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Correlation between Digit Length Ratios and Risk Factors Associated with Metabolic Syndrome

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Abstract

Metabolic syndrome refers to a group of risk factors that increase a person's chance of developing cardiovascular disease and/or diabetes mellitus type II. Hypertension and insulin resistance, two factors associated with metabolic syndrome, are reflective of prenatal androgen exposure. Androgen exposure in utero is also related to the ratio of the length of the 2nd and 4th digits of the hand (2D:4D).

Objective: To test the hypothesis that the 2D:4D correlates with parameters associated with metabolic syndrome measuring in the risk range for developing metabolic disease. If our hypothesis is correct, measuring a patient's 2D:4D would be a non-invasive way to determine the risk for developing cardiovascular disease and/or diabetes mellitus type II.

Methods: The 2D:4Ds of 45 adults were measured at a health fair and correlated with the parameters associated with metabolic syndrome, and body mass index (BMI). The predictability of the 2D:4D for determining the risk of metabolic disease was also assessed.

Results: Significant correlations were found between the 2D:4D of the left and right hands with elevated concentrations of circulating triglycerides, and the right hand with BMI. The AUC for the relationship of the right and left hand 2D:4D with elevated triglycerides was 0.7538 and 0.7012, respectively.

Conclusion: The relationship between the 2D:4D and elevated triglycerides supports use of the 2D:4D as a non-invasive screening tool to assess an individual's risk for metabolic syndrome. Such a screening tool may increase the number of people willing to participate, enabling earlier detection and intervention to stave off metabolic diseases.

Keywords: 2D:4D; Androgen; Metabolic disease; Screening

Introduction

The uterine environment can impact fetal development such that offspring are predisposed to develop certain diseases later in life. For example, inappropriate exposure to androgens *in utero* – concentration and/or time of exposure, can predispose female offspring to develop polycystic ovary syndrome (PCOS). PCOS is the number one cause of infertility in premenopausal women, and frequently women with PCOS have metabolic diseases such as hypertension and insulin resistance [1]. Interestingly, treatment of various animals prenatally with testosterone produces the metabolic as well as reproductive disorders associated with PCOS [2-9]. The metabolic defects associated with prenatal androgen exposure are not limited to females, but are also seen in males [2,10,11]. Likewise, hypertension and insulin resistance are not only associated with PCOS, but also with metabolic syndrome which impacts both males and females. Therefore, prenatal androgen exposure may also contribute to the propensity for metabolic syndrome.

Another parameter that is reportedly affected by androgen exposure as a fetus is the ratio of the lengths of the 2nd and 4th digits (2D:4D) of the hand. In women, the 2nd and 4th digits are more similar in length than in men who tend to have a shorter 2nd digit, leading to a greater 2D:4D ratio in women compared to men [12,13]. An example of this relationship can be seen in women and men born with congenital adrenal hyperplasia (CAH) - a condition that exposes the fetus to increased levels of androgens during development. In these individuals, the 2D:4D ratios were smaller (i.e. more masculine) compared to non-CAH controls [14,15]. This relationship seems to be established by birth or early neonatally, and is not affected by hormonal changes associated with puberty [14,16,17].

The sex difference in the 2D:4D ratio may be not due to bone length, but rather soft tissue deposition at the tip of the finger. When measuring bone length of the 2nd and 4th digits from x-rays there was no difference between the ratio in males and females. However, when these same hands were xeroxed and the digit measurement included the whole finger, not just the bone, a significant difference between male and female 2D:4D ratios was observed [18,19]. Hence, it appears that soft tissue/adipose deposition plays a role in the sexual dimorphism of the 2D:4D ratio. Such reasoning is in agreement with

androgens tending to be lipolytic, whereas estrogens tend to be lipogenic. Taken together, it may not necessarily be absolute exposure of the fetus to androgens, but the ratio of androgen:estrogen *in utero* that is responsible for the sex differences in digit ratio [17,18,20]. Since it is this hormonal relationship that is skewed when there is inappropriate androgen exposure during fetal development, we hypothesized that the 2D:4D ratio would correlate with parameters associated with metabolic syndrome.

