Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/asgg3e75

2D:4D RATIO VARIATION, BMI AND PULSE RATE AMONG SUBJECTS WITH NORMAL AND ABNORMAL THYROID FUNCTION

Dr. Sona Truman[1*], Dr. Anand R.L.[2]

[1*]Associate Professor, Department of Physiology, Government Medical College, Ernakulam, Kerala, India.
[2]Medical Officer, Indo Tibetan Border Police Force, Trivandrum, Kerala, India.

***Corresponding Author:** Dr. Sona Truman
*Associate Professor, Department of Physiology, Government Medical College, Ernakulam, Kerala, India.

ABSTRACT

Background

The anthropometric measurement, second to fourth digit ratio (2D:4D) is an indication of prenatal testosterone exposure and not influenced by adult hormone levels. Polymorphism of the androgen receptor gene is responsible for individual difference in 2D:4D ratio. The androgen receptors polymorphism and thyroid functions have rarely been compared even though they belong to the same superfamily of receptors.

Objective

To study the relation between 2D:4D ratio, thyroid dysfunction and other metabolic markers like BMI and pulse rate.

Methods

A descriptive cross-sectional study design was conducted in the out-patient General Medicine department, of a tertiary care hospital of central Kerala. This research was conducted after obtaining ethical clearance from the institutional ethical committee. The 2D:4D ration was calculated for each subject. The pulse rate was recorded for each subject. The BMI was calculated for each subject.

Results

There is no significant change in 2D:4D ratio in the hypothyroid subjects (P = 0.944). There is no significant change in 2D:4D ratio in the hyperthyroid subjects (P = 0.987). There was no significant correlation between BMI and 2D:4D ratio. There is no significant change in pulse rate in the hypothyroid subjects (P = 0.657). There is significant change in pulse rate in the hyperthyroid subjects (P = <0.001).

Conclusions

This study did not show significant changes in 2D:4D ratio in subjects with abnormal thyroid function. There was significant increase in P value in BMI calculations in hypothyroid subjects. There was significant decrease in P value in BMI calculations in hyperthyroid subjects. There was significant increase in P value in pulse rate in hyperthyroid subjects. These are comparable to values obtained in similar studies.

Keyword: TSH, 2D:4D Ratio, BMI, Pulse Rate.

INTRODUCTION

The 2D:4D ratio[1] is considered a biological marker that measures the length of the second digit relative to the length of the fourth digit. It has been proven to be a crude measure of intrauterine androgen[2] exposure during the narrow window of digital development in the fetal life. This ratio once developed persists for life. Lower ratio indicates higher exposure to prenatal androgens. Higher ratio indicates lower exposure to prenatal androgen. Increased exposure is seen in twin pregnancies were one of the fetuses is male and the other female. 2D:4D ratio has a positive correlation with prenatal estrogen. Maternal age, health and lifestyle during pregnancy have an effect on this ratio. In normal pregnancies with normal exposure to androgens the variation in this ratio is due to polymorphism[3] in the androgen receptors. In a normal pregnancy with normal androgen exposure the variation[4] in digit length is due to variation in the sensitivity of the androgen receptors. The fetal thyroid gland is developed around 8-13 weeks of intrauterine life. The fetal digits[5] also develop around 8-13 weeks of intrauterine life. The androgen receptor (AR) and the thyroid receptor (TR) are both nuclear receptors. Nuclear receptors[6] are a family of ligand regulated transcription factors. They bind to the DNA (deoxyribo nucleic acid) and regulate expression of genes. They are also called transcription factors. These receptors have a wide distribution[7] throughout the body of both males and females. These receptors play a key role in embryonic development[8] and adult homeostasis. The 2D:4D ratio is the measure of responsiveness of the androgen receptors to polymorphism. Androgen receptors have been demonstrated in normal and in tumors of thyroid gland. Androgens have been shown to decrease serum concentration of thyroid hormones. In this study we want to see if changes in this parameter reflect polymorphism in thyroid receptors. Studies in animals have shown that 2D:4D ratio depends on the androgen and estrogen receptors situated in the ring finger and index finger. Subjects with increased androgen sensitivity may be prone to hypothyroidism. The 2D:4D ratio has been studied[9] extensively in cardiovascular diseases[10] and various psychiatric disorders.[11] There are very few studies that compare this ratio and thyroid disorders. This ratio has been linked to personality traits, psychiatric disorders, obesity[12], etc. Androgen have been shown[13] to decrease serum concentration of thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine and thyroid binding globulin[14]. Thyroid disorders[15] are the most common endocrine disorder. Early diagnosis and treatment are very important to manage thyroid disorders. The prevalence of subclinical[16] thyroid conditions is very high among the general population (10-15%). The prevalence of clinical thyroid dysfunction is 0.1-2%. The average age of diagnosis is >60 yrs. The disease usually begins at 20-40 years. It decreases the productivity of the working population[17] and this contributes to poverty. In India[18] patients ignore the symptoms due to poverty and ignorance. Numerous studies have shown that there is drastic increase in the number of patients presenting with thyroid disorders especially hypothyroidism. Autoimmune thyroid disorders have been shown to be sex-hormone dependent. In general estrogen is immunoenhancing and androgens are immunosuppressive. Autoimmune diseases are more common in females. A cheap screening test to identify people prone for thyroid disorder can be very important to identify patients with genuine disease before ordering expensive laboratory tests especially in developing countries like India.

