No Evidence for Association Between ACE Gene Insertion (I)/Deletion (D) Polymorphism and Hypertension in North Indian Punjabi Population

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KEYWORDS Hypertension, ACE Gene Polymorphism, North Indian Punjabi Population, Genetic Association Study

ABSTRACT Essential hypertension is a complex polygenic disorder influenced by many environmental factors. Previous studies have demonstrated that angiotensin converting enzyme (ACE) gene has a significant association with hypertension and other cardiovascular diseases. The objective of the study was to assess the possible role of ACE gene I/D polymorphism on hypertension in north Indian Punjabi population. The present work undertook case-control association study among a total of 90 (47 males, 43 females) unrelated hypertensive patients and 91 control subjects (47 males, 44 females). Three genetic models such as dominant, co-dominant (additive) and recessive were used to analyze the data. No significant differences were observed in either genotype (p=0.91) or allele (p=0.84) frequencies between case and control groups. The results indicated that ACE gene polymorphism has very little impact on hypertension susceptibility among males of north Indian Punjabi population, as it was evidenced in recessive genetic model (OR: 2.09, 95% CI: 0.70-6.22, p=0.18). However, no overall significant association was found between ACE I/D polymorphism and hypertension in this population.

INTRODUCTION

Hypertension is primarily a common polygenic complex disorder influenced by a variety of environmental factors and lifestyle (Morshed et al. 2002; Mondry et al. 2005; Merlo et al. 2006). It is well established that in hypertension, systolic blood pressure is consistently 140 mmHg or greater and diastolic blood pressure is consistently 90 mmHg or greater, whereas, normal blood pressure of a healthy adult human being is 120 mmHg systolic and 80 mmHg diastolic (Chobanian et al. 2003; Guyton and Hall 2006). It has been proposed that angiotensin I-converting enzyme (ACE) gene on chromosome 17 (17q23 region) with polymorphism based on insertion (present) or deletion (absence) of intron region 16 with 287 base-pair (bp) fragment is an independent risk factor for hypertension and other cardiovascular diseases (Rigat et al. 1990; Tiret et al. 1992; Raynolds et al. 1993; Higaki et al. 2000). The main function of ACE is the conversion of angiotensin I to vasoactive angiotensin II which binds to plasma membrane receptor and helps to produce the arteriolar constriction resulting in the rise of systolic and diastolic blood pressure. However, the results of association of ACE with hypertension and other cardiovascular diseases have been controversial (Saha et al. 1996; Joseph et al. 1998; Vargas-Alarcon et al. 2003). Many studies have documented significant association between ACE gene and hypertension in different ethnic groups (Duru et al. 1994; Morise et al. 1994; Chiang et al. 1996; Nakano et al. 1998), others have failed to detect any such association (Jeunemaitre et al. 1992; Harrap et al. 1993; Kamdar et al. 1994; Badaruddoza et al. 2009; Danková et al. 2009; Siváková et al. 2008, 2009). Therefore, in the view of above consideration the present study attempts to determine the impact of the ACE gene polymorphism on genetic susceptibility of essential hypertension in north Indian Punjabi population. Hypertension is very much common in Punjabi subject in Punjab and no such study is available to date in this region.

MATERIALS AND METHODS

Subjects

The study was approved by the Ethics Committee of Guru Nanak Dev University, Amritsar, India in 2009. The study included a total of 181 unrelated subjects of both sexes, consisting of 91 controls (47 males, 44 females) and 90 patients...
with hypertension (47 males, 43 females). The patients were selected in Punjabi population from the outpatients in the hospital of three districts (Phagwara, Amritsar and Jalandhar) of Punjab, a north Indian state. The subjects of control group were age matched and healthy. The mean ages of combined subjects were 52.30±6.56 years for cases and 52.36±5.01 years for control group.

