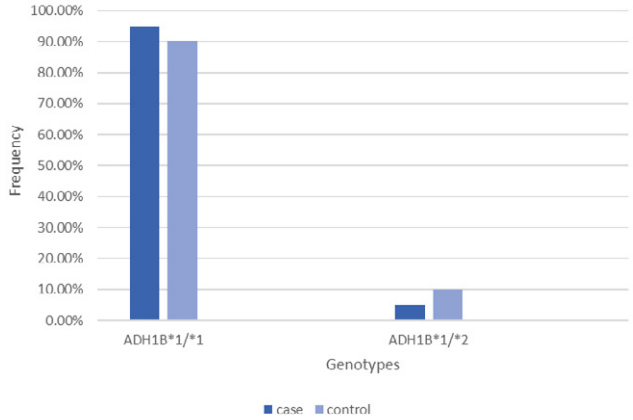

Figure A: Distribution of genotype frequency in cases and control

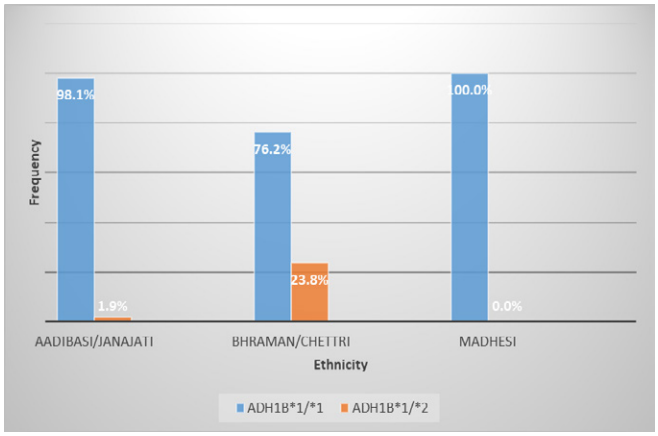

Figure B: Distribution of ADH1B*1/*1 and ADH1B*1/*2 genotypes of alcoholics in Different Ethnic Groups

Discussion

Genetic polymorphisms have been reported in ADH1B genes and genetic variations in this alcohol metabolizing enzymes is allied to alterations in alcohol metabolism, response, consumption and related problems [16, 17]. In the human evolutionary history, it is known that single nucleotide polymorphisms which are localized in autosomal chromosome are changed by effects of many factors. Determination of those polymorphisms may be a crucial data in terms of relations between societies. Nepal, a Southeast Asian country have diverse ethnic group resulting a clear heterogeneity and genetic admixture. On that ground, special importance was given in our study to investigate the allele frequencies and genotype distributions of ADH1B gene in Nepalese population. To our knowledge, our present study is the first study to determine the genotype and allele frequencies of ADH1B polymorphisms in Nepalese population. In our present study, the ADH1B*1/*1 genotype was found to be most common of all genotypes in both alcoholic and non-alcoholic subjects whereas the frequency of ADH1B*1/*2 genotype was found to be low in both alcoholics and control groups. Thus, there was no significant differences in the genotype and allele frequencies in between cases (alcoholics) and the control (non-alcoholic) groups.

A frequency of 95.1% of ADH1B*1/*1 genotype in our result is consistent with the study conducted [11] in which ADH1B*1/*1 was 93.0%. Likewise, 4.9% of ADH1B*1/*2 genotype was found to be prevalent in our study which is also similar to the findings of [11, 18] in which 6.40% and 6.7% was ADH1B*1/*2 genotype among alcoholics respectively. However, no any individuals with ADH1B*2/*2 genotype was detected in our study alike to the study conducted by Kayaalti Z et.al., 2010 [12] in which no prevalence of ADH1B*2/*2 was found among 211 turkish alcoholic subjects.

In our study, frequency of ADH1B*1(ADH2.1) i.e Arg allele and ADH1B*2 (ADH2.2) i.e His allele was found to be 97.5% and 2.45% respectively in alcoholic cases and 95.1% and 4.9% respectively in control groups. These results were similar to the results reported by Salman E et.al., 2007 [11] in which Arg allele and His allele were 96% and 4% respectively in alcoholic patients and 99% and 1% respectively in control groups. On the contrary, Kayaalti Z et.al., 2010 [12] reported 91.9% and 8.1% frequency of Arg allele and His allele respectively. Thus, in keeping with our study Arg allele (ADH1B*1) was more commonly seen in both alcoholic and non-alcoholic Nepalese populations. The study participants were stratified into three ethnic group i.e Aadibasi/Janajati, Bhraman/Chhetri and Madeshi. No significant differences were found within the presence of ADH1B*1/*1 genotype in all three ethnicities whereas ADH1B*1/*2 was found to be highest in Bhraman/Chhetri with a frequency of 13.8% and a lowest frequency of 1.9% was noted in aadibasi/janajati, and wasn't noted in madhesi ethnicity. The prevalence reported by some authors varies among different ethnic groups, ADH1B*1 allele was found to be predominant in Caucasian populations (~ 90%). Whereas ADH1B*2 occurs in Japanese, Chinese, and other Oriental population at about 85% percentage [12]. This is in contrast to our study where ADH1B*1 allele was found to be 97.55% and ADH1B*2 was found to be 2.45%. ADH1B*1/*1 and ADH1B*1/*2 genotype frequencies in Nepalese were not statistically different from Turkish populations Salman E et.al., 2007 [11], Finnish (Goedde et al., 1992) [19], Mexican (Konishi et al., 2003) [20]. However, ADH1B*2/2 genotype frequencies were statistically lower than Uzbek (Ahn et al., 2009)[21], Mongolian (Shen et al., 1997) [22], Jewish (Neumark et al., 2004) [23], Vietnamese (Iron et al., 1992) [24], Chinese (Guo et al., 2008) [25], and Japanese (Matsuo et al., 2006) [8] populations which exhibited the highest frequency values. The frequency of ADH1B*1/*1 and ADH1B*1/*2 in the abovementioned ethnic groups is shown in table 3. Our present study, also reported that, alcoholic patients having longer history of alcoholism (since more than 10 years up to

