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Original Article

Surgery Section

Relationship Between Second to Fourth Digit Ratios and Benign Prostatic Hyperplasia in Aging Men

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is the most common prostate disease, characterized by benign enlargement of the prostate gland in aging men. Testosterone is said to be the major factor in development of BPH. The relative length of 2nd and 4th digit (2D:4D) is a marker for prenatal androgen exposure. A low 2D:4D ratio is associated with a high prenatal androgen exposure. The main objective of this study was to assess the causal relationship between the 2D:4D ratio and incidence of BPH.

Materials and Methods: Thirty five patients with BPH were compared with 35 non BPH subjects and 35 controls recruited from general population for measures of 2D:4D ratio. BPH status was determined by clinical & radiological evaluation. Both hands of all the participants were scanned and their second and fourth digit lengths were measured and the ratio calculated.

Results: In the present study, 2D:4D ratio was lower in BPH patients compared to non BPH subjects in both hands. Compared with controls, BPH patients had lower 2D:4D ratio in the right hand, but the difference between the groups in left hand 2D:4D ratios was not significant. Compared with controls, non BPH subjects had higher 2D:4D ratio in the left hand, but the difference between the groups in right hand 2D:4D ratios was not significant.

Conclusion: Results of the present study indicate that individuals with lower 2D:4D ratios are at a higher risk of developing BPH and those with higher 2D:4D ratios are at a lower risk of developing BPH compared to the general population.

Keywords: BPH, 2D:4D, Testosterone

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common prostate disease, characterized by nonmalignant enlargement of the prostate gland in aging men. It is a major health issue among elderly men. BPH increases markedly after the 4th decade of life. Its incidence increases to 90% in men over 80 years [1]. Although the exact pathogenesis of BPH is not completely understood, aging, testosterone levels, lower urinary tract infections, inflammation, alteration in cell signaling are considered significant risk factors for the development of BPH [2]. Of these factors, testosterone is said to be the major factor since it is known to play an important role in growth of prostate gland. The effects of several growth factors involved in the development of BPH like fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), and insulin like growth factors (IGFs) are modulated by dihydrotestosterone (DHT), a derivative of testosterone [3].

The relative length of 2nd and 4th digit is a marker for prenatal androgen exposure. A low 2D:4D ratio is associated with a high prenatal androgen exposure. Since there are practical difficulties in measurement of testosterone exposure in the fetus, researchers have adopted a non-invasive method in the form of measurement of 2D:4D ratio, a widely accepted retrospective biomarker for prenatal androgen exposure [4]. It has been shown that alterations in digit ratio (2D:4D) is associated with a wide range of physiological & psychological characteristics like alcoholism [5], attention deficit disorder [6], visuo-spatial ability [7], susceptibility to coronary artery disease [8], assertiveness and aggression [9], homosexuality [10] and depression [11]. It is also found to be linked with prostatic cancer [12].

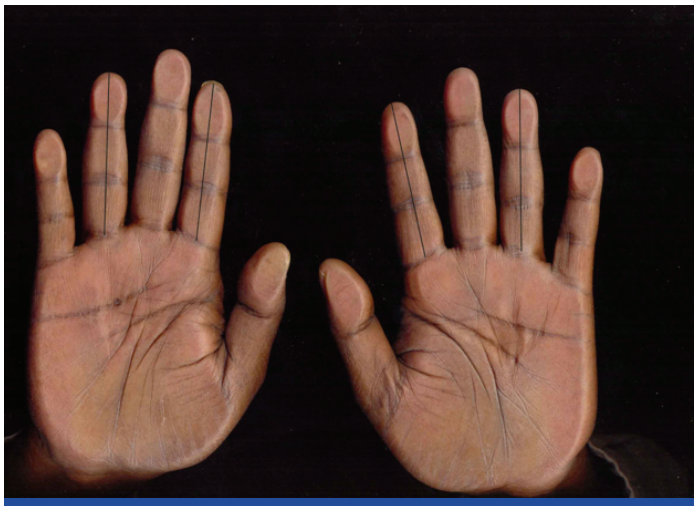
Testosterone is implicated in the development of prostate gland as it promotes prostate cell proliferation [13]. DHT is found to be a critical mediator of prostatic growth [14]. However, relatively low levels of serum testosterone are found in patients with BPH [15]. Exposure to varying levels of androgens in fetal life is found to affect several attributes of masculinity in males. This may also be true with respect to the growth of prostate in adult life and its subsequent hyperplasia in old age. Studies have not been conducted till date to determine the effect of prenatal androgen exposure on the growth of prostate gland and BPH. The present study is an indirect measure of prenatal testosterone exposure and its relation to development of BPH. The main objective of the present study was to assess the causal relationship between the 2D:4D ratio and incidence of BPH.

