Effect of Interaction Between Duration of Alcohol Consumption and Alcohol Dependence on Thyroid Function Test: Cross Sectional Observational Study

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Abstract Dependence on alcohol, nicotine and duration of alcohol consumption are known to alter thyroid function tests. This study was conducted to assess the effect of interaction between the duration of alcohol consumption and alcohol dependence on TFT. The subjects consisted of 38 male patients with alcohol dependent syndrome co morbid with nicotine dependent syndrome, 33 male patients with alcohol dependent syndrome and 30 male normal healthy volunteers. Liver function tests, haematological parameters and thyroid function tests were assayed. Two way multivariate ANOVA was used to assess the interaction effect by SPSS 21 package. Multivariate analysis of combined TFT levels revealed no significant ($P = .078$) difference amongst groups based on alcohol dependence, significant difference ($P = .001$) amongst groups based on duration of alcohol consumption and no significant ($P = .604$) interaction effect between duration of alcohol consumption and alcohol dependence. Tests of between subject effects for individual TFT revealed significant ($P = .014$) difference in T3 between groups based on alcohol dependence, significant difference in the levels of fT4 ($P = .001$), T3 ($P = .07$) and T4 ($P < .001$) between groups based on duration of alcohol consumption was observed. Interaction between the effect of duration of alcohol consumption and alcohol dependence for

individual TFT did not reveal any significance. fT4, TSH and T4 levels were significantly low in persons consuming alcohol for more than 20 years. TSH levels were significantly low in ADS compared to controls. Significant decrease in the levels of thyroid hormones was observed as the duration of alcohol consumption increased.

Keywords Alcohol dependence syndrome · Nicotine dependence syndrome · TSH · T3 · T4

Introduction

Alcohol dependence is associated with increased mortality and morbidity [1]. National Epidemiologic survey on Alcohol and related conditions (NESARC-III) indicate that 14% of adults have a current alcohol use disorder and 29% had an alcohol use disorder over their lifetime, with the rates highest among men and those of younger age [2]. Indian National Surveys suggest that around 21% of adult males in the country are current drinkers. As per conservative estimate 61 million are alcohol users among them 10 million have alcohol dependence [3]. A close relationship between excessive alcohol drinking and smoking has been recognized for many years and a common genetic vulnerability to nicotine and alcohol dependence in men, suggests that alcoholics are often dependent smokers [4]. Alcohol and Tobacco affects almost all organs and systems of the human body. Alcohol consumption can have an impact on not only on the incidence of disease injuries and other health conditions, but also on the course of disorders and their outcomes in individuals. Alcohol has multiple effects on the hypothalamo–pituitary–thyroid axis and the function of thyroid gland [5]. Chronic alcohol exposure causes the direct suppression of thyroid function by cellular toxicity,

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and indirect suppression by blunting thyrotrophin-releasing hormone response [6]. The effect of chronic alcohol consumption on peripheral thyroid hormone (T3 and T4) levels are not settled [7]. There is a paucity of studies which analyse the thyroid function test (TFT) in alcohol dependence syndrome co morbid with nicotine dependence syndrome patients. The present study is aimed to investigate the effect of interaction between the duration of alcohol consumption and alcohol dependence on thyroid function test.

Materials and Methods

The cross sectional observational study was carried out in the Department of Biochemistry, Father Muller Medical College, Mangalore. The samples were collected after obtaining a clearly written informed consent from men who were admitted to deaddiction centre of psychiatry department and who were coming for normal health checkups.

The study comprised of 101 alcohol dependent male patients of age 16–60 years. The patients were diagnosed by a treating psychiatrist as alcohol dependent syndrome (ADS) and alcohol dependent syndrome co morbid with Nicotine dependent syndrome (ADS-NDS) based on ICD-10(International Statistical Classification of Diseases, tenth revision), classification of mental and behavioural disorders: diagnostic criteria for research of World Health Organization [8, 9]. The study group included 33 ADS patients and 38 ADS-NDS patients. The control group consisted of 30 healthy volunteers without any history of alcohol abuse and smoking. To analyse the effect of interaction between alcohol consumption and duration of alcohol, the study subjects (ADS and ADS-NDS) were classified into ≤ 10 , 11–20 and >20 years based on duration of alcohol consumption.