Steroid hormones[19] like estrogen, androgen, progesterone, etc. express their biological effects with the help of a wide spectrum of ligand-dependent intracellular transcription factors. Steroid receptors and thyroid receptors[20] are both hormone-dependent regulators of gene transcription. Their nuclear proteins[21] are similar structurally and functionally. Both receptors are located on the nuclei of a wide range of cells throughout the body. Intrauterine androgen exposure can affect the length of the different digits. Studies in female Olympic athletes have shown that a lower 2D:4D ratio is associated with higher aerobic and strength performance. Many elite athletes have taken treatment for hypothyroidism. Thyroid medications are not banned by the World Anti-Doping Agency. Thyroid medications[22] are used to enhance performance by many athletes.

MATERIALS AND METHODS

This study is a descriptive cross-sectional observational study. All the guidelines as per declaration of Helsinki and good clinical care practice guidelines as per WHO were followed. It was conducted in a tertiary reference center located in central Kerala. The study was conducted for a period of two months from April 2016 to October 2016. The study was approved by the Institutional ethical committee. The subjects were included after obtaining their informed consent. This study included all apparently healthy subjects attending the Medicine out-patient department within the age group 18-60 years. This study excluded all subjects with history of drug intake which interfere with thyroid function or pulse rate, eg. lithium, amiodarone, glucocorticoids, dopamine, β-blockers, etc. Patients diagnosed with Cushing's syndrome, thyroid malignancies, pregnancy, etc. were excluded. A total of 209 subjects were studied. Their name, age, sex, address, occupation, family history and history of thyroid disease recorded. The best way to test the thyroid function is to measure the thyroid stimulating hormone (TSH) levels in blood sample. There were 66 males and 143 females. They were divided into three groups[23] based on their thyroid function test results. In the hypothyroid group the TSH values were increased. In the hyperthyroid group the TSH values were decreased. In the matched controls the TSH values were within the normal range. Fasting venous blood was drawn after aseptic precautions were followed using a disposable syringe and needle. The blood samples were sent to the Biochemistry laboratory of the same institution to estimate the TSH values. A third generation VITROS TSH3 assay is used. The VITROS TSH3 test utilizes a 'one step' immunometric[24] sandwich assay design. The serum TSH level was measured in all patients by fully automated hormone analyzer. The 2D was obtained by measuring the length of the second[25] digit of the right hand, left hand and the mean was calculated. The 4D was obtained by measuring the length of the fourth digit of the right and left hand and the mean was calculated. The length is measured from the midpoint of the basal crease on the palmar side of the hand using a digital Vernier calliper.
Vernier calliper is the standard instrument used to measure precisely the length between two markings. It consists of two scales, the fixed main scale and a moving vernier scale. The main scale has readings in millimeters. The two points on the finger to be measured are kept between the jaws of the Vernier calliper and the graduation of the Vernier scale that matches with the main scale is noted. The ratio is obtained by dividing the 2D value with 4D value obtained. The body weight (wt.) of each subject was measured and recorded in kilograms (kg). The height (ht.) of each subject was measured and recorded in meters using a measuring tape. The BMI[26] was calculated using the formula W/H^2 (weight divided by height square). The pulse rate was recorded using a digital pulse oximeter. They are reliable, accurate, relatively inexpensive and portable. The data was entered into the excel sheet. It was analyzed using the Statistical Package for Social Sciences (SPSS) version 26. The mean and standard deviation of various parameters were calculated. The mean difference between the groups were analyzed using one way Analysis of Variation (ANOVA) P value, inter group P value and Kruskal Wallis P value. ANOVA, P value of < or = 0.05 is considered significant.

