

Impact of alcohol use on thyroid function

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ABSTRACT

Alcohol is one of the commonest illicit psychoactive substances consumed globally and is the world's third largest risk factor for disease and disability. It has been reported to have multiple effects on the hypothalamo-pituitary-thyroid axis and the functioning of the thyroid gland. It has been reported to cause direct suppression of thyroid function by cellular toxicity, and indirect suppression by blunting thyrotropin-releasing hormone response. It causes a decrease of peripheral thyroid hormones during chronic use and in withdrawal. Alcohol use may also confer some protective effect against thyroid nodularity, goiter, and thyroid cancer. This article presents a review of the clinically relevant effects of alcohol on the functioning of the thyroid gland and also discusses the effect of medication used in treatment of alcohol dependence on thyroid function.

Key words: Alcohol, hypothalamus-pituitary-thyroid axis, thyroid, tobacco

INTRODUCTION

Alcohol is the world's third largest risk factor for disease and disability; causing at least 60 types of diseases and contributing to 200 others.^[1] Globally, high-income countries of the developed world have the highest alcohol consumption,^[1] with 50.1% of the US population (adults over 18 years of age) being current regular drinkers.^[2] In contrast, findings from the Indian National Survey suggest that around 21% of adult males in the country are current drinkers. Yet, the apparent advantage in proportion is lost in the sheer number of population, as even a conservative estimate puts the number of alcohol users in the country at around 61 million, of whom around 10 million have alcohol dependence.^[3] In view of the magnitude of the problem, it becomes necessary for us to understand the effect of alcohol on various body systems.

Indeed, alcohol affects almost all organs and systems of the human body.^[4] The hypothalamo-pituitary axis, through the

chemicals of dopamine and serotonin, is intricately linked with the development and continuation of dependence of all chemical substances,^[5] and therefore it is not surprising to find that most substances of abuse in return have multiple effects on the hypothalamo-pituitary-thyroid (HPT) axis and thyroid function. Of the multitude of drug-endocrine interactions reported, this review focuses on the effect of alcohol on the HPT axis. The paper is presented as a critical clinical overview for readers, and is by no means an exhaustive systematic review because of wide scope of the subject.

LITERATURE REVIEW

Databases of Medline (Pubmed), PsycINFO, and Scopus were searched from inception till July 2012. The initial decision of the authors was to limit all searches to English language original articles on human subjects, excluding all reviews, systematic reviews, and meta-analyses. The MeSH terms "alcohol-related disorders," "alcohol-induced disorders," "thyroid diseases," "thyroid gland", and "thyroid function tests" were used to build primary search queries. For the completeness of understanding, we inform the readers that searching with the term "alcohol" or the MeSH "ethanol" results in a large number of articles, primarily dealing with the use of alcohol for thyroid nodule ablation and in thyroid surgeries, and were therefore avoided in all our searches.

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DOI:
10.4103/2230-8210.113724

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To supplement the data gathered from the first round of searches, we searched with specific terms in all the above databases and Google Scholar. Such secondary search terms for thyroid functions were: thyroid, neuroendocrine, endocrine, thyroid stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), T3, T4, thyroid stimulating hormone, thyrotropin-releasing hormone, thyrotropin, thyroxine, triiodothyronine, hypothalamic-pituitary axis, hypothalamo-pituitary axis, and hormone. Each of these secondary terms was combined with terms for alcohol to generate the search results.

We also identified previous reviews and systematic reviews on the topic, which were rare, and manually searched all cross-references for further studies [Table 1]. Last but not least, while writing we were surprised to find paucity of human studies on fetal and neonatal thyroid functioning in relation to maternal alcohol use. There was also lack of consensus in studies as regards the effect of alcohol on the levels of peripheral thyroid hormone. For the purpose of completeness, we went back to our original database and hand searched articles related to these particular topics for inclusion.

All abstracts were individually considered by both the reviewers for inclusion into the study. For the included abstracts, full texts were subsequently procured. Figure 1 depicts the search strategy and the studies included.

A majority of the selected studies were descriptive and often contradictory, suggesting a complex interrelation of alcohol

with the thyroid function. Randomized control trials (RCTs) were rare though comparison groups were often used. Lack of consensus in clinical findings also hampered the development of theoretical models of causation. Theoretical constructs for how these changes in thyroid functioning are brought about by alcohol were rare. When present, they were often untested and offered as suppositions by authors. Despite these limitations, clinically important patterns of interaction between alcohol use and thyroid axis emerged from these studies, which this article tries to summarize.