40 years) have higher frequency of ADH1B*1/*1 genotype and ADH1B*1 allele. This resembles a study done by Yin G et.al 2016 which revealed that alcohol intake were greater in subjects with the ADH1B 47Arg/Arg (ADH1B*1/*1) compared with each ADH1B 47His allele in men and women [26]. Similarly Yin G et.al., 2011 showed that both current alcohol drinkers (hatched bar) and heavy alcohol drinkers (black bar) were slightly more frequent with increasing numbers of the ADH1B*47Arg allele and disclosed the effect modification of the ADH1B Arg47His (ADH1B*1/*2) polymorphism on association with alcohol consumption [27].

Thus, it can be inferred from the study that the presence of ADH1B*1 allele and its genotype is responsible for inducing alcohol tolerance and promote alcoholism, as ADH1B*1 allele are associated with slower ADH activity. This is consistent with the result reported by Salman E et.al., 2007 [11] in which patients with history of maximum years of alcohol consumption and having alcohol induced liver cirrhosis have the higher frequency of ADH1B*1/*1 genotype. Similarly, population with Chinese, Mongolian and Japanese ethnicities have higher rate of prevalence of the heterozygous genotype (ADH1B*1/*2) and ADH1B*2 allele of ADH1B gene. Thereafter, it indicates the sensitivity of these ethnicities towards alcohol as ADH1B*2 are associated with higher ADH activity and increases the offensive effects of alcohol.

Conclusion

To my knowledge this is the first study conducted in Nepal, to demonstrate the frequency of SNP in ADH1B gene (i.e frequency of ADH1B*1 allele and ADH1B*2 allele and genotypic frequency of ADH1B*1/*1, ADH1B*1/*2 and ADH1B*2/*2) and its effect in the metabolism of alcohol and its tolerance. The study demonstrate the allele frequency of ADH1B*1 allele (Arg allele) is 97.5% and ADH1B*2 allele (His allele) is 2.45%. Also the genotype frequency of ADH1B*1/*1, ADH1B*1/*2 and ADH1B*2/*2 was found to be 95.1%, 4.9% and 0% respectively in alcoholic patients. The study found that the ADH1B*1/*1 genotype was most prevalent in all three ethinic groups i.e aadibasi/janajati, bhraman/chhetri, and madhesi. Similarly, the study also reported that patients having longer history of alcohol consumption have higher frequency of ADH1B*1/*1 genotype. Based on the results obtained from the study, our study concluded that the presence of ADH1B*1/*1, ADH1B*1/*2 and ADH1B*2/*2 genotype affects the metabolism of alcohol, consumption of alcohol and its tolerance. It was reported that presence of ADH1B*1/*1 genotype (have slow ADH activity), increases the tolerance towards alcohol making individual more susceptible towards alcoholism and precede the onset of alcohol use disorders. The presence of ADH1B*2/*2 genotype (with high ADH activity), exceeds ethanol metabolism and results in the accumulation of acetaldehyde, a highly toxic metabolite which exhibits unpleasant effects like facial flushing, headache, tachycardia and hypotension even after consumption of minute quantity of ethanol. Thus, these limiting factors might be helpful to refrain from alcoholism and its subsequent consequences for individuals with ADH1B*2/*2 genotype.

Glossary

Alcohol dehydrogenase

Alcohol Dehydrogenase 2

Alcohol dehydrogenase 1 B

Aldehyde dehydrogenase

Arginine allele

Alcohol use disorders identification test

Ethylene diamine tetra-acetic acid

Ethidium Bromide

Histidine allele.

Polymerase chain reaction with confronting two- pair primers

Pico mole per liter

Single Nucleotide Polymorphism

Tris acetate EDTA

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Approval of the Study

This study has been approved for Master's level thesis by Department of Biochemistry and Department of Gastroenterology Medicine., Institute of Medicine.

Ethical Approval

The study has given ethical clearance by the Institutional Review Committee, Institute of Medicine and the letter has been submitted along with the manuscript submission.

Deceleration of Conflict of Interest: None

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