RESULTS

The normal subjects were 120. The hypothyroid subjects were 54. The hyperthyroid subjects were 35. Total normal subjects were 57.4%, hypothyroid cases were 25.8% and hyperthyroid cases were 16.7% (Table 1). The mean age of the hypothyroid group was about 40 yrs. and the mean age of the hyperthyroid group was about 36.74 yrs. (Table 2). Hypothyroidism is more in older age group compared to hyperthyroidism. The prevalence of hypothyroidism and hyperthyroidism were significantly higher (P value 0.001) in females (Table 3). The median TSH value in the control group is about 1.94. The median TSH value for the hypothyroid group is about 12.07. It is significant (P value is <0.001). The median TSH value for the hyperthyroid group is about 0.21. It is significant (P value is <0.001). The Kruskal Wallis P values is <0.001 (Table 4). The mean 2D:4D ratio in the control group was about 0.97. The ratio in the hypothyroid group was about 0.97. Compared to the controls the P value is 0.944 which is not significant. The ratio in the hyperthyroid group was also 0.97. Compared to the controls the P value is 0.987 which is not significant. The One Way ANOVA P value is 0.998 which is insignificant (Table 5). The mean BMI among the control

group was found to be about 24.10. The mean BMI in the hypothyroid group was about 27.05. This value is significant (P value <0.001). The mean BMI in the hyperthyroid group was 23.34. This value is not significant (P value 0.381). The One Way ANOVA P value is <0.001 which is significant (Table 6). The mean arterial pulse in the control group was about 78.43. The mean arterial pulse rate in the hypothyroid group was about 79.35. The P value when compared to control is not significant 0.657. The mean arterial pulse rate in the hyperthyroid group was about 100.46. The P value when compared to the controls is significant <0.001. The One Way ANOVA P values is significant <0.001 (Table 7).

	Frequency	**Percentage**
Normal	120	57.4%
Hypothyroidism	54	25.8%
Hyperthyroidism	35	16.7%
Total	209	100%

Table 1: Descriptive analysis of study group in study population

Group	**N**	**Age Mean ± SD**	**Inter group P value**	**One Way ANOVA P value**
Normal	120	38.21 ± 12.81	N vs Hypo: 0.375 N vs Hyper: 0.537	0.455
Hypothyroidism	54	40 ± 10.46		
Hyperthyroidism	35	36.74 ± 13.05		
Total	209	38.43 ± 12.28		

Table 2: Comparison of mean age across study group

	Normal	**Hypothyroidism**	**Hyperthyroidism**	**Total**
Male	53 (44.2%)	8 (14.8%)	5 (14.3%)	66 (31.6%)
Female	67 (55.8%)	46 (85.2%)	30 (85.7%)	143 (68.4%)
Total	120 (100%)	54 (100%)	35 (100%)	209 (100%)

Table 3: Comparison of gender with study group

Chi Square: 20.668

P value: 0.001 (Significant)

Group	**N**	**TSH Median (IQR)**	**Inter group P value**	**Kruskal Wallis P value**
Normal	120	1.94 (1.11, 2.83)	N vs Hypo: <0.001 N vs Hyper: <0.001	<0.001
Hypothyroidism	54	12.07 (8.54, 22.32)		
Hyperthyroidism	35	0.21 (0.07, 0.34)		

Table 4: Comparison of median TSH across study group

Group	**N**	**2D:4D Ratio Mean ± SD**	**Inter group P value**	**One Way ANOVA P value**
Normal	120	0.97 ± 0.03	N vs Hypo: 0.944 N vs Hyper: 0.987	0.998
Hypothyroidism	54	0.97 ± 0.03		
Hyperthyroidism	35	0.97 ± 0.05		
Total	209	0.97 ± 0.04		