Metabolic syndrome, also known as syndrome X, is a term referring to a group of risk factors that increase a person's chance of developing cardiovascular disease and/or diabetes mellitus type II [21]. People with metabolic syndrome are also more likely to die from all cause events [21,22]. Various groups have defined diagnostic criteria for metabolic syndrome, one of which is the Adult Treatment Panel III [23,24]. The standards established by this group include clinical measures of central adiposity, hypertension, glucose intolerance, and dyslipoproteinemia. If an individual has any three of these measures in the defined risk range they are considered to have metabolic syndrome.

The goal of the current study was to assess the correlation of the 2D:4D ratio with known risk factors for developing cardiovascular disease and diabetes mellitus type II. Because it is reflective of fetal androgen exposure, we hypothesized that the 2D:4D ratio would correlate with parameters associated with metabolic syndrome measuring in the risk range for developing metabolic disease. If our hypothesis is correct, measuring a patient's 2D:4D ratio would be a non-invasive way to determine their risk for developing cardiovascular disease and/or diabetes mellitus type II. Such screening may increase the number of people willing to participate, enabling earlier detection and intervention to stave off metabolic disease states.

Methods

Study population

Participants were recruited from a community adult health screening clinic hosted by the West Virginia School of Osteopathic Medicine on September 29, 2012 in Lewisburg, WV, using announcements at the conclusion of the screening exams. All adults who attended the clinic were eligible for inclusion in the study. Exclusion criteria were previous or current damage to the 2nd and/or 4th digits (i.e. fracture) or medical conditions affecting the digits (i.e. arthritis). The protocol for the present study was approved by the Institutional Review Board at the West Virginia School of Osteopathic Medicine. All participants provided signed informed consent at the time of digit measurement. Measurements of the 2nd and 4th digits of each hand were performed by one individual.

Data collection

The digits were measured using a Vernier caliper bilaterally and the ratio of the length of the 2nd and 4th digits of each hand (2D:4D) calculated. Data relating to parameters that are risk factors for metabolic syndrome according to the ATP III guidelines (Table 1) were collected during the health screening process and coded as either 1=present or 0=not present [23,24]. Risk factors were combined to assess the prevalence of metabolic syndrome. The presence of three or more risk factors was indicative of the presence of metabolic syndrome. Because the majority of participants were not fasted (56%), circulating concentrations of glucose were not included in the analysis.

Assessed parameters	Risk level
Waist Circumference	
Men	>40 in
Women	>35 in
Circulating Concentrations of High Density Lipoprotein (HDL) Cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Circulating Concentrations of Triglycerides	≥ 150 mg/dL
Blood Pressure	≥ 130/≥ 85 mmHg or currently on antihypertensive medication
Circulating Concentrations of Glucose (Fasting)	≥ 110 mg/dL

Table 1: Parameters measured to assess risk of developing metabolic syndrome. Levels of each parameter indicating risk for developing metabolic syndrome reflect guidelines established by ATP III.

Statistical Analysis

Data were analyzed using StataIC Version 13 [25]. Ratios of the second and fourth digits of each hand were assessed for normality. Descriptive statistics of each risk factor and pairwise correlations with 2D:4D ratios were conducted. A $p<0.05$ was considered significant. Area under the curve (AUC) analyses using under receiver operator curves assessed predictive performance of the 2D:4D ratio on the defined parameters measuring in the risk range for metabolic syndrome. AUC values greater than 0.70 were considered to be adequate. For parameters with AUC>0.7, cut points for potential use clinically were determined [26]. Post-estimation analysis of sensitivity and specificity were conducted and cut points determined based on correct classification.

Results

This study investigated the relationship between the 2D:4D ratio of the left and right hands with the parameters for metabolic syndrome as defined by the ATP III (Table 1). Forty-five participants were recruited into the study. Two of the participants did not consent to have blood drawn, resulting in forty-three samples analyzed for circulating concentrations of HDL and triglycerides.

There were thirty women (66.7%) who participated in the study and 15 (33.3%) men. In this sample population, 30/45 participants had a waist circumference in the risk range for metabolic syndrome (Table 2). There were 27/43 participants with circulating concentrations of HDL in the risk range for metabolic syndrome, and 28 individuals had circulating concentrations of triglycerides ≥ 150 mg/dL. Twenty-four of 45 participants had systolic and/or diastolic blood pressure ≥ 130/≥ 85 mmHg, and five individuals were on antihypertensive medications resulting in 29/45 participants with blood pressure in the risk range for metabolic syndrome (Table 2). We calculated BMI for each participant and 22/45 were obese (BMI ≥ 30 kg/m^2).

