RESEARCH ARTICLE

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The 2nd to 4th Digit Length Difference and Ratio as Predictors of Hyperandrogenism and Metabolic Syndrome in Females

ABSTRACT
Objective: In this study we evaluated the usefulness of 2nd to 4th (2nd:4th) digit length difference and ratio in determining hyperandrogenism in females and the relationship with metabolic syndrome.
Methods: We designed a cross-sectional clinical study and examined 150 females who visited our clinic; 137 completed the study. We measured blood pressure and anthropometric values. Biochemical parameters associated with metabolic syndrome were also measured.
Results: The mean age of our patient is 46.1 yrs. The 2nd:4th digit length difference and ratio were correlated slightly with total testosterone levels and positively with free testosterone levels (*p=0.028, p=0.016, p=0.003, p=0.016*). Sex hormone-binding globulin levels and 2nd:4th digit length difference and ratio were mildly negatively correlated (*p=0.011, p=0.016*). No statistically significant differences were found between 2nd:4th digit length difference and ratio, and metabolic syndrome parameters. Thus, the 2nd:4th digit length difference and ratio are significantly correlated with androgens.
Conclusion: The 2nd:4th digit length difference and ratio, which are easily measurable values, can be used as an important predictor of hyperandrogenism in females. In the present study, 2nd:4th digit length difference and ratio were not statistically significantly correlated with metabolic syndrome; however, additional studies with a larger group of patients are necessary.
Keywords: Fingers, Hyperandrogenism, Metabolic Syndrome

Kadınlarda Hiperandrojenizm ve Metabolik Sendrom Belirleyicisi Olarak 2. ve 4. Parmak Uzunluk Farkı ve Oranı

ÖZET
Amaç: Bu çalışmada kadınlarda 2. ve 4. parmak uzunluk farkı ve oranının hiperandrogenizm ve metabolik sendrom ile ilişkisinin belirlenmesi amaçlanmıştır.
Yöntem: Bu kesitsel klinik çalışmada, kliniğimize başvuran 150 kadın incelendi ve 137'si çalışmayı tamamladı. Kadınların kan basıncı ve antropometrik değerleri ölçüldü. Metabolik sendrom ile ilişkili biyokimyasal parametreler değerlendirildi.
Bulgular: Hastalarımızın yaş ortalaması 46,1 yıl idi. Hesaplanan 2. ve 4. parmak uzunluk farkı ve oranı total testosteron düzeyi ile orta seviyede, serbest testosteron düzeyi ile ise pozitif korelasyon göstermiştir (*p=0.028, p=0.016, p=0.003, p=0.016*). Seks hormonu bağlayıcı globulin düzeyleri ile 2. ve 4. parmak uzunluk farkı ve oranı arasında hafif negatif korelasyon saptandı (*p=0.011, p=0.016*). Metabolik sendrom parametreleri ile 2. ve 4. parmak uzunluk farkı ve oranı arasında istatistiksel olarak anlamlı bir ilişki bulunmadı. Buna göre 2. ve 4. parmak uzunluk farkı ve oranının androjenler ile ilişkili olduğu görüldü.
Sonuç: Kolayca ölçülebilen 2. ve 4. parmak uzunluk farkı ve oranı, kadınlarda hiperandojenizmin önemli bir belirleyicisi olarak kullanılabilir. Bu çalışmada, 2. ve 4. parmak uzunluk farkı ve oranı metabolik sendrom ile ilişkili bulunmadı, ancak daha geniş hasta grubu ile ek çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Parmaklar, Hiperandrojenizm, Metabolik Sendrom

INTRODUCTION

The Homeobox genes HoxA and HoxD control the differentiation of the urinogenital system and may therefore indirectly influence the prenatal production of testosterone and estrogen and the development of the digits (1,2). The sexual dimorphism in the 2nd to 4th (2nd:4th) digit length ratio has long been known, and studies now provide direct and indirect evidence that sex differences in the 2nd:4th digit length ratio arise from *in utero* concentrations of sex hormones and are negatively related to prenatal testosterone and positively associated with prenatal estrogen. This observation has led to the hypothesis that patterns of digit formation may relate to gonad function (3).

