American Journal of Human Biology

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American Journal of Human Biology

ORIGINAL ARTICLE OPEN ACCESS

Second to Fourth Digit Ratio (2D:4D) in Hypertension Disease

Refik Servi[1] | Ramazan Fazil Akkoc[1] | Feyza Aksu[1] | Seda Cetin[2] | Ahmet Kavaklı[1] | Murat Ogeturk[1]

[1]Department of Anatomy, Faculty of Medicine, Firat University, Elazig, Turkey | [2]Department of Anatomy, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey

Correspondence: Ramazan Fazil Akkoc (ramazan_fazil@hotmail.com)

Received: 30 October 2024 | **Revised:** 29 April 2025 | **Accepted:** 30 April 2025

Keywords: 2D:4D | anthropometry | digit ratio | hypertension

ABSTRACT

Objectives: The second to fourth digit ratio (2D:4D) is a sexually dimorphic trait thought to reflect prenatal exposure to sex hormones. 2D:4D has been proposed as a potential biomarker for various adult diseases, and evidence suggests that it may also predict cardiovascular disease risk. This study aimed to ascertain the 2D:4D of both hands in patients with hypertension and to determine whether there were any differences between this ratio and that of a control group.

Methods: The study was carried out on 400 subjects with a hypertension diagnosis, 200 males and 200 females, and the same number of 400 healthy subjects. 2D:4D was calculated by measuring the lengths of both hands' second and fourth fingers for males and females. The height, weight, and mean body mass index were also calculated for the hypertension and control groups.

Results: The mean BMI was significantly higher in the hypertension group, in the overweight category, whereas it was in the normal weight category in the control group ($p < 0.001$). The 2D:4D was significantly higher in both males and females with hypertension compared to controls. In males, the 2D:4D was elevated in both the right and left hands in the hypertension group compared to controls ($p = 0.001$). A similar trend was observed in females, with significantly higher 2D:4D in both hands in the hypertension group ($p < 0.001$).

Conclusion: The 2D:4D may be regarded as a significant factor in determining a person's risk of hypertension from birth, allowing those in the risk group to lead more preventive lives.

1 | Introduction

Hypertension is a systolic blood pressure value ≥140 mmHg and/or diastolic blood pressure value ≥90 mmHg in patients without diabetes (Williams et al. 2018). Hypertension represents a significant global public health challenge, with cardiovascular diseases (CVDs) accounting for the majority of deaths worldwide. Hypertension, a condition affecting approximately 1.3 billion adults, has been identified as a primary risk factor for numerous CVDs. Uncontrolled hypertension can result in a range of adverse clinical outcomes, including myocardial infarction (MI), stroke, heart failure, and kidney failure (WHO 2024).

It is well known that hypertension risk factors include genetics, sedentary lifestyle, and other factors. Sex hormones contribute to the pathophysiology of hypertension and are responsible for the development of gender disparities (Austin et al. 2013). In 1987, the National Institutes of Health reported a female-to-male ratio of 1.7:1 for hypertension (Rich et al. 1987). In recent years, an epidemiological study of the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management has shown that 79.5% of adult hypertension patients were female, with a predominant female prevalence observed across nearly all subtypes of the disease (Benza et al. 2010). Additionally, a study conducted in the United Kingdom and Ireland reported

that, between 2001 and 2009, 69.9% of hypertension cases occurred in females (Ling et al. 2012). Some diseases observed in adults have a fetal origin, and an adverse environment for the fetus is a critical factor associated with the development of adult diseases (Barker and Osmond 1986). Animal studies indicate that prenatal exposure to elevated levels of androgens can result in alterations to cardiovascular function and blood pressure regulation mechanisms, which may contribute to the development of hypertension (King et al. 2007; Demissie et al. 2008). Low levels of androgens in males and increased levels of androgens in females are both associated with increased risk for CVDs and elevated blood pressure (Reckelhoff 2019).