Measurements

**Blood Pressure:** Blood pressure was measured using manual mercury sphygmomanometer after resting for 10 minutes in sitting position, as recommended by the American Heart Association (Kirkendal et al. 1980). All efforts were made to minimize the factors which might affect blood pressure such as anxiety, fear, stress, laughing and recent activity (Badaruddoza and Afzal 1999). Hypertension was defined as systolic blood pressure (SBP) 140 mmHg/ diastolic blood pressure (DBP) 90 mmHg. Pulse rate was calculated through radial artery at wrist and was counted over one minute. Pulse pressure was calculated through SBP minus DBP.

**Anthropometric Measurements:** Body mass index (BMI) was calculated by dividing weight of the subject in kilogram by square of height in meters. Waist circumference (cm) was measured using steel tape. The measurement is taken mid-way between the interior margin of the last rib and the crest of the ilium in a horizontal plane. Waist to hip ratio is calculated as waist circumference (cm) divided by hip circumference (cm). Biceps and triceps skin folds were taken with the help of Harpenden’s caliper. All the anthropometric measurements were taken on each individual using standard anthropometric technique (Singh and Bhasin 1968; Weiner and Lourie 1981).

**Collection of Blood Samples:** Approximately 5 ml of peripheral fasting blood samples were collected in a screw cap tube, containing EDTA as an anticoagulant, for the determination of metabolic profiles and molecular analysis.

**Metabolic Profiles:** Plasma was separated by centrifugation at 1000 x g for 20 minutes at room temperature within 2 hours of blood sample collection. The metabolic variables included were total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL). However, LDL was calculated using the following formula:

\[ \text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5) \]

All metabolic variables were estimated in mg/dl using semi-automatic Erba Mannheim dichromatic analyzer with standard protocol.

**DNA Extraction and Determination of Genotype:** Genomic DNA was extracted from whole blood containing EDTA as an anticoagulant by a standard procedure (Gustincich et al. 1991). The I/D polymorphism of ACE gene was detected by the PCR-RFLP method (Yoshida et al. 1996). The sense oligonucleotide was 5’ – GAT GTG GCC ATC ACC CCC CTG CTT TCT – 3’ and the antisense primer was 5’ - GAT GTG GCC ATC ACA TTC GTC AGA TTT – 3’. The PCR mixture contained 20ng genomic DNA, 0.2µM of each primer, 200µM of each dNTP, 1.5 mM of tris-HCL buffer (pH 9.0), 1.5 mM Mgcl₂, and 0.024 unit of Taq DNA polymerase in a final reaction volume of 15µl. The amplification cycle was performed on Mastercycler personal (Eppendorf AG 5332). After initial denaturation at 95°C for 5 min, the DNA was amplified by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 72°C for 30 seconds and primer extension at 72°C for 30 seconds followed by final elongation at 72°C for 10 min. The amplified PCR products were separated by electrophoresis on 2% agarose gel and DNA was visualized under UV transilluminator after staining with etidium bromide. The insertion (I) allele was detected as band of 490 bp fragment and deletion (D) allele was recognized as a band of 190 bp fragment. Therefore, after electrophoresis, each DNA sample would be recognized as II genotype for 490 bp band; DD genotype for 190 bp bands and ID genotype for both 490 and 190 bp bands (Rigat et al. 1992).

**Statistical Analysis:** Statistical analysis was performed using SPSS version 17.0. Genotype and allele frequencies of ACE gene in case and control groups were compared and tested using Pearsons χ²–statistic. Deviations from Hardy-Weinberg equilibrium (HWE) were calculated using a χ² goodness-of-fit test. Analyses have also been done for dominant, co-dominant (additive) and recessive genetic models and their odds ratio (ORs) with 95% CI ranges and corresponding p-values using the Web-Assotest program. Two-tailed student’s t test was performed to compare the clinical data quantitatively among case and control groups.
Two tailed probability levels for statistical significance were reported at p<0.05 for all analysis.