Prenatal androgen exposure can be determined by the different length ratios between the second and fourth digits in the postpartum period. This relationship has been explained by the involvement of the same genes (HoxA, HoxD) in the development of the genital system and the digits (4). Previous studies showed that prenatal testosterone affects cognitive and behavioral functions in humans and differs among genders (5). The 2nd:4th digit length ratio is associated with size at birth in males (6), sperm count (3), family size (7), age at breast cancer presentation (8) and age at myocardial infarction (9). Understanding the factors affecting the development of the 2nd:4th digit length ratio is important. Indirect evidence shows that sex difference in 2nd:4th digit length ratio is causally related to relative concentrations of testosterone and estrogen. The mother's waist-to-hip ratio (WHR), and a positive correlate of testosterone and negative correlate of estradiol levels, are negatively related to the 2nd:4th digit length ratio of their male and female children (10).

Some behavioral traits predominantly found in males have been shown to be associated with low 2nd:4th digit length ratio values; e.g., left hand preference (11), good visual ability (12), autism and Asperger's syndrome (13). Males and females with congenital adrenal hyperplasia, a trait associated with high prenatal testosterone, have low 2nd:4th digit length ratio values compared to controls (14,15). Traits mainly associated with females; e.g., high verbal fluency (16) and high levels of emotional behavior (17), are associated with high 2nd:4th digit length ratios. Hyperandrogenism in metabolic syndrome; especially in the female gender has been questioned. However polycystic ovarian syndrome in patients with hyperandrogenism and metabolic syndrome are associated, but in the present study we investigated the relationship between metabolic syndrome and hyperandrogenism parameters and the 2nd:4th digit length difference and ratio in females. The aim of this study was to evaluate the relationship finger length and metabolic syndrome.

MATERIALS AND METHODS

Subjects

Of the 150 females over the age of 18 years who visited Ankara Training and Research Hospital, 1st Internal Medicine Clinic between May 2010 and June 2010 and were enrolled in this prospective, cross-sectional clinical study, 137 completed the study. Informed consent was obtained from patients and was approved by the local ethics committee. The patients were questioned regarding smoking, exercise status, hypertension, DM and use of antihyperlipidemic medication.

Anthropometric measurements

Weight and height measurements were taken with shoes off and the patients wearing thin and light clothes. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters (kg/m^2).

Neck circumference was measured immediately below the Adam's apple (cricoid cartilage) at the base of the neck; chin parallel to the ground with the patient's arms at their sides and facing the person taking the measurements.

Waist circumference was measured at the end of expirium at the point between the lowest rib and the superior border of iliac crest while the patient was standing. Hip circumference was measured at the widest point of the hip. Height, waist and hip circumference were recorded in centimeters and weight in kilograms to one decimal point. Thigh circumference was measured at the widest point of the thigh with the patient standing (just under the gluteal fold).

Blood pressure

Blood pressure was measured on the right arm using a quicksilver sphygmomanometer after at least five minutes of rest while the patient was sitting upright. For patients with inaudible Korotkoff sounds, measurements were taken from both arms and the average calculated.

Laboratory analyses

Biochemical parameters associated with metabolic syndrome were measured. The patient's blood was drawn between 9:00 and 11:00 am following 12 h of fasting. Fasting glucose levels (mg/dL), fasting insulin levels, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were measured. Total testosterone, free testosterone and sex hormone-binding globulin (SHBG) levels were also measured for comparison to metabolic syndrome and associated parameters.

Measurements were performed in the central biochemistry laboratory of Ankara Training and Research Hospital. Glucose, total cholesterol and HDL cholesterol levels were measured using the Roche Diagnostics kit with the Roche Modular DP analyser. LDL cholesterol levels were

calculated using the Friedewald formula (LDL=total cholesterol-triglyceride/5-HDL).

Insulin levels were measured using DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits. Albumin was measured using autoanalyzer spectrophotometry with an Olympus 2700 device and TSH was measured using the chemoluminescence method with the Centaur XP device. Total testosterone was measured using the chemoluminescence method with the Advia Centaur XP device, free testosterone was measured using the RIA method and SHBG was measured using the chemoluminescence method. Free androgen index (FAI) or free testosterone index was calculated by the ratio of total testosterone to SHBG. The homeostatic model assesment of insulin resistance (HOMA-IR) was used for evaluation of insulin resistance. HOMA values [fasting serum insulin (μIU/mL) × fasting plasma glucose (mmol)/22.5] were calculated for each patient.