Patients with systemic illness such as non alcoholic liver disease, known cases of thyroid dysfunction, cancer, inflammatory diseases, infections, psychiatric illness, substance use other than alcohol and nicotine dependence, abstinence from alcohol for more than 10 days prior to admission for treatment and drugs altering thyroid function tests were excluded from the study.

Demographic variables like age in years and duration of alcohol consumption in years were collected. Blood samples were collected between 9 and 11 am aseptically in anticoagulated EDTA (ethylene diamine tetra acetate) tubes, ESR (Erythrocyte sedimentation rate) tubes and plain tubes, for analysis of haematological and biochemical parameters respectively. Serum was separated after 20 min of collection by centrifuging the vacutainer at 3000g for

10 min. The separated serum samples were preserved at -20°C until analysis was performed.

All the chemistry and immunological tests were done in Roche cobas 6000 fully automated analyser. Haematological tests were done in Beckman coulter counter. Relevant quality control checks were performed prior to analysis.

Serum Total protein and albumin were assayed by Biuret and Dye binding (Bromocresol green) method respectively [10, 11]. Activities of alanine amino transferase and aspartate amino transferase were assayed by modified IFCC method [12]. γ -Glutamyl transferase activity was assayed by carboxy substrate method [13]. The activity of alkaline phosphatase was assayed by PNPP Kinetic method [14]. Total bilirubin was assayed by Diazo method [15]. Levels of serum urea and creatinine were assayed by coupled enzymatic method and Kinetic Jaffe's method respectively [16, 17]. Haemoglobin concentration was measured by using cyanide free lytic reagent and other haematological parameters were determined by coulter counters, using the principle of electrical impedance. Serum triiodothyronine (T3), thyroxine (T4), free thyroxine (fT4), and thyroid stimulating hormone (TSH) levels were analysed by Electrochemiluminescence method.

Shapiro–wilk test was used to test the normal distribution of data. Two way multivariate ANOVA test was used to assess the interaction effect between dependence and duration of alcohol on the levels of thyroid function tests collectively. Statistical analysis was performed using SPSS version 21. $P < .05$ was considered as statistically significant.

Results

Demographic data and biochemical profile are shown in Table 1. Result of the two way multivariate ANOVA analysis for effect of interaction between duration of alcohol consumption and alcohol dependence on TFT levels are shown in Table 2.

Since two way MANOVA (Multivariate analysis of variance) did not reveal significant interaction between duration of alcohol consumption and alcohol dependence, post hoc multiple group comparison was done for TFT using the estimated marginal means.

Multiple group comparison by post hoc analysis, two way multivariate ANOVA for TFT in different groups are shown in Table 3. Interaction effect between duration of consumption and dependence of alcohol on various TFT is shown graphically in Fig. 1a–d.

Table 1 Demographic, haematological, hepatic and renal profile characteristic of population