RESULTS

The clinical characteristics of the hypertensive and control subjects of male, female and total have been presented in Table 1. The two study groups were well matched for age and sex. The mean systolic and diastolic blood pressure (SBP and DBP) and triglycerides (TC) were significantly (p<0.001) higher in the hypertensive males, females and total subjects. The mean waist to hip ratio (WHR) was significantly (p<0.001) higher in hypertensive subjects of both males and females. However, the mean age, body mass index (BMI), waist circumference (WC), triceps skin fold and pulse pressure for males and biceps skin fold, pulse rate (PR), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) for males and biceps skin fold, pulse rate (PR), total cholesterol (TC), high density lipoprotein (HDL), very low density lipoprotein (VLDL), LDL-HDL ratio and CHO-HDL ratio were also significantly higher (p<0.001) in hypertensive combined (male plus female) subjects. There were, however, no significant differences in BMI, WC, WHR, biceps and triceps skinfolds, pulse rate and LDL, between cases and control groups were found among total subjects.

Table 2 represents ACE allele and genotype frequency distributions of control and hypertensive subjects of male, female and total. The genotype and allele distribution of ACE gene were almost similar and did not differ significantly between control and case groups among males (p=0.39 and 0.47, respectively), females (p=0.77 and 0.64, respectively) and total (p=0.91 and 0.84, respectively) subjects. However, the researchers observed a significant deviation from HWE within control group of males (p=0.02), while no deviation was observed in any other groups. In addition, homozygosity for DD genotype tended to be more common in cases for males (12.7 vs 23.4%) and combined subjects (19.8 vs 22.2%). There was also a suggestive evidence of an association in a recessive model (DD vs II/ID; OR: 2.09, 95% CI: 0.70-6.22) among males, however, this association is not statistically significant (p=0.18). Furthermore, the researchers found no indication of a recessive model of action of ACE gene polymorphism with hypertension among females (OR: 0.71, 95% CI: 0.26-1.90, p=0.49) and combined samples (OR: 1.16, 95% CI: 0.57-2.37, p=0.69).

The same was observed for the association test of dominant model of action (ID/DD vs II) in males (OR: 1.00, 95% CI: 0.37-2.69, p=1.00), females (OR: 0.97, 95% CI: 0.39-2.38, p=0.94) and combined subjects (OR: 0.99, 95% CI: 0.51-1.91, p=0.96). Similarly, no significant association has been observed in co-dominant model of action among males, females and combined groups. It is also interesting to note that the homozygosity of DD genotype was more common in control group of females (27.3% vs 20.9%) but, this relationship was not reflected to be true for the male population.