Statistical analyses

Statistical analysis was performed using SPSS 11.5 for Windows. The distribution of quantitative variables was evaluated using Kolmogorov-Smirnov (Lilliefors) test. Correlation analysis was used to investigate the relationships between variables. Pearson's correlation coefficient was used when the distribution was normal and Spearman's test was used when it was not normal. The significance of the difference between more than two groups was evaluated using unidirectional variance analysis. The relationship between metabolic syndrome criteria and androgens was evaluated using the independent samples *t*-test. The Mann-Whitney U test was used for heterogenous values. We investigated the parameters with the highest degree of contribution to predict values associated with the androgens studied using linear regression.

RESULTS

Subjects

The mean age of our patient is 46.1 yrs.

Anthropometric measurements

The 2nd:4th digit length difference and ratio were mildly correlated with total testosterone levels (p=0.028, p=0.016, respectively). The 2nd:4th digit length difference and ratio were positively correlated with free testosterone levels (p=0.003, p=0.016, respectively).

SHBG levels showed a strongly negative correlation with neck circumference (p<0.001), negative correlation with Waist-hip ratio (WHR) (p=0.001) and mildly negative correlation with waist circumference, waist-thigh ratio (WTR), 2nd:4th digit length difference and ratio (p=0.026, p=0.023, p=0.011, p=0.016, respectively), (Table 1, Table 2).

Metabolic syndrome parameters

There was no statistically significant association between metabolic syndrome parameters and 2nd:4th digit length difference and ratio. Patients with or without metabolic syndrome showed no significant differences in 2nd:4th digit length difference and ratio (p=0.465, p=0.540, respectively) (Table 3). In our study the most powerful predictors of SHBG was found 2nd:4th digit length difference (Table 4).

Table 1. Mean and correlation coefficients (r) between antropometric and androgen parameters (n=137)

	Median±SD	Total T	Free T	Free/Total T	SHBG	FAI
BMI	28.55±5.61	-0.029 (0.738)	-0.052 (0.544)	-0.184 (0.031)	-0.150 (0.080)	-0.042 (0.626)
Neck C	35.4±2.27	0.027 (0.753)	0.108 (0.209)	0.099 (0.250)	-0.309 (<0.001)	0.273 (0.001)
Waist C	93.80±12.99	-0.043 (0.617)	-0.007 (0.935)	-0.091 (0.292)	-0.190 (0.026)	-0.014 (0.875)
Hip C	99.0±10.41	-0.090 (0.297)	0.043 (0.620)	0.119 (0.165)	-0.084 (0.327)	0.033 (0.704)
Thigh C	53.42±5.11	-0.091 (0.288)	-0.009 (0.919)	0.100 (0.247)	-0.032 (0.707)	-0.007 (0.937)
Waist-to-hip ratio	0.946±0.069	0.004 (0.959)	0.085 (0.323)	0.068 (0.427)	-0.291 (0.001)	0.245 (0.004)
Waist-to-thigh ratio	1.76±0.21	-0.005 (0.962)	0.029 (0.733)	-0.041 (0.635)	-0.195 (0.023)	0.039 (0.653)
2nd digit	7.61±0.53	0.114 (0.184)	0.133 (0.122)	0.076 (0.375)	-0.072 (0.402)	0.076 (0.378)
4th digit	7.75±0.55	0.006 (0.942)	-0.014 (0.873)	-0.025 (0.769)	0.077 (0.369)	-0.086 (0.319)
2nd:4th digit ratio	0.984±0.047	0.205 (0.016)	0.261 (0.002)	0.128 (0.136)	-0.206 (0.016)	0.260 (0.002)
2nd:4th digit LD	-0.137±0.371	0.188 (0.028)	0.252 (0.003)	0.131 (0.128)	-0.217 (0.011)	0.268 (0.002)

T: testosterone, SHBG: sex hormone-binding globulin, FAI: free androgen index, BMI: body mass index, SD: standard deviation. Data are given as r (p value), C: circumference, LD: length difference

Table 2. The p values for the correlations between 2nd:4th digit length difference and ratio and antropometric parameters

	Waist circumference	**BMI**	**Neck circumference**	**WHR**
2nd:4th digit length difference	0.939	0.932	0.628	0.566
2nd:4th digit ratio	0.945	0.988	0.632	0.603