In humans, the digit ratio (2D:4D) reflects the exposure to sex hormones in the early stages of the fetal period, and this feature does not change with increasing levels of testosterone and estrogen hormones later in life (Manning and Fink 2018). In males, the relative length of the fourth digit is longer than the second digit, resulting in a lower 2D:4D than in females. A high 2D:4D is associated with low prenatal testosterone exposure and high prenatal estrogen exposure. In contrast, a low 2D:4D indicates high prenatal testosterone exposure and low prenatal estrogen exposure (Manning 2011). In studies on 2D:4D, it has been hypothesized that there is a connection between these hormones in the fetal period and the general and sexual health of individuals (Kalichman et al. 2013). The 2D:4D has been reported to differ in diseases in which gender disparities are evident or in which prenatal effects are suspected, such as breast cancer, prostate cancer, Alzheimer's disease, and multiple sclerosis (Muller et al. 2011, 2012; Vladeanu et al. 2014).

It was reported that 2D:4D of males with MI is statistically higher than that of the control group. However, this ratio was higher in females with MI compared to the control group (Kyriakidis et al. 2010). A study conducted on male autopsy cases found that individuals with atherosclerotic plaques in the right coronary artery had a higher 2D:4D compared to those without plaques. The study linked the relationship between the 2D:4D and atherosclerosis formation to prenatal sex hormones (Ozdogmus et al. 2010). In a similar study, it was detected that males with coronary artery disease had a higher 2D:4D for both hands compared with the control group. No statistically significant relation was reported among females (Wu et al. 2013). In another study investigating the relationship between the 2D:4D and cardiovascular risk factors in males, it was specified that higher BMI and systolic blood pressure were significantly associated with the 2D:4D of the right hand. In males with hypertension, 2D:4D was higher in both hands than in the control group, and this ratio of the left hand was only associated with systolic blood pressure (Bagepally et al. 2020). A study investigated the relationship between left-hand 2D:4D and blood pressure in children and adolescents, and the authors reported no significant correlation (Zhang et al. 2019).

Genetic changes in hypertension have been identified in estrogen-metabolizing enzymes and estrogen receptors (Hester et al. 2019). Given the gender disparity in hypertension prevalence, we think that 2D:4D may be associated with hypertension. There are few studies in the literature revealing the relationship between 2D:4D and hypertension, especially in females. Research in males of Indian ethnicity has shown a positive association between a higher 2D:4D and elevated blood pressure levels (Yadav and Bala 2016; Kumar and Ali 2024), suggesting that the digit ratio, a presumptive marker of prenatal androgen exposure, may be associated with cardiovascular risk factors in males. However, studies examining this association, particularly in females, remain limited. Research on postmenopausal females has reported no significant relationship between the 2D:4D and CVDs (Fischer Pedersen et al. 2021). However, findings in Japanese females with idiopathic pulmonary arterial hypertension indicate a higher 2D:4D in affected individuals (Yamamoto et al. 2015).

The relatively limited number of studies conducted so far underscores the need for further investigation into the potential association between 2D:4D and hypertension. Therefore, the objective of this study is to examine the relationship between 2D:4D and hypertension through the evaluation of data obtained from a large sample of both male and female participants.

2 | Material and Method

2.1 | Ethics Statement

The ethics committee approval required for this study was obtained from the Non-Interventional Research Ethics Committee of Firat University, Faculty of Medicine (Number: 2021/08-43, date: 07.12.2021). The signed informed consent form was obtained from the participants, the patients, and the control groups participating in the study.

2.2 | Study Population

In this study, 200 males and 200 females diagnosed with hypertension, aged 20–72 years, who applied to Firat University Hospital, and 200 males and 200 females as the control group, a total of 800 subjects were included. The control group comprises subjects who are hospital visitors for routine check-ups or to visit patients. All subjects who voluntarily participated in the study were informed verbally before starting the measurements. After the participants had signed the written informed consent form, height, body weight, and second and fourth finger lengths were measured. Those with any chronic disease other than hypertension and those with edema, fractures, or structural anomalies were excluded from the study.

2.3 | Measurements

This study measured the second and fourth digit lengths for both hands using calibrated calipers (SCITOOLS, China). The digital scale (0–180 kg) (Crown; Jasper International Trading Co. Ltd., China) was used for body weight measurement.