DISCUSSION

The study describes the associations between the ACE variant and hypertension in north Indian population. Many studies have shown a significant association of ACE gene D allele with essential hypertension (Duru et al. 1994; Morise et al. 1994; Chiang et al. 1996; Nakano et al. 1998; Turgay et al. 1999; Higaki et al. 2000; Hsich et al. 2000; Mesbahuddin and Azam 2007). On the other hand, several researchers have shown no significant differences in the allele and genotype distribution of ACE gene polymorphism between control and hypertensive groups (Mondry et al. 2005; Badaruddoza et al. 2009; Danková et al. 2009; Siváková et al. 2008, 2009). In the present study, the overall frequencies of D allele were in control group 45.7% for males, 47.7% for females and 46.7% for total subjects as compared to cases 51.1% for males, 44.2% for females and 47.8% for total subjects (cases vs control; χ² =0.469, p=0.79). Therefore, D allele association hypothesis was not reflected to be true in the present study. The same is also true for I allele (cases vs control; χ² =0.253, p=0.88). Surprisingly, the cross-sectional study presented here showed equal prevalence of II genotype in control and hypertensive groups (26.4 vs 26.7%). ACE II genotype was associated with lowering the risk of hypertension in females (odds ratio- II vs DD: 0.75; 95% CI: 0.240-2.34; p=0.62) but in combined sub-
Table 1: Clinical characteristics of the study subject. Data are mean±S.D. The statistical significance of differences between case and control were analyzed by student t test.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male</th>
<th>Case (n=47)</th>
<th>Control (n=47)</th>
<th>p-value</th>
<th>Female</th>
<th>Case (n=43)</th>
<th>Control (n=44)</th>
<th>p-value</th>
<th>Combined</th>
<th>Case (n=90)</th>
<th>Control (n=91)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57.20±7.39</td>
<td>54.10±5.37</td>
<td>0.022</td>
<td></td>
<td>52.27±5.27</td>
<td>50.50±4.46</td>
<td>0.094</td>
<td></td>
<td>52.30±6.54</td>
<td>52.36±5.01</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.48±3.44</td>
<td>24.41±2.92</td>
<td>0.002</td>
<td></td>
<td>27.67±2.54</td>
<td>28.44±2.69</td>
<td>0.17</td>
<td></td>
<td>27.05±3.08</td>
<td>26.36±2.84</td>
<td>0.11</td>
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<tr>
<td>WC (cm)</td>
<td>97.14±6.08</td>
<td>90.69±5.55</td>
<td>0.001</td>
<td></td>
<td>94.67±10.36</td>
<td>96.81±11.87</td>
<td>0.37</td>
<td></td>
<td>95.96±8.78</td>
<td>93.65±9.27</td>
<td>0.087</td>
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<td>WHR</td>
<td>0.98±0.10</td>
<td>0.94±0.07</td>
<td>0.027</td>
<td></td>
<td>0.90±0.06</td>
<td>0.95±0.08</td>
<td>0.001</td>
<td></td>
<td>0.96±0.08</td>
<td>0.94±0.08</td>
<td>0.094</td>
<td></td>
</tr>
<tr>
<td>Biceps skinfold (mm)</td>
<td>9.05±3.88</td>
<td>7.70±2.95</td>
<td>0.06</td>
<td></td>
<td>13.54±4.17</td>
<td>15.23±3.18</td>
<td>0.036</td>
<td></td>
<td>11.20±4.34</td>
<td>11.34±3.10</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>14.65±2.08</td>
<td>12.90±2.40</td>
<td>0.001</td>
<td></td>
<td>22.45±5.99</td>
<td>22.27±5.02</td>
<td>0.88</td>
<td></td>
<td>18.38±4.45</td>
<td>17.43±3.94</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150.90±10.69</td>
<td>131.40±11.40</td>
<td>0.001</td>
<td></td>
<td>143.54±12.06</td>
<td>131.54±11.32</td>
<td>0.001</td>
<td></td>
<td>147.38±11.49</td>
<td>131.46±11.49</td>
<td>0.001</td>
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<tr>
<td>DBP (mmHg)</td>
<td>92.60±10.41</td>
<td>78.90±8.93</td>
<td>0.001</td>
<td></td>
<td>92.45±10.04</td>
<td>80.14±8.97</td>
<td>0.001</td>
<td></td>
<td>92.53±10.35</td>
<td>79.50±9.05</td>
<td>0.001</td>
<td></td>
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<tr>
<td>PP (mmHg)</td>
<td>70.90±11.69</td>
<td>52.50±10.01</td>
<td>0.001</td>
<td></td>
<td>51.09±10.61</td>
<td>51.41±7.79</td>
<td>0.87</td>
<td></td>
<td>61.44±11.31</td>
<td>51.97±9.11</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>PR (counts/min)</td>
<td>77.5±10.15</td>
<td>75.40±8.09</td>
<td>0.27</td>
<td></td>
<td>74.36±5.39</td>
<td>78.54±3.96</td>
<td>0.001</td>
<td></td>
<td>76.00±8.32</td>
<td>76.92±6.51</td>
<td>0.408</td>
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<tr>
<td>TC (mg/dl)</td>
<td>182.17±22.50</td>
<td>178.03±25.50</td>
<td>0.40</td>
<td></td>
<td>199.02±23.08</td>
<td>163.72±28.40</td>
<td>0.001</td>
<td></td>
<td>190.22±23.04</td>
<td>171.11±27.24</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>252.71±30.17</td>
<td>231.67±35.00</td>
<td>0.004</td>
<td></td>
<td>209.82±25.54</td>
<td>170.42±23.75</td>
<td>0.001</td>
<td></td>
<td>232.22±28.37</td>
<td>202.05±30.95</td>
<td>0.001</td>
<td></td>
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<tr>
<td>HDL (mg/dl)</td>
<td>46.88±9.15</td>
<td>43.06±10.67</td>
<td>0.066</td>
<td></td>
<td>59.10±18.39</td>
<td>45.16±14.83</td>
<td>0.001</td>
<td></td>
<td>52.18±14.49</td>
<td>44.06±12.99</td>
<td>0.001</td>
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<tr>
<td>LDL (mg/dl)</td>
<td>84.75±21.73</td>
<td>83.84±20.13</td>
<td>0.83</td>
<td></td>
<td>97.94±24.38</td>
<td>87.38±23.08</td>
<td>0.04</td>
<td></td>
<td>91.05±23.29</td>
<td>85.04±21.85</td>
<td>0.075</td>
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<tr>
<td>VLDL (mg/dl)</td>
<td>50.54±19.23</td>
<td>46.33±18.97</td>
<td>0.288</td>
<td></td>
<td>41.96±16.31</td>
<td>34.08±14.75</td>
<td>0.009</td>
<td></td>
<td>46.44±18.10</td>
<td>40.41±17.25</td>
<td>0.023</td>
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<tr>
<td>LDL-HDL ratio</td>
<td>1.87±0.84</td>
<td>1.96±0.95</td>
<td>0.628</td>
<td></td>
<td>1.88±1.04</td>
<td>2.19±1.22</td>
<td>0.208</td>
<td></td>
<td>1.39±1.55</td>
<td>2.07±1.01</td>
<td>0.001</td>
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<tr>
<td>CHO-HDL ratio</td>
<td>3.97±0.92</td>
<td>4.49±1.71</td>
<td>0.07</td>
<td></td>
<td>3.64±1.18</td>
<td>3.99±1.54</td>
<td>0.38</td>
<td></td>
<td>2.63±3.02</td>
<td>4.25±1.65</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

