Relationship between anthropometric variables and the cross-sectional area of the median nerve by ultrasound assessment in healthy subjects

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ABSTRACT

Objective: Ultrasound study of the wrist in patients with suspected entrapment syndrome has severe limitations due to the variability of what is considered normal for the cross-sectional area of the median nerve and where to measure it. We aim to determine the extent to which different anthropometric variables influence the median nerve area in subjects without carpal tunnel syndrome.

Methods: We conducted an observational study based on a multivariable linear regression analysis using as a dependent variable the area of the median nerve cut at two specific points in the wrist of healthy subjects. The independent variables were sex, age, height, weight, body mass index, finger flexor strength, and carpal circumference.

Results: The measurements of the median nerve cross-sectional area were normalised using a quadratic fixing procedure. Of all the variables included in the linear regression analysis, only carpal circumference and sex (0: female, 1: male) contributed significantly in the final model using the wrist fold as the measurement point (Constant B=-209.4, carpal circumference coefficient=21.1, sex coefficient 10.9). At four centimeters distal to the carpal fold, the model included the same variables (carpal circumference coefficient=24.0, and sex coefficient=11.4).

Conclusion: Both the wrist circumference and the sex are variables that should be considered to determine cut-off points of normality in future validation studies about the cross-sectional area of the median nerve.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is the most prevalent nerve entrapment pathology, 40% more frequent in females than males, with an estimated incidence of about 125 cases per 100.000 person-year[1]. This condition is characterised by pain and paresthesias into the second, third, and fourth fingers and the corresponding area of the hand dependent of the median nerve; however, in severe clinical scenarios, it can also develop muscle impairment and even atrophy[1,2].

Its diagnosis is clinically suspected and confirmed by nerve conduction studies (NCS) [3]. However, ultrasound study (US) is being used as an additional test to establish the diagnosis and determine the severity of the nerve entrapment[4,5]. Using this non-invasive and easily accessible technique is possible to measure the cross-sectional area (CSA) of the median nerve as it passes through the carpal tunnel. Different studies have validated the CSA of the median nerve from 10 to 13 mm^2 [6,7] as the cut-off point of physiology size without considering the anthropometric characteristics of the individual. However, for instance, a study in healthy Asian population shows an average of the CSA of the median nerve of 7.2 mm^2 [8]. According to this, a US study performed in an asymptomatic caucasian subject could be considered pathological. This issue can explain most of the lack of specificity of the CSA of the median nerve compared to the gold standard[4–6]; however, some initiatives to link the body mass index (BMI) to the CSA of the median nerve have not been successful[9]. So far, other anthropometric measures have not been formally analysed.

This study aims to determine which anthropometric variables affect the cross-sectional area of the median nerve in healthy subjects and which, therefore, should be considered when establishing cut-off points.

METHODS

OBSERVATIONAL CROSS-SECTIONAL STUDY

Subjects

Healthy adult subjects of both sexes up to the age of 45 were included. To avoid subjects with non-symptomatic osteoarthritis, volunteers older than this age were not included. Consecutive recruitment was performed for over three months. The subjects were medical students, accompanying relatives of patients in the rheumatology clinic, hospital paramedical staff, and other volunteers not related to the groups mentioned above. All volunteers were clinically assessed previously to their inclusion (interview and physical examination). The study was performed at the University Hospital HLA Moncloa and University Hospital Ramón y Cajal of Madrid. Since this study does not seek to validate any particular anthropometric measure with the CTS diagnosis but simply to determine to what extent any anthropometric measure correlates with the CSA of the median nerve, we did not include patients in the study.

Subjects diagnosed with hypothyroidism, diabetes, previous non-dominant hand surgery, recent trauma, or carpal pain were excluded. Also, an expert conducted a clinical interview with the enrolled subjects to rule out any subjective manifestation of CTS.

Primary outcome

The primary outcome variable was the CSA of the median nerve measured by a grayscale US (square millimetres) using a Nemio XG Toshiba® ultrasound imaging system provided by a 13 MHz linear probe. The measurement was made at two anatomical locations.