All participants' heights and body weights were measured barefoot in their daily clothing. The height was determined as the distance between the tip of the finger and the crown of the head on a straight and hard surface. The measurement of the second and fourth

finger lengths, the distance from the palmar face from the midpoint of the proximal fold of the proximal phalanx to the distal end of the distal phalanx was measured vertically (Akkoc et al. 2023). Two researchers independently obtained all measurements, each blinded to the other's assessments. Each observer performed a single measurement for each participant. The recorded values were then compared, and when there was an inter-researcher discrepancy of 2 mm or more in a measurement, all measurements with discrepancies were excluded. Compatible measurements were averaged. The 2D:4D was calculated by dividing the length of the second finger by that of the fourth finger.

2.4 | Statistical Analysis

The statistical analyses of the study were performed using the "IBM SPSS Statistics Version 22.0" package program. The categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation. The data were expressed as mean ± standard deviation. p values <0.05 were considered statistically significant. The Chi-square test statistics were used to compare categorical measures between groups. Whether continuous measurements provided the assumption of normal distribution was tested with the Kolmogorov–Smirnov test. The independent group t-test was used to compare continuous measurements between groups.

3 | Results

The mean age of hypertensive males (51.04 ± 8.01 years) was found to be significantly higher than that of the control group (41.83 ± 12.7 years) ($p<0.001$). A similar trend was observed in hypertensive females, where the mean age was 49.96 ± 9.3 years, significantly higher than the 42.18 ± 10.1 years recorded in the control group ($p<0.001$). No significant difference was observed in height between hypertensive and control groups in either males ($p=0.060$) or females ($p=0.063$). However, hypertensive individuals revealed significantly higher body weight compared to the control group, both in males (83.76 ± 10.6 kg vs. 76.02 ± 6.8 kg, $p<0.001$) and in females (77.05 ± 10.2 kg vs. 63.86 ± 8.02 kg, $p<0.001$) (Table 1).

Regarding the 2D:4D, hypertensive males exhibited significantly higher values compared to controls in both the right hand (0.9695 ± 0.01 vs. 0.9631 ± 0.02, $p=0.001$) and the left hand (0.9685 ± 0.01 vs. 0.9633 ± 0.01, $p=0.001$). Similarly, hypertensive females demonstrated significantly higher 2D:4D in both the right hand (1.04 ± 0.01 vs. 1.01 ± 0.01, $p<0.001$) and the left hand (1.03 ± 0.02 vs. 1.00 ± 0.01, $p<0.001$) (Table 1).

4 | Discussion

Hypertension is the primary risk factor for CVDs, damage to vital organs such as the heart, brain, and kidneys, premature death, and disability worldwide. The pathophysiology of hypertension is complex and influenced by many factors, including gender. Sex hormones affect blood pressure regulation, cardiovascular risk factors, and comorbidities differently (Mills et al. 2020). Although there are both human and animal studies suggesting that sex hormones influence the 2D:4D during the fetal period (Lutchmaya et al. 2004; Manning and Fink 2017, 2023), some studies argue that fetal hormone exposure does not affect 2D:4D (Richards et al. 2021, 2022). Research on the 2D:4D remains a prominent area of interest, particularly regarding its association with diseases and conditions linked to sex differences.

In our study, the 2D:4D in both hands of the hypertensive male and female groups was higher than that of the control group and was statistically significant. The 2D:4D was found to be dimorphic between the sexes in the control group, and the ratio was higher in females than in males. This result is consistent with previous studies. It supports the hypothesis that testosterone in the embryonic period affects the growth of the fourth finger and estrogen affects the growth of the second finger (Muller et al. 2012; Oyeyemi et al. 2014).

Bagepally reported that higher BMI and systolic blood pressure values were significantly associated with 2D:4D of the right hand. They reported that the 2D:4D was higher in both hands in people with hypertension than in the control group and that the 2D:4D of the left hand was only associated with systolic blood pressure. Since the study was conducted only on males, no information is available about females (Bagepally

TABLE 1 | Comparison of age, height, body weight, body mass index (BMI), and 2D:4D by gender of the control and hypertension groups.