	Healthy control (n=30) (SEM) (95% CI)	Alcohol dependence syndrome (n=33) (SEM) (95% CI)	Alcohol and nicotine dependence syndrome (n=38) (SEM) (95% CI)
Age in years	35 ± 0.93 (33.09–36.90)	40.22 ± 2.08 (35.81–44.62)	37.25 ± 2.25 (32.4–42.06)
Alcohol consumption in years	NA	16.38 ± 1.5 (13.21–19.56)	16.56 ± 2.1 (12.06–21.06)
Hb in g/dl	15.08 ± 0.11 (14.85–15.32)	14.13 ± 0.48 (13.12–15.14)	14.62 ± 0.41 (13.73–15.51)
RBC count in ×10 ⁶ per cumm	5.02 ± 0.06 (4.89–5.14)	4.68 ± 0.23 (4.19–5.17)	4.65 ± 0.16 (4.31–5.0)
Neutrophil in %	62.46 ± 0.55 (61.33–63.60)	58.72 ± 3.41 (51.52–65.9)	57 ± 3.02 (50.55–63.44)
Lymphocyte in %	35.53 ± 0.35 (34.81–36.25)	30.72 ± 3.24 (23.88–37.55)	33.37 ± 2.87 (27.25–39.5)
MCV in fl	85.12 ± 0.30 (84.49–85.75)	92.98 ± 2.7 (87.28–98.68)	94.5 ± 1.63 (91.02–97.97)
Albumin in g/dl	4.21 ± 0.07 (4.05–4.36)	4.64 ± 0.09 (4.26–4.66)	4.41 ± 0.13 (4.12–4.69)
ft4 in ng/dl	1.31 ± 0.04 (1.23–1.4)	1.24 ± 0.04 (1.14–1.34)	1.24 ± 0.05 (1.14–1.33)
T4 microg/dl	7.78 ± 0.19 (7.4–8.2)	6.76 ± 0.37 (6–7.5)	6.5 ± 0.27 (5.6–7.1)
TSH microIU/ml	2.37 ± 0.15 (2.1–2.7)	1.74 ± 0.24 (1.2–2.2)	2 ± 0.23 (1.5–2.5)
T3 ng/ml	1.1 ± 0.03 (1–1.1)	1.16 ± 0.07 (1–1.3)	0.94 ± 0.04 (0.86–1)
	Median (IQR) (95% CI)	Median (IQR) (95% CI)	Median (IQR) (95% CI)
Daily consumption of alcohol since in years	NA	4 (6.5) (2.34–7.63)	6.5 (3.8) (4.35–10.24)
ESR in mm Hg	3.0 (1.25) (2.63–3.29)	10 (13.75) (7.48–17.29)	5 (9) (5.21–12.28)
Eosinophils in %	3 (0.25) (2.82–3.3)	2.5 (3) (2.5–4.05)	1 (1.75) (1.02–3.47)
Total protein in g/dl	7.19 (0.87) (7.11–7.5)	7.29 (0.42) (7–7.56)	7.51 (1.01) (7.12–7.86)
Total bilirubin in mg/dl	0.69 (0.10) (0.67–0.72)	0.64 (0.52) (0.53–1.15)	0.64 (0.39) (0.54–0.89)
AST in IU/L	20 (4) (19.28–20.85)	83.5 (70.75) (62.27–133.95)	77 (151.75) (80.28–198.71)
ALT in IU/L	19.5 (3) (18.78–20.21)	65 (56.5) (44.84–84.6)	39 (99.50) (41.88–122.99)
GGT in IU/L	19 (4.25) (18.11–20.15)	160 (106.5) (115.41–225.36)	127 (285.75) (76.89–408.98)
ALP in IU/L	66 (10.25) (63.31–70.61)	90 (40.25) (71.35–121.64)	100 (46.25) (84.83–130.16)
Urea in mg/dl	25.5 (3.25) (24.72–26.21)	15.5 (8.25) (13.84–20.48)	18 (12.25) (14.59–23.15)
Creatinine in mg/dl	0.88 (0.08) (0.88–0.91)	0.74 (0.13) (0.70–0.82)	0.71 (0.17) (0.67–0.81)

Data with normal and non normal distribution are represented using (SEM) mean ± standard error and median with interquartile range (IQR) respectively. There was no statistical age difference between ADS, ADS-NDS and healthy controls. Both ADS and ADS-NDS patients had increased levels of liver function tests whereas urea and creatinine levels were decreased compared to healthy controls. Among the haematological parameters the levels of Haemoglobin, RBC count, neutrophils, lymphocytes were lower than healthy controls. Daily consumption of alcohol was low in ADS compared to that of ADS-NDS

CI confidence interval, ADS alcohol dependence syndrome, ADS-NDS alcohol dependence syndrome co morbid with nicotine dependence syndrome, NA not applicable

Discussion

This study indicated a moderate suppression of serum T3, T4, ft4 and TSH levels in ADS and ADS-NDS compared to non alcoholic healthy controls but it was not statistically significant. However serum TSH, T4 and ft4 levels significantly decreased as the duration of alcohol consumption increased (Table 3) T3 did not show such difference. Interaction effect, though not significant between duration of consumption and dependence of alcohol was seen on T3, T4 and ft4 but there was such interaction effect on TSH levels. Earlier studies reported that effect of chronic alcohol consumption on peripheral thyroid hormones T3 and T4 levels are not settled [7]. Some studies reported the suppression of peripheral

thyroid [18] hormones and a few reported no alteration in their levels done in animal studies [19]. Human studies revealed a moderate suppression of T4 levels with more significant suppression of T3 levels in chronic alcoholics [20, 21].