Independent variables

The remaining variables included in the correlation tests were: age, sex, height (cm), weight (kg), body mass index (BMI), flexor handgrip strength of the fingers of the non-dominant hand (Kg) and wrist circumference (cm) measured at the level of the styloid process with a flexible tape measure. The flexor handgrip strength was measured by means of an electronic hand dynamometer (EH-101, Camry®). Except for the flexor handgrip strength, the remaining variables were chosen from previously published studies [8–10] and the observational experience of the research team (not published).

Procedures

Once volunteers signed the inform consent, they were interviewed and examined by a clinician, and after that, all anthropometric measurements were taken. A CAMRY handheld dynamometer, model EM101, was used to measure the flexural traction force of the fingers. In order to perform the US, subjects were seated facing the sonographer, with the non-dominant arm supported to keep a position of the wrist, with the forearm supinated. Two measurements of the CSA of the median nerve were performed: one at the wrist fold using the cortical surface of the scaphoid bone as a reference of perpendicularity[4], and 4 cm distal to this point as recommended by a previous study of accuracy for best points of measuring[5]. The studies were carried out by a single expert rheumatologist (C.G.) with 12 years of experience in a two weekly monographic musculoskeletal ultrasound clinic, certified by the national scientific society of rheumatology in musculoskeletal ultrasound and recurrent staff of many ultrasound courses. The measurements were made using the standard software of the ultrasound machine. Images of each measurement were obtained for subsequent quality control performed by an independent radiologist specialised in musculoskeletal ultrasound. For this purpose, a proportion of the difference of measurements of both operators was calculated. The two cross-sectional measurements of the median nerve area were made in the non-dominant hand to avoid the potential effect of involuntary overexertion[11].

Each volunteer spent about 20 minutes from anthropometric measurements to US assessment. No participant received financial or other compensation from the research team. All participants were informed of the purpose of the study and had access to reports of anthropometric variables or any abnormal findings of the US study.

The local Ethics Committee approved this study in March 2019 (File number A04/19).

STATISTICAL ANALYSIS

A multivariable, linear regression statistical analysis was planned. The independent variable was the median nerve cross-sectional area measured at two anatomical locations: at the wrist flexor fold and 4 cm distal to this point. We planned to include seven variables in the model: age, weight, height, BMI, handgrip strength, wrist circumference and sex. The stepwise method was used to build the model using the F probability of less than 0.05 to include a variable into the model and more than 0.1 to exclude it. For each variable to be considered in the model, the need for ten subjects was established, so the calculated sample size was 70.

The expression of results of the measurements made was done by means of central tendency and dispersion descriptors. Direct comparisons of anthropometric measurements were analysed through Student's T or Mann-Whitney tests as appropriate. The dependent variable was normalised through a square adjustment once its normality was analysed using the Kolmogorov-Smirnov's test.

In multivariable linear regression analysis, the inclusion of variables followed the stepwise method. The variable sex was treated as dichotomous, allocating a 0 for females and 1 for males. A p-value of less than 5% was considered statistically significant.

RESULTS

Three hundred fifteen healthy volunteers were included, with an average age ± standard deviation of 31.3 ± 8.1 years old. One hundred and seventy-seven subjects were women (56.2%).

The distribution of anthropometric variables, according to sex, is detailed in Table I. The CSA of the median nerve averaged 11.0 ± 2.0 mm^2 at the wrist fold and 12.5 ± 2.00 mm^2 at four centimetres distal to this point. In both cases, the distribution of measurements was not normal (Kolmogorov-Smirnov statistic 0.076 and 0.069, respectively, and $P < 0.001$ for both distributions).

Pearson's correlation coefficient for the carpal circumference with the median nerve CSA at the carpal fold was 0.744 ($P < 0.001$) and 0.743 ($P < 0.001$) 4 cm distal to this point. Table II shows the results of the correlation coefficients with all the remaining variables: age, weight, height, fingers flexor strength, BMI and sex.

Considering the entire population, the regression model using the square of the median nerve CSA at the wrist fold level included two variables using the stepwise method: carpal circumference and sex. In this model (R^2=0.569, F change=11.4; P=0.01), constant B was -209.4, and the coefficients for carpal circumference and sex were respectively 21.1 and 10.9. Four centimetres distal to the fold, the model, included the same variables. In this scenario (R^2=0.565, F change=9.6; P=0.02), constant B was -221.8, and coefficients for carpal circumference and sex were respectively 24.0 and 11.4.

