Abstract

Juvenile diabetes is a multifactorial disease characterized by destruction of insulin producing β-cells of pancreas because of interaction and integration of immune response genes with environmental factors. The current study was designed to evaluate the role of environmental factors interacting with Vitamin D Receptor (*VDR)* considered as candidate gene in the onset of Type 1 Diabetes (T1D) in Pakistani population. Juvenile diabetic individuals (n = 300) were interviewed for assessment of the clinical, physical, social and economic life-domain. Three SNPs from *VDR* gene (rs731236 (*Taq*I), rs7975232 (*Apa*I) and rs10735810 (*Fok*I) were selected for genetic analysis. Cases (n = 102) and (n = 100) controls were age and sex matched. Basic technique of genotyping was PCR-RFLP whereas direct sequencing was performed for identification of genotypes. Males were at higher risk of disease development as compared to females. It was found that the onset of disease before 10 years of age was significantly associated. Loss of weight ($p < 0.01$), positive maternal and parental family history of T1D ($p < 0.05$) was highly significant to T1D onset in both genders. Overall the average annual cost 26942.18 PKRs (272 US$) of treatment per person was calculated. Statistical analysis showed that genotype frequency of rs10735810 (*Fok*I) polymorphism differed significantly between case and controls. Genotype CC and allele C was more common in patients ($p = 0.001$). The change in nucleotide at *Fok*I site lead to the change in amino acid sequence (Tryptophan changes into Arginine). No significant association was observed in genetic frequencies of rs731236 (*Taq*I) and rs7975232 (*Apa*I) polymorphism. A novel mutation on intron 8 (G replaced by C) was identified in Pakistani population that lead to the change of tryptophan into cysteine. Two haplotypes CCT and CCG found significantly associated with disease development. On the other hand, CTG and CTT haplotypes were protective against T1D. In conclusion, current study indicated that underweight (BMI < 18.5 Kg/m^2), positive family history and rs10735810 (*Fok*I) polymorphism and mutation at intron 8 was significantly associated with the development of juvenile diabetes in Pakistani Population. Moreover each family was spending 13% of their income on treatment and management of disease as a direct

medical cost. Further survey and genetic association studies at large scale can be helpful in prevention of juvenile diabetes.