Table 5: Comparison of mean 2D:4D ratio across study group

Group	N	BMI Mean ± SD	Inter group P value	One Way ANOVA P value
Normal	120	24.10 ± 4.04	N vs Hypo: <0.001 N vs Hyper: 0.381	<0.001
Hypothyroidism	54	27.05 ± 5.24		
Hyperthyroidism	35	23.34 ± 4.92		
Total	209	24.74 ± 4.71		

Table 6: Comparison of mean BMI across study group

Group	N	Pulse Mean ± SD	Inter group P value	One Way ANOVA P value
Normal	120	78.43 ± 11.52	N vs Hypo: 0.657 N vs Hyper: <0.001	<0.001
Hypothyroidism	54	79.35 ± 11.96		
Hyperthyroidism	35	100.46 ± 16.66		
Total	209	82.36 ± 14.97		

Table 7: Comparison of mean pulse across study group

DISCUSSION

The prevalence of hypothyroidism is more than hyperthyroidism in the study population. This is similar[27] to the prevalence seen is various similar studies. Hypothyroidism is more in older age group compared to hyperthyroidism. This is comparable with other similar studies. The prevalence of thyroid disorders was significantly higher among woman compared to men. This is similar to other studies. The TSH values were significantly higher in the hypothyroid group. The TSH values were significantly lower in the hyperthyroid group. Inter group TSH values comparison, the P value was significantly high in the hypothyroid group and significantly low in the hyperthyroid group. This is comparable[28] with similar studies. There is no significant correlation between thyroid disorders in adults and 2D:4D ratio in this study population. This is different from studies in Chinese children showing positive correlation between right hand 2D:4D ratio and TSH values. This may due to the fact that this study is conducted in adults. In this study we took the average 2D:4D ratio of both hands.

There are many studies that support taking the average ratio of both hands is a better parameter. In this study we have included both adult males and females. Studies with increased number of subjects may be helpful to confirm the findings of this study. In this population under study, BMI was more in the hypothyroid group compared[29] to the hyperthyroid group. This is comparable with similar studies. Thyroid hormone plays an important role on the basic metabolism of the body. The body metabolism is decreased in hypothyroidism and it is increased[30] in hyperthyroidism. Decrease in metabolism causes weight gain and increase in metabolism causes weight loss. There is no significant correlation between BMI and 2D:4D ratio in this study. This is comparable to other similar studies.

There are a few studies that showed significant correlation between BMI and 2D:4D ratio. The P value of pulse rate was significant in the hyperthyroid group. Excess thyroid hormone[31] increases body temperature due to increased metabolism. Thyroid hormone act directly on the heart muscles to increase the speed of cardiac contraction and the heart rate. Both these factors explain the increase in pulse rate in hyperthyroidism. This is comparable to other studies.

CONCLUSION

The above study does not show significant correlation between the 2D:4D ratio and TSH values even though the thyroid receptors and androgen receptors belong to the same superclass of nuclear receptors. The thyroid and the fingers embryonically develop during the same period but the androgen level during that period does do not affect thyroid development. These parameters have never been studied together. This makes this study unique. In this era of studies trying to understand

the long term effects of androgen exposure in the male and female babies in their development of their brain, personality, cardiac disorders, psychiatric disorders, etc. this is a unique study.

Author contributions

Dr Sona Truman designed, analyzed and wrote the paper. Paper is approved by all the contributing authors.

Conflict of interest

The authors declare no conflict of interests.