TABLE I. CHARACTERISTICS OF THE POPULATION STUDIED GROUPED ACCORDING TO SEX

	Female (N=177)			Male (N=138)			
Variable	Mean ± SD	25th percentile	75th percentile	Mean ± SD	25th percentile	75th percentile	P value
Age (years)	31.8 ± 8.5	25.0	41.0	30.7 ± 7.5	25.0	37.0	0.226
Wrist circumference (cm)	15.5 ± 1.5	14.3	16.5	15.9 ± 1.3	14.9	16.9	0.012
CSA of MN at crease (mm2)	10.6 ± 1.9	9.8	12.1	11.52 ± 1.97	10.0	13.2	<0.001
CSA of MN at 4cm distal of the crease (mm2)	12.1 ± 1.9	11.4	13.5	12.9 ± 2.0	11.4	14.7	<0.001
Weight (kg)	69.5 ± 14.2	58.7	81.0	69.4 ± 14.8	58.0	74.0	0.963
Height (cm)	168.7 ± 8.5	162.0	175.0	172.1 ± 5.6	170.0	175.0	<0.001
BMI	24.2 ± 3.4	21.6	26.7	23.3 ± 4.0	19.8	24.8	0.026
Finger flexor strenght (kg)	29.7 ± 6.7	23.3	34.7	35.7 ± 8.4	30.7	39.8	<0.001

Comparisons were made using the Student T statistic (bilateral significance)
SD: Standard deviation; CSA: Cross sectional area; MN: Median nerve; BMI: Body mass index.

TABLE II. RESULTS OF THE UNIVARIABLE CORRELATION STUDY (PEARSON'S TEST) TAKING AS REFERENCE THE SQUARE OF THE MEDIAN NERVE CROSS-SECTIONAL AREA AT THE TWO ANATOMICAL LOCATIONS

	Wrist fold		4 cm distal to wrist	
Variables	Correlation coeficient	P value	Correlation coeficient	P value
All subjects				
Age	0.1	0.015	0.1	0.014
Wrist circumference	0.7	<0.001	0.7	<0.001
Weight	0.5	<0.001	0.5	<0.001
Height	0.6	<0.001	0.6	<0.001
Fingers flexor strenght	0.4	<0.001	0.4	<0.001
BMI	0.3	<0.001	0.3	<0.001
Sex	0.2	<0.001	0.2	<0.001
Only female				
Age	0.2	<0.001	0.2	0.013
Wrist circumference	0.7	<0.001	0.7	<0.001
Weight	0.5	<0.001	0.5	<0.001
Height	0.7	<0.001	0.7	<0.001
Fingers flexor strenght	0.4	<0.001	0.4	<0.001
BMI	0.2	0.004	0.2	0.004
Only male				
Age	0.1	0.092	0.1	0.085
Wrist circumference	0.8	<0.001	0.8	<0.001
Weight	0.5	<0.001	0.5	<0.001
Height	0.4	<0.001	0.4	<0.001
Fingers flexor strenght	0.3	<0.001	0.3	<0.001
BMI	0.4	<0.001	0.4	<0.001

BMI: Body mass index

Due that sex was a dichotomic variable, we conducted two new multivariable linear regression analysis grouping subjects according to this variable. Considering only the female population, the regression model using the CSA at the wrist fold as the dependent variable included carpal circumference, height, and BMI. The constant B value was -276.3, and the coefficients of the variables were 15.0, 1.3, and -2.3, respectively. Using the CSA as the dependent variable at 4 cm distal to the wrist fold, the constant B value was -305.8, and the coefficients for the same variables were 17.1, 1.5, and -2.7, respectively. Considering only the male population, the regression model using CSA at the wrist fold as a dependent variable included only the carpal circumference. The constant B was -289.3, and the coefficient of the variable was 26.8. Using the CSA at 4 cm distal to the wrist fold as the dependent variable, the constant B was -310.3, and the coefficient of the variable was 30.3.

Using the linear regression models obtained, we made a dispersion diagram of predicted and actual values of the CSA of the median nerve (Figure 1).

Table III summarises the results of the comparison of predicted and actual means using the Student's T-test for related samples (real *vs* predicted by the model).

