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Original Article

Evaluation of 2D:4D digit ratio and diagonal earlobe crease as markers of coronary artery disease

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ABSTRACT

Introduction: Coronary artery disease (CAD) is increasing in prevalence worldwide. In this regard, the extravascular markers in evaluating atherosclerosis is of importance in clinical evaluation.
Methodology: After informed consent from fifty CAD patients (confirmed from coronary angiographic studies) were recruited into the study. Similar number of age and sex matched controls without CAD were selected. We evaluated digit ratio (2D:4D) and diagonal ear lobe crease (DELC) in patients and compared with healthy individuals. Measurement of digit ratio was by photographic method. Ear lobe of all patients were photographed and evaluated for presence of diagonal ear lobe crease.
Results: We found that 2D:4D ratios in males with CAD are higher than the control group. There were no such differences in females. 2D:4D ratios as usual sexually dimorphic. Coden's d calculation revealed that 84% of the males with CAD will be having digit ratios above mean of the control group, and there is a 76% chance that a person picked at random from the CAD group will have a digit ratio more than the mean of control group. Diagonal ear lobe crease was found in 74% of CAD patients out of which 40% creases were unilateral and 34% were bilateral.
Discussion: It is concluded that 2D:4D ration and Diagonal ear lobe crease are the two extravascular atherosclerotic markers are invaluable in clinical evaluation of CAD patients.
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1. Introduction

Coronary artery disease (CAD) is rapidly increasing in prevalence across the world.[1,2] Therefore, it would be useful to identify a group of simple and reliable indicators for the identification of the persons at risk of CAD in the earlier stages in order to enable appropriate health interventions. High androgen levels have historically been with an increased risk for CAD. Recent research has shown that higher prenatal testosterone may be relate to the series of phenomena and disorders.[3,4] including left-handedness, autism, dyslexia, migraine, stammering, ventricular septal defect, pulmonary stenosis and patent ductus arteriosus.[5,6]

Manning et al. suggested that the ratio between 2nd digit and 4th digit of hand, 2D:4D ratio is a marker for testosterone and estrogen levels towards the end of the first trimester of pregnancy.[7] The 2D:4D may therefore be a predictor of fertility,

and the pattern of differentiation of the central nervous system. During past decades, the relationship between 2D:4D and sex steroids related diseases including infertility, gastric cancer, breast cancer and prostate cancer, Down syndrome have been discussed in several ethnic groups.[8,9,10]

A diagonal ear lobe crease (DELC) or Frank's sign has been characterized in the medical literature as a marker that can identify high-risk patients with atherosclerosis. DELC was first reported to be associated with CAD in 1973.[11] It is independently and significantly associated with increased prevalence, extent, and severity of CAD according to recent studies.[12,13]

Four previous studies have shown a significant association between 2D:4D and atherosclerotic diseases. Manning et al. found a negative relationship between 2D:4D ratio and age at first myocardial infarction (MI), that is men with low 2D:4D ratio tended to have their first attack later in life than men with high 2D:4D ratios.[14] Fink et al. reported a significant positive correlation between 2D:4D and neck circumference for men.[15] They suggested that 2D:4D as proxy indicator of predisposition for men to CAD. A study including 50 men and 50 women in Greece reported that in men with MI, 2D:4D ratios were significantly higher than the

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respective ratios in healthy men, but no significant differences were observed in the ratios between women with MI and healthy women. It was proposed that 2D:4D may be a useful biomarker for predisposition to MI in Greek men, but not in Greek women.[16] Consequently, Ozdogmus et al. reported that high right hand 2D:4D ratio is associated with right coronary artery atherosclerosis after examining 100 male autopsies.[17,18] Such data is missing from Indian subcontinent. In this study we evaluated any such relations in 2D: 4D ratios to presence of CAD.

Many previous studies support the idea that DELC is an important extravascular sign of CAD. These studies have considered occurrence of DELC who are having CAD as evidenced by clinical examination or coronary angiography.[19–21] There are reports wherein DELC have been found in association with atherosclerotic changes in postmortem examination. Recent reports have also considered correlation of B-mode scan of carotid arteries with DELC.[22] Verma et al. have studied prevalence of DELC and ear canal hair in patients with CAD. They concluded that combined assessment of DELC and ear canal hair is a sensitive index of underlying CAD.[23] Previous studies have documented occurrence of DELC in 40–75% of CAD patients.[11,19–24] However, a few studies have failed to record any association between DELC and CAD. It was found that there is no positive association between DELC and CAD in Oriental patients, native American Indian patients, and children with Beckwith's syndrome.[21] In this background, we tried to evaluate incidence of DELC in patients with diagnosed CAD. This extravascular sign of CAD, is expected to help clinicians for a better evaluation of patients with CAD.