ALCOHOL AND PERIPHERAL THYROID HORMONE LEVELS

The effect of chronic alcohol consumption on peripheral thyroid hormone (T3 and T4) levels is not settled.^[6] Even in animal models, both a suppression of peripheral thyroid hormones^[13-15] and an absence of alteration in their levels^[14] have been reported.^[13]

Human studies on current alcohol users are less, as most studies are conducted in detoxification programs and researchers face the practical difficulty in recruiting active drinkers. Some consensus seems to be developing for alcohol causing a moderate suppression of peripheral serum thyroxine (T4) levels with more significant suppression of triiodothyronine (T3) levels in chronic alcohol users [Table 2].^[17,25] In addition, alcohol-dependent individuals may present with a “euthyroid sick syndrome,” evidenced by low levels of T3, high levels of reverse T3 (rT3), and normal levels of T4.^[26-28] Extrapolation of baseline data from longitudinal studies on patients undergoing detoxification similarly suggests a decrease in peripheral T3 and T4 levels (or free T3, free T4) during chronic alcohol use.^[29-31] Finally, in patients who relapsed and returned to their regular amount of alcohol consumption, re-lowering of plasma T4 concentrations supports this observation.^[31]

In contrast, a wealth of data exists on the thyroid profile of alcoholics during withdrawal and abstinence. Peripheral thyroid hormones are suppressed during withdrawal and the degree of suppression of their levels has been associated with the severity of withdrawal.^[18,32] This phenomenon is clinically interesting as thyroid suppression may accentuate

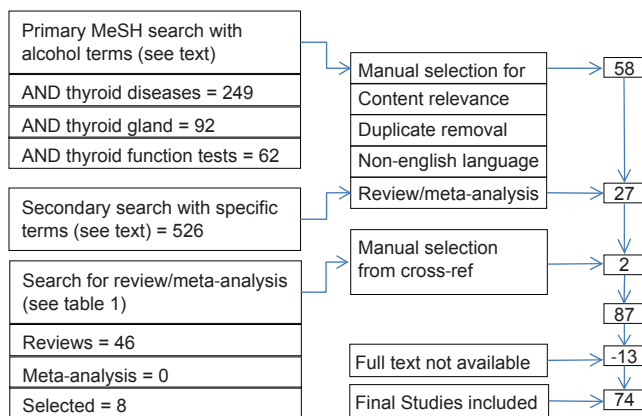


Figure 1: Search methodology

Table 1: Reviews and systematic reviews on the effect of alcohol on thyroid function

Principal author	Year	Topic of review	Reference no.
Hermann	2002	Dysregulation of the hypothalamic-pituitary-thyroid axis in alcoholism	6
Loosen	1988	Thyroid function in affective disorders and alcoholism	7
Loosen	1988	Thyroid function in affective disorders and alcoholism	8
Fink	1984	The effects of alcohol on endocrine function	9
Noth	1984	The effects of alcohol on the endocrine system	10
Rawat	1981	Neuroendocrinological implications of alcoholism	11
Ylikahri	1980	Hormonal changes during alcohol intoxication and withdrawal	12

the withdrawal dysphoria,^[25,33] thereby increasing the relapse risk in alcoholism.^[34]

Making clear sense of thyroid hormonal changes during abstinence is difficult as studies report conflicting results. For all phases of abstinence (early as well as late), there are always more number of studies that show normal values of peripheral thyroid hormones, as compared to studies that report abnormality. Hermann *et al.* reviewed 19 studies in 2002^[6] and showed that 63–66% of studies reported normal findings of T3 and T4 for early abstinence (less than 3 weeks),

whereas 75–83% studies reported normal findings for late (more than 3 weeks) abstinence. When considering the free fraction of the hormones (fT3/fT4), the proportion of studies reporting no abnormalities becomes as high as 88–100%. Therefore, the effect of alcohol withdrawal on the levels of peripheral thyroid hormone must be small and dependent on multiple other variables like comorbid mood state, hepatic status, preexisting thyroid profile, etc.

Yet, in longitudinal studies that do show abnormality [Table 3], patterns seem to emerge. One pattern is the suppression

Table 2: Effect of alcohol on thyroid hormone levels from cross-sectional studies reporting positive results

Study	Cases and controls	T4	T3	fT4	fT3	rT3	TSH
Valeix <i>et al.</i> , 2008 ^[16]	1493 subjects with no known thyroid disorders	↓	-	-	-	-	N
Garbutt <i>et al.</i> , 1996 ^[17]	TRH response in alcoholic compared to depressed men	-	-	-	-	-	↓ ^a
Pienaar <i>et al.</i> , 1995 ^[18]	28 patients in acute withdrawal symptoms, 29 abstinent for 5-8 weeks, 16 patients abstinent for >2 years compared to 22 healthy male controls	-	-	-	-	-	↓ ^a
Anderson <i>et al.</i> , 1992 ^[19]	21 non-depressed alcoholic inpatients	-	-	↑	-	-	↓ ^a
Sellman <i>et al.</i> , 1992 ^[20]	66 alcoholic men abstinent for at least 4 weeks	-	-	-	-	-	↓ ^a
Müller <i>et al.</i> , 1989 ^[21]	35 alcoholic inpatients at admission and 17 retested after "several weeks" of sobriety	-	-	-	-	-	↓ ^a
Hegedüs <i>et al.</i> , 1988 ^[22]	21 consecutive chronic alcoholics without liver cirrhosis compared to matched controls	N	↓	N	↓	-	N
Casacchia <i>et al.</i> , 1985 ^[23]	Alcoholic men abstinent for more than 20 days	-	-	-	-	-	↓ ^a
Hegedüs, 1984 ^[24]	40 alcoholic patients with cirrhosis, compared to 40 sex-, age-, and weight-matched normal subjects	N	↓	N	↓	-	↑