MATERIALS AND METHODS

The present study recruiting 105 participants was conducted between June 2013 and February 2014 in the Department of Urology, Kempegowda Institute of Medical Sciences Hospital and Research Centre, Bangalore. They were divided into three groups – BPH, non BPH and controls with 35 participants in each group. Written informed consent was obtained from all the study subjects/ legal representatives, after fully explaining the study procedure to their satisfaction. The study was conducted in accordance with international conference on harmonization guidelines on good clinical practice and the Helsinki declaration of 1975, revised in 2000. The study was registered retrospectively with Clinical Trial Registry, India (CTRI/2013/10/004111). Participants of BPH and non BPH groups were aged above 50 years. Subjects for BPH group were recruited from the patients attending Urology department of our hospital. The non BPH group was recruited from the same hospital population who visited the hospital for complaints unrelated to BPH. These 70 participants were subjected to ultrasound examination of the abdomen & pelvis and the size of the prostate was recorded. Diagnosis of BPH was done based upon the prostate volume. Prostate volumes less than 20cc were considered as non-BPH and a prostate volume of more than 20cc were termed BPH. Those who had undergone surgery for BPH or subjects on medical treatment addressing the static component of BPH were excluded from the study as they alter the ultrasonographic assessment of prostate. Clinical assessment of these patients was also done using the International Prostate Symptom Score (IPSS) to confirm

the presence of lower urinary tract symptoms secondary to BPH. All the subjects underwent serum Prostate Specific Antigen (PSA) measurements and those with PSA ≥ 4 ng / ml were excluded from the study as it is a marker of prostatic cancer, though not highly reliable. Thirty five age matched subjects who did not have BPH formed the non BPH group. The controls were healthy young adult volunteers aged 25-30 years, selected from the general population. These subjects were relatives / attendants of the patients attending Urology OPD at our hospital and consented to participate in the present study. Clinical or radiological evaluation for BPH was not done and therefore their BPH status remained undetermined.

Both the hands of all 105 participants were scanned with a HP scan jet scanner. Participants placed their relaxed hands lightly on the surface of the scanner with second to fifth fingers held parallel and the tip of the middle finger aligned with the wrist and elbow. Scaling of the scanned hand images was done and the same was printed using a HP laser jet printer. A single reader blinded to the study groups, who had done similar measurements in earlier studies comparing 2D:4D ratios among various sport disciplines conducted all the measurements. The distance between the tip of the finger and the basal crease (proximal crease in case of two creases) was measured in the images of the second and fourth digits taken from printouts using vernier calipers (Quasmo – Range 0 – 150 mm, accuracy ± 0.05 mm) [Table/Fig-1]. The length of the second digit was divided by the length of the fourth digit to calculate the 2D:4D ratio. (Δ r –l) was calculated as the difference between right and left 2D:4D.



[Table/Fig-1]: Scaling of distance between the tip of the finger and basal crease of the second and fourth digits in the scanned images

STATISTICAL ANALYSIS

Studies have shown that the prevalence of BPH increases with age and can be as high as 90%. With the margin of error set at 10% and confidence interval at 95%, the number of subjects to be recruited in each group was calculated to be 35. Analysis was done using SPSS V 11.0. Descriptive statistics like Mean, Standard Deviation, Standard Error & 95 % confident intervals were computed. The difference in mean between the three groups was analysed using one-way ANOVA and Post-Hoc test was done using Tukeys HSD. Results were considered significant whenever p-value was ≤ 0.05.

RESULTS

The mean ratio of 2nd to 4th digit for the left hand was 0.948 in BPH patients, 0.982 in Non BPH and 0.962 in control group ($p < 0.001$). For the right hand, the values were 0.944, 0.975 and 0.963 respectively ($p < 0.001$) [Table/Fig-2]. BPH patients had a lower 2nd to 4th digit ratio in the right hand (p=0.033) but not in the left (p=0.192) and Non BPH subjects had higher 2nd to 4th digit ratio in the left hand (p=0.033) but not in the right (p=0.275) when compared to the controls [Table/Fig-3].