To verify the relevance of variables sex and wrist circumference into the model, we tested both variables using the original not normalised values of the CSA of the median nerve at the two anatomical locations of US assessment. At the wrist fold, average ranks for males and females were 173.7 and 145.8, respectively (Mann-Whitney U-test 10046.5; P=0.007). At 4 cm distal to the wrist fold same ranks were as follows: 173.0 and 146.3 (10139.0; P=0.01). Spearman s Rho coefficient for the wrist circumference and the CSA was 0.7 (P<0.0001) at the wrist fold and 0.9 (P<0.0001) 4 cm distal to this point. The other variables not included in the model had coefficients less remarkable: 0.4 for fin-

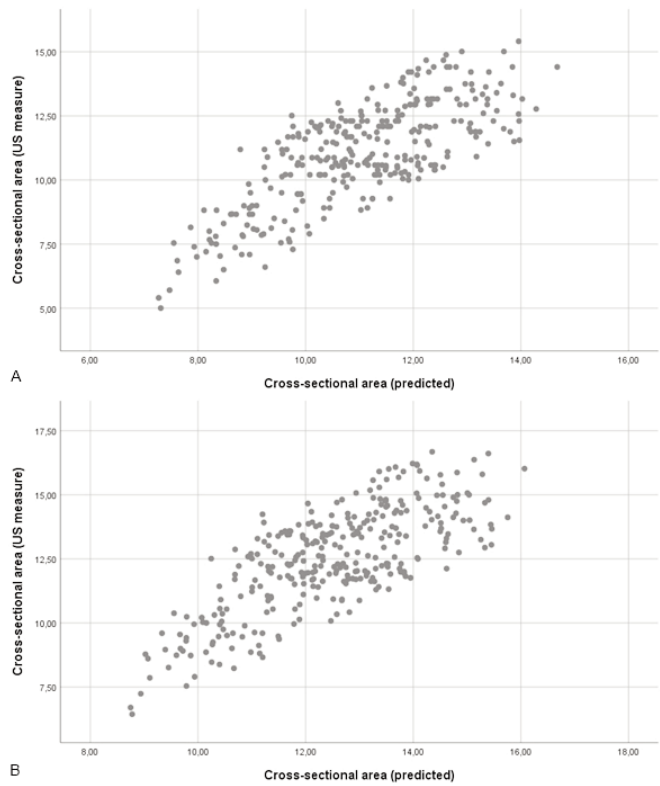

FIGURE 1. Scatter plots showing the correlation between predicted and real measurement of the CSA of the median never (mm2) at the wrist fold (A) and 4 cm distal to this point (B)

ger flexor strength and 0.2 for BMI.

Quality control assessment of measures was tested by an independent radiologist who compared 20 randomised measures performed by our explorer and himself. In the worst case, the proportion of difference did not exceed 5%.

DISCUSSION

Several problems are surrounding the confirmation of a CTS clinical suspicion. While the clinical manifestations are easily recognisable, osteoarthritis may explain the presence of very similar symptoms and is, therefore, a differential diagnosis of interest or even a causal factor that is needed to be ruled out[12]. Symptoms of CTS can also be observed in patients without nerve entrapment at the wrist but proximal to it in the forearm[13]. Therefore, the accurate diagnosis of this condition requires NCS to demonstrate entrapment.

The place where to allocate the probe to assess the median nerve has been tested at the entrance and exit of the median nerve, at the level of the square pronator or at different distal points at the exit of the tunnel[7,14–16]. There is evidence in favour of measuring the CSA at the entrance of the tunnel -which coincides with the carpal fold- and 4 cm distal to this point[5]. Concording with this evidence, in our study, no significative difference in the relationship of CSA and wrist circumference was detected between both points.