The ratios of the second and fourth digits of each hand were normally distributed. The mean left hand 2D:4D ratio was 1.007, and 1.003 for the right hand. Our results show a correlation between the

2D:4D ratio of both the left and right hands with triglyceride levels (Table 2). The correlation with triglyceride levels is more robust between the digit ratio of the right hand (r^2=0.4257, p<0.05) compared with that of the left hand (r^2=0.2954, p<0.05; see Table 2).

Metabolic Syndrome Risk Factor	Participants in Risk Range	Left Hand 2D:4D		Right Hand 2D:4D	
		Correlation	AUC	Correlation	AUC
Waist Circumference	30/45	-0.06	0.5756	-0.02	0.5296
HDL	27/43	0.01	0.4850	0.05	0.5412
Triglycerides	28/43	0.30*	0.7012	0.43*	0.7538
Blood Pressure	29/45	0.22	0.6369	0.27†	0.6364
Glucose Blood (Fasting)	9/20	-	-	-	-
BMI	22/45	0.24	0.5457	0.39*	0.5548
Metabolic Syndrome	23/43	0.16	0.5756	0.28†	0.5296

Table 2: Correlations and AUC analyses between risk factors for metabolic syndrome, BMI, and metabolic syndrome (as defined by having 3 or more parameters in the risk range) with the 2D:4D of the left and right hands. Limited sample size precluded analysis of fasting concentration of glucose, *p<0.05; †p<0.10.

The AUC for the relationship of the right hand 2D:4D ratio with elevated triglycerides is greater than that for the left 2D:4D ratio (0.7538, CI 0.598-0.910 versus 0.7012, CI 0.537-0.866, respectively; Figure 1). The usefulness of the 2D:4D ratio to predict an individual having circulating concentrations of triglycerides in the risk range for metabolic syndrome was determined. The sensitivity and specificity for the 2D:4D ratio being predictive of circulating concentrations of triglycerides being greater than 150 mg/dL are 89.3% and 26.7% for the left hand, and 84.6% and 53.3% for the right hand, respectively. Post-estimation analysis of cut points identified that a left hand 2D:4D ratio>0.9821, and/or a right hand 2D:4D ratio>0.9811 corresponds to the highest percent correctly classified (72.1% and 75.6%, respectively). Given the small sample size, less stringent significance cutoffs indicate that the right hand 2D:4D ratio is also correlated with blood pressure (r^2=0.2741, p<0.10). Our results do not support a relationship between the 2D:4D ratio of either hand with waist circumference, or circulating concentrations of HDL (Table 2).

Metabolic syndrome is diagnosed when a patient has at least three of the five defined parameters assessed in the risk range. More than half (n=23) of the participants had at least three parameters in the risk range as defined by the ATP III. Given the small sample size, cutoff of less stringent significance indicates that the right hand 2D:4D ratio is correlated with metabolic syndrome (r^2=0.2804; p<0.1).

We investigated the correlation between BMI and finger digit ratio even though this parameter is not used to diagnose metabolic syndrome. BMI was significantly correlated with the right hand 2D:4D ratio (r^2=0.3945, p<0.05; Table 2).

