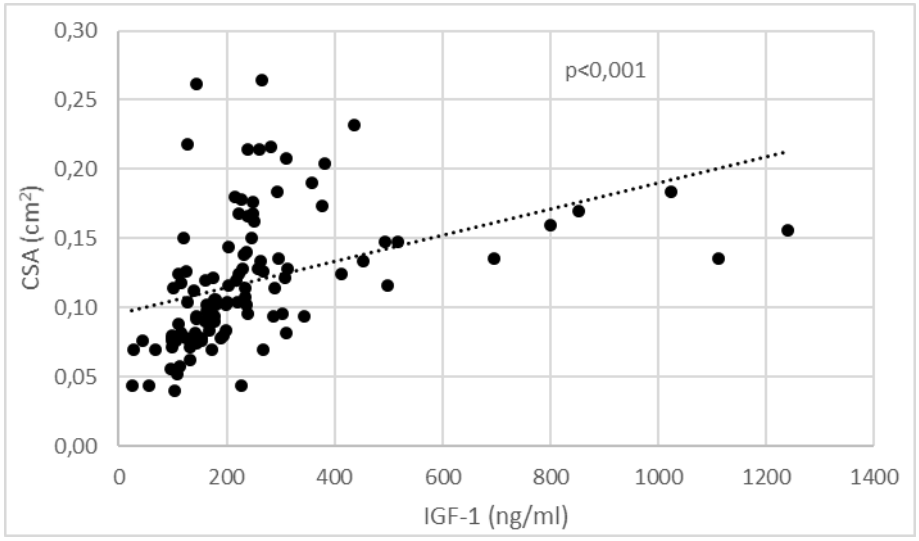
Data is presented as mean ± SD (standard deviation)
Level of significance was set at *p ≤ 0.05
GH:growth hormone, IGF-1: insulin-like-growth factor 1, BMI: body mass index, CSA: cross sectional area, DXA:dual-energy X-ray absorptiometry, FMI: fat mass/height index, LMI: lean mass/height index

Table 2. Correlation between duration / activity of acromegaly, anthropometric parameters, body composition parameters and CSA of the median nerve in acromegalic patients

	CSA of the median nerve	
	R-value (Pearson correlation coefficient)	**P-value**
Duration of acromegaly (year)	-0.031	0.754
GH (ng/ml)	0.042	0.668
IGF-1 (ng/ml)	0.400	<0.001
Weight (kg)	0.261	0.007
Height (cm)	----0.034-----	0.728
BMI (kg/m^2)	0.294	0.002
Fat mass (kg)	0.042	0.668
Lean mass (kg)	0.340	<0.001
FMI (kg/m^2)	0.045	0.645
LMI (kg/m^2)	0.424	<0.001

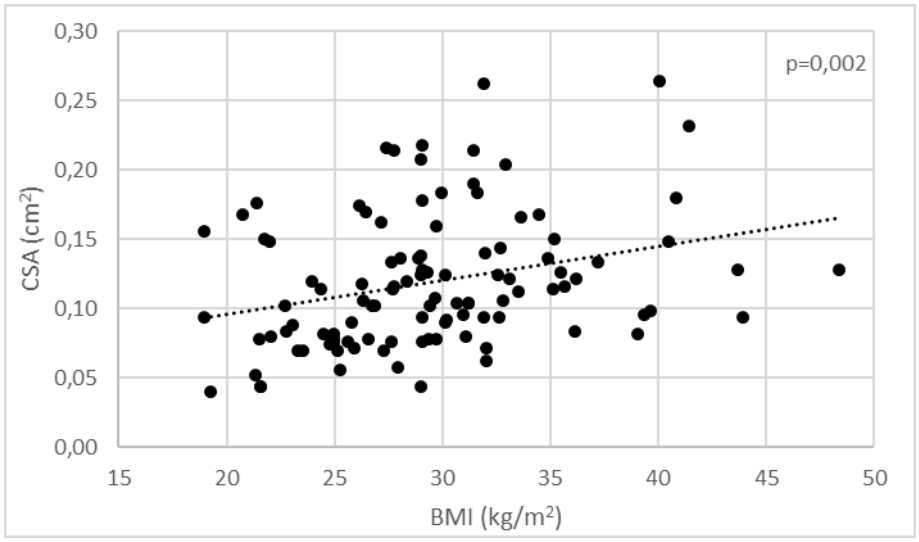
level of significance was set at *$p \leq 0.05$
CSA: cross sectional area, GH: growth hormone, IGF-1: insulin-like-growth factor 1, BMI: body mass index, FMI: fat mass/height index, LMI: lean mass/height index

FIG.1. Correlation between IGF-1 and CSA of the median nerve in acromegalic patients



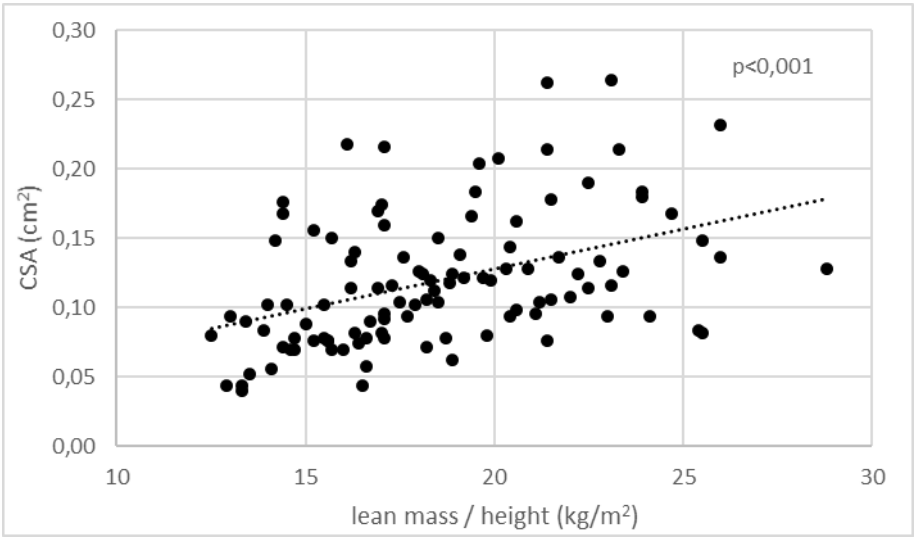
CSA : cross sectional area, IGF -1 : insulin-like-growth factor 1

FIG.2. Correlation between BMI and CSA of the median nerve in acromegalic patients



CSA : cross sectional area, BMI: body mass index

FIG.3. Correlation between lean mass/height and CSA of thhe median nerve in acromegalic patients



CSA: cross sectional area