Lower thyroid releasing hormone (TRH) levels are associated with lower TSH levels, leading to lower levels of circulating thyroid hormones. In our study the TSH levels greatly reduced as the duration of alcohol consumption increased consistent with other studies [20] and more prominent in ADS-NDS than ADS (Fig. 1a) this may be due to influence of nicotine. TRH assay with TFT in such groups could reveal the cause for the above findings.

The lower TSH and high T3 in ADS (Fig. 1c) compared to non alcoholic control findings agreed with previous

Table 2 Two way multivariate ANOVA analysis for effect of interaction between duration of alcohol consumption and alcohol dependence on TFT levels

	Healthy control—no alcohol consumption (n-) (mean $\pm$ SD) (n = 30)	ADS— $\leq$ 10 years alcohol consumption (n-) (mean $\pm$ SD) (n = 5)	ADS—11–20 years alcohol consumption (n-) (mean $\pm$ SD) (n = 17)	ADS— $>$ 20 years alcohol consumption (n-) (mean $\pm$ SD) (n = 5)	ADS-NDS— $\leq$ 10 years alcohol consumption (n-) (mean $\pm$ SD) (n = 10)	ADS-NDS—11–20 years alcohol consumption (n-) (mean $\pm$ SD) (n = 16)	ADS—NDS— $>$ 20 years alcohol consumption (n-) (mean $\pm$ SD) (n = 7)	Between groups based on alcohol dependence (P)	Between groups based on duration of alcohol consumption (P)	Interaction effect of duration of alcohol consumption on dependence of alcohol (P)
FT4 in ng/dl	1.31 $\pm$ 0.218	1.50 $\pm$ 0.375	1.18 $\pm$ 0.217	1.07 $\pm$ 0.079	1.32 $\pm$ 0.176	1.20 $\pm$ 0.289	1.04 $\pm$ 0.228	.359	.001	.422
T4 microg/dl	7.78 $\pm$ 1.01	8.69 $\pm$ 2.82	6.60 $\pm$ 1.55	5.28 $\pm$ 0.665	7.13 $\pm$ 1.50	6.39 $\pm$ 1.69	5.6 $\pm$ 1.09	.256	<.001	.223
TSH microIU/ml	2.37 $\pm$ 0.819	1.96 $\pm$ 0.331	1.61 $\pm$ 0.905	0.83 $\pm$ 0.601	2.05 $\pm$ 1.58	2.16 $\pm$ 1.30	1.63 $\pm$ 1.15	.117	.131	.679
T3 ng/ml	1.07 $\pm$ 0.125	1.29 $\pm$ 0.321	1.19 $\pm$ 0.449	0.87 $\pm$ 0.119	0.92 $\pm$ 0.187	0.96 $\pm$ 0.244	0.89 $\pm$ 0.217	.014	.070	.181

Multivariate analysis of combined TFT levels revealed no significant ($P = .078$) difference amongst groups based on alcohol dependence, significant difference ($P = .001$) amongst groups based on duration of alcohol consumption and no significant ($P = .604$) interaction effect between duration of alcohol consumption and alcohol dependence. Tests of between subject effects for individual TFT revealed significant ($P = .014$) difference in T3 between groups based on alcohol dependence, significant difference in the levels of FT4 ($P = .001$), T3 ($P = .07$) and T4 ($P < .001$) between groups based on duration of alcohol consumption was observed. Interaction between the effect of duration of alcohol consumption and alcohol dependence for individual TFT did not reveal any significance

Table 3 Multiple group comparison by post hoc analysis two way multivariate ANOVA