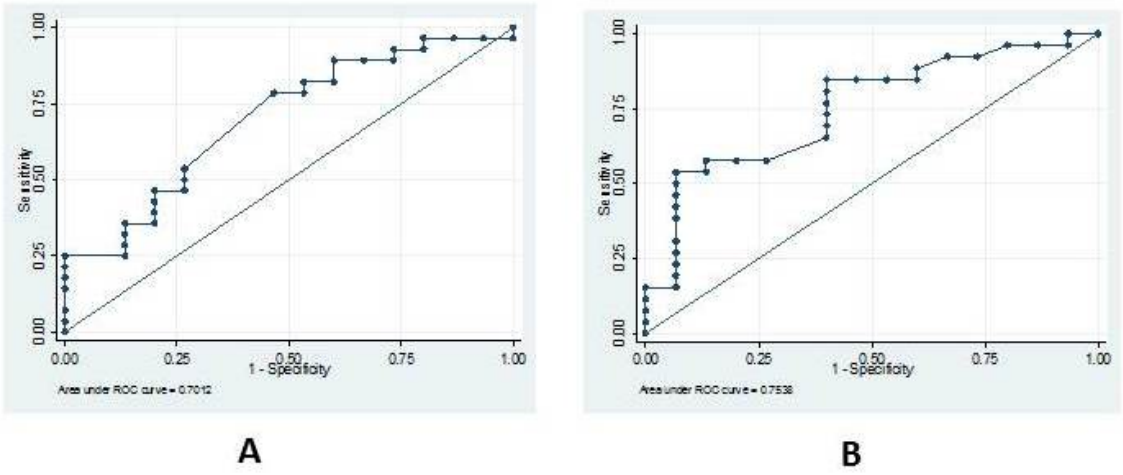

Figure 1: ROC analyses for predictability of A) the left and B) right hand 2D:4D on triglyceride levels being in the risk range for metabolic syndrome as defined by ATP III.

Discussion

The results of this study present evidence that the 2D:4D ratio may be a useful tool to assess risk for elevated triglycerides, and metabolic syndrome. The 2D:4D ratio of the left hand was associated with elevated triglycerides, while the 2D:4D ratio of the right hand was correlated with elevated triglycerides and BMI, and tended to be associated with blood pressure and metabolic syndrome. The weaker relationship between the 2D:4D ratio of the left hand compared with that of the right hand with any of the parameters measured may be explained, at least partially, by findings from other studies suggesting differences between the left and right hands regarding apparent fetal androgen exposure. There are reports in the literature illustrating that the relationship of fetal androgen exposure to the 2D:4D ratio is stronger between digit measurements of the right hand compared to the left [9,13]. The stronger association of the right hand 2D:4D ratio with various traits assumed to be impacted by *in utero* androgen exposure is in line with previous findings where masculinizing traits are found to be more pronounced on the right side of the body [13]. Hence, our data are not unique in indicating a difference in association

of the 2D:4D ratio of the right hand, but not the left, with physiological factors.

The present study is not without limitations. The primary limitation is the small size of the sample. Although the sample allowed for the discovery of significant relationships between the left and right 2D:4D ratio and variables associated with metabolic disease, a larger sample would provide power to limit the potential for bias in predictive models. Data were collected at a health fair which impeded obtaining circulating concentration of glucose from fasted individuals, one of the criteria for determining metabolic syndrome as defined by the ATP III [23,24]. Additionally, because this was a self-selected population (voluntary attendance at the health fair) these individuals may have been more prone to be actively involved in maintaining their health, unwittingly biasing the data. It might be argued that the use of non-fasted triglyceride levels weakens the findings. However, there is ample evidence in the literature regarding nonfasted concentrations of triglycerides being a valid parameter to assess future cardiovascular risk [27,28]. Indeed, some data indicate that non-fasted lipid levels might be a better predictor of risk assessment for cardiovascular disease than fasted levels [29-31]. Because waist measurements were taken by a number of different individuals, there is the possibility of inter-operator variability which may be why no relationship was found between this measurement and the 2D:4D ratio of either hand. Future study designs could include advanced advertising and recruiting to promote individuals to fast prior to their participation in health screens.

Use of the 2D:4D ratio as reflective of *in utero* androgen exposure is considered by some, arguable [27]. Variation in study design and mode of digit measurement may introduce variability that could result in differing outcomes when reporting data. However, for the purpose of the current study, the reason or causative factor for the association of the right hand 2D:4D ratio with defined metabolic parameters is not as important as the finding that it does reflect the metabolic status of an individual. Therefore, determining the 2D:4D ratio of an individual offers a non-invasive tool to facilitate screening for the risk of developing metabolic disease.

Conclusion

The relationship between the 2D:4D and elevated concentrations of triglycerides supports use of the 2D:4D as a non-invasive screening tool to assess an individual's risk for metabolic syndrome. Such a screening tool may increase the number of people willing to participate, enabling earlier detection and intervention to stave off metabolic diseases.

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