	Groups (n=35)	Mean ± S. D	Std. Error	95% C I for Mean		f-value	p-value
				Lower Bound	Upper Bound		
2D:4D Left	BPH	0.948±.031	.006	.936	.959	9.388	<0.001
	Non BPH	0.982±.032	.006	.970	.994		
	Controls	0.962±.030	.005	.951	.973		
2D:4D Right	BPH	0.944±.030	.005	.933	.955	8.586	<0.001
	Non BPH	0.975±.030	.006	.964	.987		
	Controls	0.963±.029	.005	.953	.974		

[Table/Fig-2]: Comparison of 2D:4D ratio among BPH, Non BPH & Control groups using one-way ANOVA

			Mean Difference	Std Error	p-value	95% C I	
						Lower Bound	Upper Bound
2D:4D Left	BPH	Non BPH	-.0346013*	.0080312	<.001	-.053752	-.015451
		Controls	-.0140776	.0080312	0.192	-.033228	.005073
	Non BPH	Controls	.0205236*	.0080312	0.033	.001373	.039674
2D:4D Right	BPH	Non BPH	-.0313963*	.0076528	<.001	-.049644	-.013148
		Controls	-.0195664*	.0076528	0.033	-.037814	-.001318
	Non BPH	Controls	.0118299	.0076528	0.275	-.006418	.030078

[Table/Fig-3]: Comparison of mean differences between the groups using Post-Hoc test (Tukey HSD)
*. The mean difference is significant at the 0.05 level

DISCUSSION

2D:4D ratio has been found to be a reliable marker of fetal testosterone exposure. This finding has been substantiated by a number of studies [4,16]. However 2D:4D ratio is unaffected by testosterone fluctuations later in life or circulating levels of testosterone in adulthood [17]. Therefore, this ratio is considered as an important non invasive marker of fetal testosterone exposure [18].

Results of the present study have shown that the BPH patients had the lowest 2D:4D ratio scores, non BPH subjects had the highest ratio and controls had values in between the two groups. Low digit ratio found in BPH patients in the present study suggests that increased exposure to testosterone in prenatal life may be a cause for development of BPH later in life. Studies have shown that alteration in the balance between testosterone and estrogen levels in prostate tissue contribute to BPH development. The present study supports those studies which have shown positive relation between BPH and androgens. Studies have shown that men castrated before puberty do not develop BPH [19] and men with hypopituitarism, which leads to low serum androgens, also do not develop BPH [20]. However, in contrast, few studies have shown that androgens may not influence development of prostate. One such study has shown that androgen supplementation in men does not appear to increase the risk of developing BPH [21].

Many of the diseases having an onset in adult life are suggested to be linked to intrauterine exposure to testosterone. This has been studied by measuring 2D:4D ratios in subjects with osteoarthritis [22], alcohol dependency [5], eating disorders [23], infertility [24], depression [11] and schizophrenia [25]. Recently two studies on prostate cancer have shown a negative association of prostate cancer with digit ratio [12,26]. However another study has found no association between 2D:4D ratio and risk of prostate cancer [27]. The present study results suggest that lower 2D:4D ratio is suggestive of increased risk of developing BPH. Further, the results show a higher digit ratio in non BPH subjects compared to controls

& BPH patients, which further reinforces our findings of relationship between digit ratios and risk of developing BPH. High 2D:4D ratio hand pattern seen in non BPH subjects in the present study can act as a marker of low prenatal testosterone activity, suggesting the importance of exposure to prenatal testosterone in the development of BPH.

It is found that prenatal androgenization is better indicated by right hand than the left hand [28]. Right hand but not the left 2D:4D ratios were positively associated with running speed in men [29]. A high 2D:4D ratio in right hands of males was associated with germ cell failure due to azoospermia or oligospermia [30]. This may be the reason for presence of significant difference between BPH group and controls in right hand but not in the left, and absence of significant difference between Non BPH group and controls in the left hand but not in the right.

BPH & Non BPH group subjects were aged above 50 years, whereas, the controls were aged 25-30 years. This differential selection of age was purposely done to get an unbiased control group which may fall into either category at a later age. As the 2D:4D ratio becomes stable by two years of age and does not change further [31,32], this differential selection of groups with respect to age will not assume significance.

CONCLUSION

Results of the present study indicate that individuals with lower 2D:4D ratios are at a higher risk of developing BPH and those with higher 2D:4D ratios are at a lower risk of developing BPH compared to the general population. Thus, 2D:4D ratio measurement can be used as a screening method to identify those at risk of developing BPH and can be specifically monitored to reduce the risk of development of BPH and its troublesome complications like acute urinary retention, urinary tract infections, bladder stones, bladder decompensation, urinary incontinence, upper urinary tract deterioration and azotemia.

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