BMI: body mass index, WHR: waist-hip ratio

Table 3. The *p* values for the correlations between 2nd:4th digit length difference and ratio and metabolic syndrome parameters

	Waist circumference	Hypertension	DM	HDL	TG
2nd:4th digit length difference	0.822	0.352	0.921	0.797	0.605
2nd:4th digit ratio	0.895	0.369	0.824	0.724	0.811

DM: Diabetes Mellitus HDL: High density lipoprotein TG: Triglycerid

Table 4. The usefulness of study parameters in predicting the androgen levels of patients

Model	Total T	Free T	Free/Total T	SHBG	FAI
1	FGL (30.1%)	Neck C (3.4%)	BMI (3.3%)	2nd:4th digit difference (11.6%)	Neck C (3.7%)
2	FGL+HOMA (32.7%)	Neck C+Hip C (8.8%)	BMI+Hip C (6.7%)	2nd:4th digit difference+Neck C (18.6%)	Neck C+Hip C (14.2%)
3	FGL+HOMA+hsCRP (34.8%)	Neck C+Hip C+FGL (32.2%)			Neck C+Hip C+FGL (37.4%)

T: testosterone, FGL: fasting glucose level, C: circumference, BMI: body mass index, hsCRP: high sensitivity C-reactive protein, HOMA: Homeostasis Model Assessment, SHBG: sex hormone binding globulin, FAI: free androgen index
Values in parantheses show the adjusted coefficient of determination (adjusted R^2) High Sensitivity C-Reactive Protein

DISCUSSION

Prenatal androgen exposure can be evaluated using the difference in length and ratio between the second and fourth digits in the postpartum period. The underlying hypothesis is that Homeobox genes HoxA and HoxD are responsible for the urogenital system differentiation, prenatal androgen synthesis and digit development. In animal models, prenatal and neonatal androgen exposure has resulted in increased adiposity, insulin resistance and changes in adipose tissue lipolysis in adulthood (18).

Various studies have shown that these measurements, which can differ between genders or even in the same gender, are related to prenatal androgen production (4).

Lutchmaya et al. measured free and total testosterone in the amniotic fluid of 33 fetuses and evaluated the same children for digit length at 2 years of age. They also reported a positive correlation between 2nd:4th digit length ratio and free and total testosterone (4).

In another study conducted in the USA with 39,913 patients (22,521 females), Fisher et al. reported a positive correlation between 2nd:4th digit length ratio and androgen levels (19).

In our study was found statistically significant relationship between 2nd:4th digit length ratio and androgen levels in adult female gender. Prenatal androgen exposure has been hypothesized to be related to adult anthropometric measures, especially abdominal adiposity (20).

Some studies have linked the WHR with the 2nd:4th digit length ratio. Thus, the WHR in females is positively correlated with serum levels of testosterone and negatively correlated with 2nd:4th digit length ratios (21).

McIntyre et al. found a weak inverse association between right 2D:4D and waist circumference in a sample of 42 men between the ages of 31–76 years (22).

Fink et al. investigated several anthropometric measures in a sample of 50 males and 70 females and found moderately strong inverse associations between waist circumference, hip circumference and waist-to-chest ratio and both right and left 2nd:4th digit length ratios in females. This study also found that BMI was strongly positively correlated with the left 2nd:4th digit length ratio in males (23).

Muller et al. studied 24,469 females and 17,045 males and found no strong associations between 2nd:4th digit length ratios and height, weight, BMI, waist circumference, hip circumference, WHR, fat mass, fat-free mass or fat mass percentage. Several studies have investigated possible associations between adult anthropometric measures and 2D:4D, with largely inconsistent result (24). In our study was found no statistically significant relationship between 2nd:4th digit length ratio and anthropometric measures and likewise did not have a relationship with 2nd:4th digit length ratio and metabolic syndrome. It's important; to date, no study in which digit length difference and ratio were used to predict androgen exposure and that investigated the relationship to metabolic syndrome has been reported.

In conclusion, since digit measurement is relatively easy and requires no laboratory work, it can be used as a marker for hyperandrogenism. In the present study, no statistical significance was found due to the limited number of patients. Therefore, future studies with a larger cohort of patients are necessary.

Conflict of Interest: *None declared*

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