The cut-off point for setting the limit of a physiological CSA of the median nerve is critical to estimate the validation parameters. In a study using a cut-off point of 10mm^2 sensitivity was 70%, and specificity was 100%[14]. In contrast, in other study aimed at associating the different degrees of severity with the area of the median nerve, it was determined that healthy subjects had a mean area of 9.4 ± 2.1 mm^2, while the different degrees of severity were associated with areas greater than 12 mm^2 and the most severe with a mean

TABLE III. COMPARISON BETWEEN THE MEASUREMENTS MADE AND THE PREDICTED MEASUREMENTS APPLYING THE LINEAR REGRESSION MODELS OBTAINED FOR THE TWO MIDLINE NERVE CSA MEASUREMENT POINTS IN THE ENTIRE POPULATION STUDIED AND ACCORDING TO SEX

Group of sample	Square of the measured area	Predicted square of the area	P-value
CSA at the wrist fold(whole sample)	125.5 ± 42.6	125.5 ± 32.2	0.999
CSA 4 cm distal to fold (whole sample)	159.5 ± 48.6	159.5 ± 36.5	0.997
Female population			
CSA at the wrist fold	116.9 ± 37.9	116.9 ± 32.7	0.999
CSA 4 cm distal to fold	150.1 ± 43.8	150.8 ± 37.3	0.997
Male population			
CSA at the wrist fold	136.6 ± 45.8	136.6 ± 27.9	1.000
CSA 4 cm distal to fold	171.5 ± 51.8	171.5 ± 31.8	0.998

P values are adjusted to the comparison of related samples by the Student T-test. Data are expressed as average ± standard deviations.
CSA: Cross-sectional area.

of 15.4 mm^2. They demonstrated a specificity of 91.4% using a cut-off point of 14 mm^2, only for the detection of severe CTS, but with a sensitivity of 42.3%[16]. Cut off points also are selected according to ethnic considerations: From as low as 7.2 mm^2 in healthy Asian volunteers[8] or as high of 10mm^2 on white people[7]. These last two studies suggest that the use of US has a more critical role stratifying the severity of the CTS than ruling it out. In most studies based on the measurement of the CSA of the median nerve at one or more points, anthropometric variables are not included. This issue could explain the variability of the CSA cut-off points detected by different studies.

Other studies have been published concerning the use of US in the diagnosis of STC based on the use of more than one measurement per patient and establishing physiological limits based on relationships between these measurements: the delta of the area at the entrance and exit of the tunnel or the ratio between the area at the wrist fold and the square pronator. In these cases, the sensitivity improves slightly but doubles the risk of measurement error[15,17]. Present study is, as far as we know, the first to demonstrate a strong relationship between a single anthropometric variable and a single CSA determination by US.

US-based studies have an intrinsic limitation due to the interobserver error, and this error can be much relevant in measures of very little structures such as CSA of a nerve. To cope with this potential limitation, all US studies were performed by a single operator, and a quality control test was allocated.

It is understandable to assume that the thickness of the median nerve will depend on the constitution of the individual, which also depends on multiple anthropometric variables. Of all anthropometric variables tested in our study, we have identified that wrist circumference and sex of the individual significantly affect the CSA of the median nerve. Correlation coefficients of certain other anthropometric variables such as BMI or flexor strength were also tentative to be considered into the model; however, both were excluded due to F change P-value. Both variables are linked to wrist circumference and sex, so it is reasonable that their participation in the model was as intermediate variables of wrist circumference. For that reason, we consider that in order to improve the diagnostic capability of grayscale US, limits of physiological CSA of the median nerve should be established based on the sex of the individual and other anthropometric variables. According to our results, the most critical anthropometric predictor variable is the wrist circumference, which, on the other hand, is easy to obtain. We recommend that to validate the US as a diagnostic tool versus nerve conduction studies, a sex and wrist circumference-adjusted CSA should be used as a cut-off point.

The limitations of our study are the intrinsic intraobserver bias, the need for an artificial normalisation of the dependent variable and the arbitrary sole inclusion of young subjects. As we stated before, the intrinsic intraobserver bias is difficult to avoid even in experts US users; however, the minimal difference observed in the quality control assessment allows us to keep our measurements as valid. The normalisation of the dependent variable in a multivariable regression analysis is a critical requisite. Due to that our modelisation was planned using a quadratic adjustment; however, as we showed before, both variables which demonstrated a significative influence into the dependent variable also kept that condition using a non-parametric test (Mann-Whitney test and Spearman s Rank order correlation, for sex and wrist circumference, respectively). Finally, since this study only included healthy young volunteers, it could be considered not representative of patients who develops a CTS. This selection was chosen deliberately to minimise the possibility to include subjects with osteoarthritis or other degenerative conditions that can affect the US assessment or the median nerve. In further studies to validate our index to distinguish CTS patients from healthy subjects, different samples should be considered.

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