Physical indicators of atherosclerosis will grossly simplify the clinical evaluation of CAD patients. Both 2D: 4D digit ratio and DELC being valuable extra vascular and easily identifiable parameters of predicting and evaluating the CAD, it is expected to be of great value while evaluating patients with risk factors for atherosclerosis. Our study is the first such Indian study showing light on association of these physical markers with CAD.

The objectives of the study were to evaluate the 2D: 4D ratio in CAD patients in comparison with age and sex matched controls and to check the prevalence of DELC in CAD patients. Effort was made to evaluate the discriminative power of 2D: 4D digit ratio and DELC in patients CAD.

2. Methodology

2.1. Study subjects

This was a cross-sectional study comprising of 50 patients attending outpatient department of general medicine. Age and sex matched controls was selected to the study from the various outpatient departments. History of first episode of CAD manifestation, co-morbid conditions were noted in each case.

2.2. Exclusion criteria

Individuals with history of hand lesions, upper limb deformities, infertility, endocrinopathies, chromosomal abnormalities, non-hetrosexuals, left-handers, and those with breast cancer, prostate cancer and other cardiac problems are excluded.

Written informed consent was obtained and the study was approved by our institutional ethics committee.

2.3. Diagnostic Criteria

CAD was defined by definite myocardial infarction with any degree of stenosis, or >50% stenosis in more than one epicardial branch as revealed by coronary angiography. Subjects without CAD will be those without stenosis in any branch. Study interpretation on severity of coronary artery stenosis was approved by radiologists.

2.4. Measurements of Digit Length and 2D:4D ratio

The digits lengths was determined by taking photographs of the hands of the selected patients by using Digital camera (Sony India) with 8MP resolution, auto ISO having light background. The digit lengths was measured from the ventral proximal crease to the tip of the fingers both on ulnar and radial aspect (in order to account the sloppy proximal crease) by using 'measure tool' of Adobe Photoshop CS5.[25] As 2D:4D is ratio, the units of measurements cancel out and a number indicating the relationship of digits is generated (Fig. 1).

2.5. Assessment of DELC

The sign was considered present if the crease extended for a distance >1/3 of the earlobe length, either unilaterally or bilaterally. In addition, no particular depth of crease was defined for the DELC to be present.[26]

2.6. Statistical analysis

Data was tabulated and expressed as mean $\pm$ standard deviation. P values of <0.05 was regarded as statistically significant. Comparison of the variables between groups was carried out using student 't'-test for numerical variables. Cohen's d was calculated to evaluate effect sizes of group differences. All statistical analysis was conducted using SPSS (Statistical Package for Social Sciences, release 19.0) for Windows.

3. Results

Total number of CAD patients studied was 50 with 25 males and 25 females. The mean age of the patients was 44 ($\pm$0.5) years. Control group of 100 subjects with mean age of 44 ($\pm$0.8) years with 30 males and 30 females. There were no significant difference in age, prevalence of diabetes mellitus between CAD patients and control group.

3.1. Digit ratio differences

There was no significant difference between each individual's first and second measurements of each digit length (p > 0.05). There was no significant right – left difference in males and females both in CAD patients and in controls. In control group digit ratios were sexually dimorphic with males ratio (mean right and left digit ratios – 0.982) statistically lower (p < 0.05) than females ratio
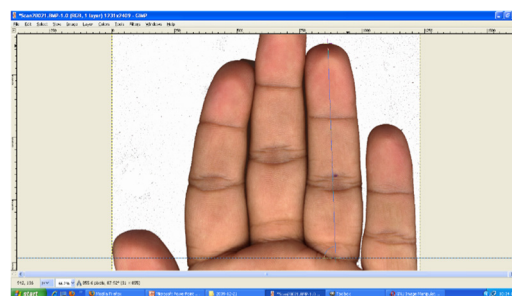

Fig. 1. Screenshot of measurement of digit ratio. Measurements were taken from the tip of the digit to the ventral proximal crease over metacarpo-phalangeal joint.

(mean right and left digit ratios – 1.016). In CAD group similar statistically significant (p < 0.05) dimorphic ratios were recorded (mean male digit ratio – 0.947 vs. mean female digit ratio – 1.027). Digit ratios of patients with CAD, control group are tabulated in Table 1. The 2D: 4D ratio in patients with CAD are statistically significantly higher in both right and left hands than the control group (p < 0.05). Such statistical significant difference is not observed in females hands between CAD group and control group (p = 0.73).