REFERENCES

[1] McIntyre MH, Ellison PT, Lieberman DE, Demerath E, Towne B. The development of sex differences in digital formula from infancy in the Fels Longitudinal Study. Proceedings of the Royal Society B: Biological Sciences 2005; 272(1571): 1473-9.
[2] Meera Jacob M, Avadhani R, Nair B, Nallathamby R. Cross sectional study of second and fourth digit ratio with physical attributes in South Indian population. Int J Anat Res 2015; 3(2): 1133-37.
[3] Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmune 2009; 32(3-4): 231-9.
[4] Lutchmaya S, Baron-Cohen S, Raggatt P, Knickmeyer R, Manning JT. 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Hum Dev 2004; 77(1-2): 23-8.
[5] Ventura T, Gomes MC, Pita A, Neto MT, Taylor A. Digit ratio (2D: 4D) in newborns: influences of prenatal testosterone and maternal environment. Early Hum Dev 2013; 89(2): 107-12.
[6] Olsen NJ, Kovacs WJ. Gonadal Steroids and Immunity. Endocr Rev 1996; 17: 369-84.
[7] Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice 2012; 18(6): 988-1028.
[8] Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018; 14: 301-16.
[9] Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. J Indian Med Assoc 2009; 107: 72-7.
[10] Kumar R, Thompson EB. The structure of the nuclear hormone receptors steroids. 1999; 64: 310-9.
[11] Carson-Jurica MA, Schrader WT, O'Malley BW. Steroid receptor family: structure and function. Endocr Rev 1990; 11(2):201-20.
[12] Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1988; 240(4854):889-95.
[13] Manning JT, Bundred PE, Newton DJ, Flanagan BF. The second to fourth digit ratio and variations in the androgen receptor gene. Evol Hum Behav 2003; 24: 399-405.
[14] Hampson E, Sankar J. S. Re-examining the Manning hypothesis: androgen receptors polymoephism and the 2D:4D digit ratio. Evolution and Human Behaviour 2012; 33(5):557-61.
[15] Zhang C, Dang J, Pei L, Guo M, Zhu H, Qu L, et al. Relationship of 2D:4D finger ratio with androgen receptor CAG and GGN repeat polymorphism. American Journal of Human Biology 2013; 25(1):101-6.
[16] Zheng Z, Cohn MJ. Developmental basis of sexually dimorphic digit ratios. Proceedings of the National Academy of Sciences 2011; 108(39):16289-94.
[17] Jacob M, Avadhani R, Nair B, Nallathamby R, Soman MA. Cross sectional study of second to fourth digit ratio with physical attributes in South Indian population. Int J Anat Res 2015; 3(2):1133-7.

[18] Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1998; 240(4854):889-95.
[19] McIntyre MH. The use of digit ratios as markers for perinatal androgen action. Reproductive Biology and Endocrinology 2006; 4:10.
[20] Oyeyemi BF, Iyiola OA, Oyeyemi AW, Oricha KA, Anifowoshe AT, Alomukii NA. Sexual dimorphism in ratio of second and fourth digits and its relationship with metabolic syndrome indices and cardiovascular risk factors. Journal of Research in Medical Sciences: The official Journal of Isfaham University of Medical Science 2014; 19(3): 234.
[21] Gild ML, Stuart M, Clifton-Bligh RJ, Kinahan A, Handelsman DJ. Thyroid hormone abuse in elite sports: the regulatory challenge. J Clin Endocrinol Metab 2022; 107(9):e3562-73.
[22] Voracek M, Loiblx LM. Scientometric analysis and bibliography of digit ratio (2D:4D) research, 1998-2008. Psychological Reports 2009; 104: 922-56.
[23] Gobrogge KL, Breedlove SM, Klump KL. Genetic and environmental influences on 2D: 4D finger length ratios: A study of monozygotic and dizygotic male and female twins. Archives of Sexual Behavior. 2008; 37(1): 112-8.
[24] Xu Y, Zheng Y. The digital ratio (2D:4D) in China: a meta-analysis. Am J Hum Biol 2015; 27(3): 304-9.
[25] Mirochnik Y, Veliceasa D, Williams L, Maxwell K, Yemelyanov A, Budunova I, et al. Androgen receptor drives cellular senescence. PloS One 2012; 7(3):e31052.
[26] Hoermann R, Midgley JE, Larisch R, Dietrich JW. Homeostatic control of the thyroid–pituitary axis: perspectives for diagnosis and treatment. Front Endocrinol 2015; 6: 177.
[27] Spencer CA, Takeuchi M, Kazarosyan M. Current status and performance goals for serum thyrotropin (TSH) assays. Clinical Chemistry 1996;42(1):140-5.
[28] Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrine Metab Clin North Am 2014; 43: 517-28.
[29] Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nature Rev Drug Discov 2009; 8: 308-20.
[30] Brent GA. Mechanisms of thyroid hormone action. J Clin Invest 2012; 122: 3035-43.
[31] Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med 2008; 168: 587-92.