Parameter	Male (control, n:200)	Male (hypertension, n:200)	p	Female (control, n:200)	Female (hypertension, n:200)	p
Age (years)	41.83 ± 12.7	51.04 ± 8.01	<0.001	42.18 ± 10.1	49.96 ± 9.3	<0.001
Height (cm)	174 ± 0.04	173 ± 0.04	0.060	163 ± 0.05	162 ± 0.03	0.063
Weight (kg)	76.02 ± 6.8	83.76 ± 10.6	<0.001	63.86 ± 8.02	77.05 ± 10.2	<0.001
BMI (kg/m^2)	24.89 ± 2.3	27.69 ± 3.5	<0.001	23.87 ± 3.02	29.13 ± 4.04	<0.001
2D:4D (right hand)	0.9631 ± 0.02	0.9695 ± 0.01	0.001	1.01 ± 0.01	1.04 ± 0.01	<0.001
2D:4D (Left Hand)	0.9633 ± 0.01	0.9685 ± 0.01	0.001	1.00 ± 0.01	1.03 ± 0.02	<0.001

Note: $n=800$, where each group consists of 200 participants.

et al. 2020). Similar studies have reported that hypertensive males demonstrated higher right and left 2D:4D than the control group, which are statistically significant (Yadav and Bala 2016; Kumar and Ali 2024). Notably, the results of these studies are consistent with our findings. Since these comparative studies were conducted on Indian male participants, further investigation of this association across different ethnicities is needed. Expansion of such studies will help determine whether the association between blood pressure and 2D:4D is consistent across different populations. Several studies have suggested that a higher 2D:4D in males is associated with an increased risk of coronary heart disease and earlier onset of MI (Manning et al. 2019). In addition, Manning reported a positive association between the 2D:4D in males and levels of fibrinogen, a key protein involved in blood viscosity and coagulation. Elevated levels of fibrinogen have been associated with an increased risk of MI, stroke, and other CVDs (Davalos and Akassoglou 2012). In consideration of the established correlation between hypertension and both vascular resistance and blood rheology, our findings lend support to the hypothesis that males exhibiting high 2D:4D may be predisposed to hypertension as a consequence of altered hemodynamics.

The extant literature on the subject is limited, and the existing studies have produced conflicting results. Yamamoto et al. (2015) reported a positive correlation between higher 2D:4D and idiopathic pulmonary arterial hypertension in females; however, the sample size in that study was relatively small, which limits the generalizability of their findings. In contrast, a study conducted among Chinese females reported that lower 2D:4D was associated with coronary artery disease when compared to control groups (Wang et al. 2018). The inconsistent findings regarding 2D:4D in females may be due to the use of different measurement techniques and the inclusion of different ethnic groups in the studies. While CVD remains the foremost cause of mortality among females, female subjects have historically been underrepresented in cardiovascular research, resulting in clinical guidelines primarily derived from male-centered data (The Lancet 2019). This exclusion has resulted in a paucity of studies that have developed preventive and treatment strategies tailored to females' unique cardiovascular health needs. The present study contributes to this growing body of research by demonstrating a significant association between higher 2D:4D and hypertension in females. Compared with the study by Yamamoto et al. (2015), the present study includes a larger sample size, which strengthens the reliability of the findings. The findings of this study suggest a potential link between prenatal sex hormone exposure, as indicated by 2D:4D, and blood pressure regulation in females. Further studies focusing on females are necessary to strengthen this hypothesis and bridge the significant gap in the literature.

One of the limitations of our study is that participants in the control group were classified based on self-reported data without direct blood pressure measurements. Similarly, individuals in the hypertensive group had either been diagnosed with hypertension or were using antihypertensive medication, but no blood pressure measurements were conducted in this group either. As a result, we lacked objective data on the actual blood pressure values of the participants. Although there was no significant difference in height between males and females, significant differences were observed in age and weight. Future studies should incorporate direct blood pressure measurements and ensure comparable age and weight distributions between groups to better assess the relationship between the 2D:4D and blood pressure levels.

The results of this study suggest that the 2D:4D may serve as a potential biomarker for hypertension susceptibility in both males and females. However, there are limited studies in the literature investigating the relationship between hypertension and the 2D:4D, highlighting the need for further research. Future studies may provide insights into implementing preventive measures against hypertension from birth based on 2D:4D assessments.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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