BMI=Body mass index, WC=Waist circumference, WHR=Waist to hip ratio, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PP=Pulse pressure, PR=Pulse rate, TC=Total cholesterol, TG=Triglycerides, HDL=High density lipoprotein, LDL=Low density lipoprotein, VLDL=Very low density lipoprotein
Table 2: Distribution of frequency of Angiotensin Converting Enzyme (ACE) genotypes and alleles in Punjabi population. Data are number of subjects with each genotype and allele (frequency in percentage). OR- Odds Ratio, CI-Confidence Interval. ORs for different modes of inheritance were calculated

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotype (%)</th>
<th>Allele (%)</th>
<th>P-value</th>
<th>Dominant model</th>
<th>Co-dominant model</th>
<th>Recessive model</th>
<th>Test for H.W.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male Subjects (case, n=47; control=47)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Genotype (%)</td>
<td>Allele (%)</td>
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<td></td>
<td>II ID DD</td>
<td>I D</td>
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<tr>
<td></td>
<td>Male Subjects (case, n=47; control=47)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>10(21.3) 31(66) 6(12.7)</td>
<td>51(54.3) 43(45.7) 48(51.1)</td>
<td>0.39 0.47</td>
<td>1.00(0.37-2.69) 1.00</td>
<td>1.31(0.68-2.52) 0.41</td>
<td>2.09(0.70-6.22) 0.18</td>
<td>5.08 0.02</td>
</tr>
<tr>
<td>Case</td>
<td>10(21.3) 26(55.3) 11(23.4)</td>
<td>46(48.9) 48(51.1)</td>
<td>0.05 0.70</td>
<td>0.99(0.51-1.91) 0.96</td>
<td>1.05(0.68-1.60) 0.83</td>
<td>1.16(0.57-2.37) 0.69</td>
<td>0.61 0.436</td>
</tr>
<tr>
<td>Female Subjects (case, n=44; control=44)</td>
<td></td>
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<tr>
<td>Control 2</td>
<td>14(31.8) 18(40.9) 12(27.3)</td>
<td>46(52.3) 42(47.7)</td>
<td>0.05 0.70</td>
<td>0.99(0.51-1.91) 0.96</td>
<td>1.05(0.68-1.60) 0.83</td>
<td>1.16(0.57-2.37) 0.69</td>
<td>0.61 0.436</td>
</tr>
<tr>
<td>Case</td>
<td>14(32.6) 20(46.5) 9(20.9)</td>
<td>48(55.8) 38(44.2)</td>
<td>0.05 0.70</td>
<td>0.99(0.51-1.91) 0.96</td>
<td>1.05(0.68-1.60) 0.83</td>
<td>1.16(0.57-2.37) 0.69</td>
<td>0.61 0.436</td>
</tr>
<tr>
<td>Combined Subjects (case, n=91; control=91)</td>
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<tr>
<td>Control 3</td>
<td>24(26.7) 49(53.8) 18(19.8)</td>
<td>97(53.3) 85(46.7)</td>
<td>0.05 0.70</td>
<td>0.99(0.51-1.91) 0.96</td>
<td>1.05(0.68-1.60) 0.83</td>
<td>1.16(0.57-2.37) 0.69</td>
<td>0.61 0.436</td>
</tr>
<tr>
<td>Case</td>
<td>24(26.7) 46(51.1) 20(22.2)</td>
<td>94(52.2) 86(47.8)</td>
<td>0.05 0.70</td>
<td>0.99(0.51-1.91) 0.96</td>
<td>1.05(0.68-1.60) 0.83</td>
<td>1.16(0.57-2.37) 0.69</td>
<td>0.61 0.436</td>
</tr>
</tbody>
</table>

