ABSTRACT

Essential hypertension has become a public health problem because of the associated co-morbidities require life-long treatment which may itself impact health-outcome. Both, genetic and environmental factors have a role in its etiology with heritability estimates of 56-57%. A wide array of genes are involved in maintaining blood pressure levels with the pathophysiology of hypertension resulting from increased oxidative stress and endothelial and vascular dysfunction. Oxidative stress tends to damage macromolecules and damage to DNA can lead to neoplasia. Metabolic genotypes of cytochrome P450 (CYP2D6) which regulate drug-metabolism and Glutathione-S-transferase (GST), which have antioxidant action, also modulate genetic damage besides having shown association with hypertension in various population groups. However, early detection of DNA damage can facilitate interventions for age-related changes and malignancies. Against the backdrop of sparse studies relating CYP2D6 and GST gene polymorphisms with hypertension and being responsible for inter-individual variation to genetic damage, the present case-control study was undertaken as a first of its kind to determine genetic damage, oxidative stress and genotypes of GST (T1, M1 and P1) and CYP2D6 (*2, *4 and *10) genes in an ethno-specific hypertensive group (Jat Sikh with rural background) on Atenolol drug-treatment (n=200) and 200 normotensive controls. The study was carried out after ethical clearance from the Institutional ethics committee and with written consent of the participants.

Hypertensive patients (61.59±0.80y) and normotensive controls (60.36±0.89y) had almost equal gender-representation and were matched for baseline characteristics of age, socioeconomic status, dietary habits, alcohol-consumption, residential area, mobile phone usage, menopausal status (in female) and central obesity but differed for BMI with more obese controls. Systolic and diastolic blood pressure levels were significantly higher in patients, as was dyslipidemia and the presence of metabolic syndrome and metabolic phenotypes.

Patients were for two-years on daily oral therapy of Atenolol (50mg) with disease-onset of 59.83±0.81y with 12.5% in stage I, 19.00% in stage II and 9% in stage III hypertension categories. The CYP2D6*4 and GST P1 minor alleles were significantly higher in patients as were the GST P1 genotypes (heterozygous and homozygous variants). Oxidative stress biomarkers of Total oxidant status (TOS), oxidative stress index (OSI) and lipid peroxidation (MDA) were also significantly (p≤0.001) higher in patient group with total antioxidant capacity significantly lower.
Genetic damage was assessed using single cell gel electrophoresis (SCGE/comet) assay as per cent tail DNA, tail moment (TM), Olive tail moment (OTM), damage index (DI) and damage frequency (DF). All these parameters were significantly (p≤0.001) higher in patients. Also treated vs. untreated patients had significantly lower genetic damage but increased oxidative stress index. Principal component factor analysis (PCA) revealed that all the genetic damage parameters are equally valuable for defining genetic damage in the present study group. There were no effects by stratification of data for genders, age, and menopausal status (in females), blood pressure categories, metabolic syndrome and metabolic phenotypes. However, duration-of-treatment, late age-of-onset of disease, and CYP2D6*4 heterozygous vs. homozygous wild type had significantly higher DI values; and non-obese vs. obese patients had significantly higher percent DNA in tail.

On correlation and linear regression analyses, obesity-status, blood pressure levels, oxidative stress and dyslipidemia emerged as predictors of genetic damage. Multifactor dimensionality reduction (MDR) analysis revealed CYP2D6*4, *10 and GSTP1 in two- and three-factor combinations as best predictors for disease-risk. The best-fit models for disease prediction were the recessive model of CYP2D6*4 and additive models each of CYP2D6*2, CYP2D6*10 and GST P1. There was increased likelihood of developing hypertension (odds-ratio analysis) in those with the heterozygous and homozygous variant genotypes of CYP2D6*4 and GST P1 and the CYP2D6*10 heterozygous genotype, even after Bonferroni correction, but which was lost on adjustment for various confounders. However no haplotypes were generated.

The prevalent risk factors (as known contributors to disease) in patients by PCA were dyslipidemia, obesity, blood pressure levels, genetic damage and molecular genotypes of CYP2D6*2, *4, and *10, and GST P1. Gene-environment interactions for disease-status by MDR analysis revealed the combinations in which those with higher levels of MDA, OSI, DF and lower levels of TAC were at increased risk for developing the condition. The hypertension-risk gene-gene combinations were CYP2D6 *2, CYP2D6*10 and GST P1. The increased genetic damage, oxidative stress and dyslipidemia in the hypertensive patients with increased minor allele frequencies of CYP2D6 *4 and GSTP1 and of the homozygous variant and heterozygous GSTP1 genotypes and the effects of the genotypes along with their modulating effects on genetic damage in an ethno-specific group add informational content about the prognosis of the disease and provide for a database for susceptibility genotypes of essential hypertension.