	Healthy control versus ADS	Healthy control versus ADS-NDS	ADS versus ADS-NDS	No alcohol versus ≤10 years	No alcohol versus 11–20 years	No alcohol versus >20 years	≤10 versus 11–20 years	≤10 versus >20 years	11–20 versus >20 years
Mean difference ± SE (95% CI) and sig									
fT4 in ng/ dl	−0.09 ± 0.06 (−0.24 to 0.058) <i>P</i> = .320	0.10 ± 0.05 (−0.03 to 0.25) <i>P</i> = .168	0.018 ± 0.06 (−0.12 to 0.16) <i>P</i> = .954	0.06 ± 0.07 (−0.12 to 0.262) <i>P</i> = .799	−0.12 ± 0.06 (−0.272 to 0.03) <i>P</i> = .194	0.25 ± 0.08 (0.048–0.468) <i>P</i> = .010	0.18 ± 0.073 (−0.005 −0.37) <i>P</i> = .059	0.32 ± 0.090 (0.087 to 0.56) <i>P</i> = .003	0.14 ± 0.08 (−0.068 to 0.34) <i>P</i> = .299
T4 microg/ dl	−1.037 ± 0.38 (−1.95 to −0.12) <i>P</i> = .022	−1.33 ± 0.36 (−2.20 to −0.46) <i>P</i> = .001	0.29 ± 0.37 (−0.60 to 1.18) <i>P</i> = .716	0.128 ± 0.457 (−1.07 to 1.32) <i>P</i> = .992	1.28 ± 0.36 (0.32 to 2.23) <i>P</i> = .004	2.31 ± 0.49 (1.01 to 3.60) <i>P</i> < .001	1.15 ± 0.450 (−0.28 to 2.33) <i>P</i> = .058	2.18 ± 0.56 (0.71 to 3.65) <i>P</i> = .001	1.03 ± 0.48 (−0.245 to 2.31) <i>P</i> = .366
TSH microIU/ ml	0.84 ± 0.27 (0.18 to 1.50) <i>P</i> = .009	0.35 ± 0.26 (−0.27 to 0.98) <i>P</i> = .369	−0.486 ± 0.271 (−1.13 to 0.16) <i>P</i> = .178	0.35 ± 0.33 (−0.51 to 1.21) <i>P</i> = .717	0.49 ± 0.26 (−0.19 to 1.18) <i>P</i> = .240	1.07 ± 0.35 (0.14 to 2.0) <i>P</i> = .018	0.15 ± 0.32 (−0.703 to 1.0) <i>P</i> = .968	0.72 ± 0.40 (−0.33 to 1.78) <i>P</i> = .285	0.57 ± 0.35 (−0.35 to 1.49) <i>P</i> = .366
T3 ng/ml	−0.084 ± 0.07 (−0.25 to 0.08) <i>P</i> = .449	0.13 ± 0.065 (−0.03 to 0.28) <i>P</i> = .124	0.21 ± 0.067 (−0.08 to 0.25) <i>P</i> = .449	0.021 ± 0.082 (−0.19 to 0.23) <i>P</i> = .994	−0.013 ± 0.065 (−0.18 to 0.15) <i>P</i> = .997	0.178 ± 0.089 (−0.05 to 0.41) <i>P</i> = .196	−0.034 ± 0.08 (−0.25 to 0.17) <i>P</i> = .975	0.16 ± 0.101 (−0.108 to 0.42) <i>P</i> = .411	0.19 ± 0.088 (−0.039 to 0.42) <i>P</i> = .139

fT4 levels were significantly low in participants consuming alcohol for more than 20 years compared to participants not consuming alcohol and consuming alcohol for less than 10 years. T4 levels were significantly low in participant's consuming alcohol for more than 20 years compared to participants consuming alcohol for less than 10 and 10–20 years. TSH levels were low in ADS when compared to healthy control and in participants consuming alcohol for more than 20 years compared to non alcoholics. T3 levels were not significantly different between groups

Fig. 1 Interaction effect between duration of consumption and dependence of alcohol on thyroid function tests. **a** TSH level is low in ADS when compared with ADS-NDS in all groups based on duration of consumption of alcohol. TSH level lowers as duration of alcohol increases in both ADS and ADS-NDS. **b** fT4 level is higher in ADS when compared with ADS-NDS. fT4 level is lower in ADS compared to ADS-NDS at 10–20 years of alcohol consumption, however this interaction effect is not significant. fT4 levels lowers as the duration of alcohol consumption increases in both ADS and ADS-NDS. **c** T3 levels are higher in ADS when compared to ADS-NDS. T3