- No significant association has been found (odds ratio: II vs DD: 1.11; 95% CI: 0.47-2.59; P=0.81) (Calculation is not given in the table).
- In males of control group, the ACE genotype distribution was not in Hardy-Weinberg equilibrium (P<0.02) while no deviations from Hardy-Weinberg equilibrium were observed in females and combined groups. This may be the presence of higher frequency of ID individuals in control group.
- This study suggested no association between I/D polymorphism and hypertension in north Indian Punjabi population. Therefore, the results of the present study are sufficiently encouraging for more extensive population studies. Considering the lack of an association in this study population, we may assume that ACE gene I/D polymorphism may play a major role in inter-population variability.
- The study has also failed to identify any sex-specific association with hypertension. However, the role of ACE I/D polymorphism in regulation of blood pressure has been well studied, but not strong evidences have been found for association with essential hypertension. Therefore, the association of ACE I/D polymorphism with essential hypertension may be dependent on inter-population variability, ethnicity, and geographic location.
- Furthermore, a significantly higher association of ACE gene D allele with the essential hypertension was reported from previous studies of individuals of control group, while no deviation from Hardy-Weinberg equilibrium was reported from previous studies of individuals of control group. This study suggested no association between ACE I/D polymorphism and hypertension in north Indian Punjabi population. Therefore, the results of the present study are sufficiently encouraging for more extensive population studies. Considering the lack of an association in this study population, we may assume that ACE gene I/D polymorphism may play a major role in inter-population variability.
- The study has also failed to identify any sex-specific association with hypertension. However, the role of ACE I/D polymorphism in regulation of blood pressure has been well studied, but not strong evidences have been found for association with essential hypertension. Therefore, the association of ACE I/D polymorphism with essential hypertension may be dependent on inter-population variability, ethnicity, and geographic location.
polymorphism with hypertension among males. However, studies in north Indian Punjabi population (Badaruddoza and Kaur 2010; Kaur et al. 2010; Kumar and Badaruddoza 2010; Badaruddoza et al. 2010; Badaruddoza and Sawhney 2009) reported that diseases such as central obesity, type 2 diabetes mellitus and hyperlipidemia are more common but they have low risk for developing cardiovascular diseases due to their strong genetic background. The low frequency of ACE DD genotype in this population might provide a protective effect for cardiovascular diseases. However, in this regard not many data are available to support the present findings of this population. In the meantime, it should be noted that the present study has been carried out on small sample size, despite of this fact the findings which were on homogenous population based study cannot be ignored.

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