Cohen's d was calculated (Table 1) and showed that between males with CAD and without CAD the value was 1. With a Cohen's d of 1, 84% of the males with CAD will be having digit ratios above mean of the control group, and there is a 76% chance that a person picked at random from the CAD group will have a digit ratio more than the mean of control group. Cohen's d value in females were found to be <0.5 with medium effect.

3.2. DELC

(Table 2 and Fig. 1) Of the 50 CAD patients evaluated we found DELC in 37 patients (males = 21, females = 16). Out of thirty seven documented DELC, seventeen patients had it on both sides and remaining were unilateral (Fig. 2).

4. Discussion

The extravascular markers of CAD plays important role in clinical evaluation of patients with atherosclerosis. In this regards both the parameters considered in this study stands out as key markers. Though there are many studies correlating CAD with these parameters separately, ours is the first study to consider both parameters together. It has been widely proved and accepted that males have lower 2D:4D ratio.[9] It has been widely accepted that the sex difference in 2D:4D ratio arises early in development and the ratios are slightly lower in males than females, making it – sexually dimorphic.[10] Once established in early neonatal life digit ratio assumed to be stable in later life. The digit ratio has been reported to be associated with several characteristics such as fetal growth, congenital adrenal hyperplasia, developmental psychopathology, autism and Asperger's syndrome.[27] Evolutionary psychologist, Prof John Manning had suggested that 2D:4D may correlate with risk of myocardial infarction. Through this study we found that there males with CAD will have statistically higher in comparison with matched controls. This is consistent with Ozdogmus's previous study; wherein they have found that there are evidences of right coronary atherosclerosis with higher 2D:4D ratio.[18] This correlation significant in men with CAD; not with females. Similar association with neck circumference and 2D:4D ratio with atherosclerosis is reported by Fink et al.[15] We have found sexual dimorphism in 2D:4D ratio in accordance with many previous studies from different countries and ethnic groups.[28,7,9,10,16] Men have significantly lower digit ratios than females in both CAD and control groups.

What's the pathological relation between CAD and higher 2D:4D ratios? The answer is not very clear. Digit ratios are determined prenatally and it will be lower in presence of higher

Table 2
Diagonal ear lobe crease noted in patients with coronary artery disease.

Parameter	Observed in (total n = 50)
DELC	37 (74%)
Males and females	21 and 16
Unilateral	20 (40%)
Bilateral	17 (34%)

Fig. 2. Photograph showing Diagonal ear lobe crease (DELC, shown in dotted line along the crease) in female and male coronary artery disease (CAD) patient.

circulating testosterone and higher under the influence of estrogen. The differentiation of the digits is under the control of Homeobox or Hox genes (the posterior-most Hox-d and Hox-a genes), which also control the differentiation of the testes and ovaries.[27,29] Prenatal sex hormones especially testosterone may influence the development of cardiovascular system. Alterations in these hormones may be the causative factors linking the variations in vascular physiology and digit formation.[30] This view is supported by reports that CAD is significantly higher in postmenopausal women with higher free testosterone levels.[31]

But, study from Italy and Brazil recently showed that occurrence of CAD is not related to higher testosterone levels.[32] Endogenous estrogen but not testosterone is related to CAD in men.[33] To explain such inverse relationships, researchers have attributed differential sensitivity of androgen receptors based on CAG repeat sequences. Shorter CAG repeat of the androgen receptor gene is associated with more severe CAD.[34] This suggest that sensitivity rather than the testosterone level is important in increased frequency of CAD in males. Certainly more studies involving more subjects is required to establish a caudal association and pathological relations between digit ratio and CAD.

In our study we found DELC prevalence to be 74%. This may be an overestimate since we have included all partial DELC while defining the criteria. Though DELC is not superior to other markers

Table 1
Tabulation of digit ratios in patients with coronary artery disease (CAD); values expressed as mean ± standard deviation; *p < 0.05.

	Male with CAD	Males without CAD	Cohen's d effect size	Females with CAD	Females without CAD	Cohen's d effect size
Right hand	0.9931 ± 0.0558	0.9471 ± 0.0268*	1.0509	1.03161 ± 0.04432	1.0452 ± 0.0378	0.329
Left hand	0.9862 ± 0.0436	0.9469 ± 0.0148*	1.02070	1.02357 ± 0.02603	0.9874 ± 0.0214	0.4547

of CAD, identification of it is easy and acts as add-on sign of atherosclerosis.

5. Conclusion

Identifying subtle but significant differences in 2D:4D ratios are important in clinical evaluation of CAD male patients. Similarly noticing DELC also help clinicians in better evaluation of CAD patients.

Acknowledgement

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