level is lower in ADS when compared to ADS-NDS at >20 years of alcohol consumption. However this interaction effect is not significant. T3 level lowers as duration of consumption of alcohol increases in both ADS and ADS-NDS. **d** T4 level is higher in ADS when compared with ADS-NDS. T4 level lowers in ADS when compared with ADS-NDS at >20 years of alcohol consumption, however this interaction effect is not significant. T4 level lowers as duration of consumption of alcohol increases in both ADS and ADS-NDS (ADS alcohol dependence syndrome, ADS-NDS alcohol and nicotine dependence syndrome)

studies [19, 21, 28] may be associated with the increased craving than ADS-NDS patients. Lower levels of T3 in ADS-NDS were consistent with other studies [21].

Alcohol influences the levels of thyroid hormones and the duration of alcohol dependence further increases the suppression of thyroid hormone levels. Few studies indicated that clinically significant hormonal changes are only occasionally seen in chronic alcoholic men without liver damage [29]. Decreased thyroid hormones may result from the alterations in the hypothalamo-pituitary-thyroid (HPT) axis at the pituitary level or from the damage to thyroid gland due to chronic alcohol intake. Post-mortem autopsy studies found decreased thyroid volume in alcohol dependent patients and this damage was associated with the duration of excessive alcohol intake and dose dependent [25]. Few previous studies reported alterations in thyroid hormone levels in subjects with Alcohol dependence [30] were related to severe liver or kidney disease, psychiatric

co morbidity, physiological stress, drugs or surgery. In contrast, our study group of alcohol dependent patients admitted for deaddiction treatment did not have any psychiatric or medical co morbidities. Many studies done in the past have revealed similar results (Table 4). Our study indicated that as the duration of alcohol consumption increases there was significant suppression of thyroid hormones consistent with other studies [30], which may be due to toxic effect of long duration of alcohol consumption on the thyroid gland and related dysfunction of the thyroid gland.

Conclusion

A significantly low level of thyroid hormones was observed as the duration of alcohol consumption increased which could be due to toxic effect of long duration of alcohol

Table 4 Effect of alcohol on thyroid function tests from previous studies reporting positive results

References	Cases and controls (n)	Type of study	T3	T4	fT4	TSH	Remarks
Shimizu et al. [22]	843 (411 alcoholics and 432 non alcoholic)	Cross sectional study	–	–	↓	↓	Study groups included subjects without cardiovascular disease
Valeix et al. [23]	1493 (599 males and 894 females)	Cross sectional study	–	–	↓	N	Study groups include alcoholics with no known thyroid disorders
Hegedus et al. [24]	21	Cross sectional study	↓	N	N	N	Study group include chronic alcoholics without liver cirrhosis age matched with the controls
Heinz et al. [25]	45	Longitudinal studies	N	↓	N	↓	Study groups included alcohol dependent patients and healthy controls. Findings are of baseline values
Baumgartner et al. [26]	14 cases and 16 controls	Longitudinal studies	N	N	↓	N	Study group include alcoholics. Findings are of baseline values
Majumdar et al. [27]	39	Longitudinal studies	↓	↓	–	N	Study group included chronic alcoholics

Majority of the studies found suppressed HPT axis in alcoholics, which is revealed by low levels of TFT. In the longitudinal studies [26–28] comparison of the baseline TFT were not done post abstinence

N normal levels, ↓ lower to normal levels)

consumption on the thyroid gland and related dysfunction of the thyroid gland. There was no significant effect of interaction between duration of alcohol consumption and alcohol dependence. Small sample size, unavailability of data on amount of alcohol, nicotine and single cross sectional assessment of the subject groups before the treatment of deaddiction are the limitations of our study. Longitudinal follow up study in a large group of population on the effects of alcohol on hypothalamo pituitary thyroid axis is further needed.

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Compliance with Ethical Standards

Conflict of interest J. B. Honnamurthy, A. R. Shivashankara, S. S. Avinash, P. John Mathai, and M. Malathi declare that they have no conflict of interest.

Ethical Standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Father Muller Institutional ethics committee (FMMC/FMIEC/2039/2014).

Informed Consent All authors declare that written informed consent was obtained from all individual participants included in the study.

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