^aTRH stimulation test was done to show blunting of TSH response secretion, rather than a baseline decrease, T: Thyroxine

Table 3: Effect of alcohol on thyroid hormone levels from longitudinal studies reporting positive results

Study	Type	Cases	T4	T3	fT4	fT3	rT3	TSH	Time of measure
Ozsoy <i>et al.</i> , 2006 ^[35]	Follow-up day 1 of withdrawal and at day 28	39 male inpatients in alcohol withdrawal were compared with 28 healthy men	-	N	-	N	-	N	Day 1 of withdrawal Day 28
Liappas <i>et al.</i> , 2006 ^[25]	Follow-up baseline and at 4 weeks	100 alcohol-abusing/dependent subjects undergoing detoxification ^a	N	↑	-	-	-	N	Baseline After detox
Heinz <i>et al.</i> , 1996 ^[31]	Follow-up baseline, 8 days, 3 months, and 6 months after detoxification	45 alcohol-dependent patients during detoxification and compared to healthy controls	↓	N	N	N	N	↓	Baseline 8 th day 6 months
Sudha <i>et al.</i> , 1995 ^[28]	Follow-up baseline and at 4 weeks	Male alcohol user in inpatient deaddiction, comparison with non-alcoholics	↓	↑	-	-	-	-	Baseline At 20 days
Baumgartner <i>et al.</i> , 1994 ^[30]	Follow-up baseline and at 21 days	14 chronic alcoholics during detoxification, compared with 16 healthy volunteers	N	N	↓	↓	N	N	Baseline 3 weeks
Dackis <i>et al.</i> , 1984 ^[36]	Follow-up baseline and at 3 weeks	32 chronic alcoholics compared to healthy controls	-	-	-	-	-	↓ ^b	Baseline 3 weeks
Välimäki <i>et al.</i> , 1984 ^[29]	Follow-up baseline and at 2 weeks	32 non-cirrhotic male alcoholics	N	N	N	N	-	N	Baseline 2 weeks
Geurts <i>et al.</i> , 1981 ^[37]	Follow-up baseline and after detoxification	18 chronic alcoholics	↓	-	-	-	-	-	Baseline After detox
Majumdar <i>et al.</i> , 1981 ^[26]	Follow-up day 1 of withdrawal and at day 8	39 chronic alcoholics	↓	↓	-	-	-	N	Baseline Day 8

^aOut of the 100 patients, 70 did not have any abnormality at baseline or after detox, A subgroup of 30 patients who had baseline abnormality showed suppression after detox, ^bTRH stimulation test was done to show blunting of TSH response secretion, Rather than a baseline decrease, N: No change, TSH: Thyroid stimulating hormone, T: Thyroxine

of T4 in acute withdrawal^[25,28-31,37] which persisted for 2-4 weeks into abstinence.^[36,38] Other studies show an increase (return to normal) of T4 levels within the first week,^[31] second week,^[29,37] third week,^[30] or fourth week^[25] after initial suppression during acute withdrawal. The levels of fT4 have been found to be similarly suppressed in acute withdrawal.^[16] Total (T3) and free triiodothyronine (fT3) levels also showed a decrease in patients who had abstained from alcohol for less than 3 weeks, but mostly returned to normal in the long term.^[22-24,30] Only one study by Ozsoy *et al.* in 2006 reported a reverse pattern with no change of fT3 and fT4 in early (1 day after cessation) withdrawal, but with a significant suppression in late withdrawal (28th day of abstinence), which is in direct contradiction to the reports by others.^[35]

ALCOHOL AND TRH ABNORMALITIES

In contrast to the conflicting fluctuations in peripheral thyroid hormone levels, a blunting of the plasma TSH response after stimulation with TRH has been reported more consistently in patients of alcohol dependence when compared to healthy control subjects [Tables 2 and 3]. The TSH blunting was more frequent in early abstinence for less than 3 weeks,^[29] but was also observed after longer period of abstinence in some studies. TSH blunting also correlated positively with the severity of withdrawal symptoms in early abstinence, but not after 5-8 weeks.^[18]

Although a statistically significant abnormality of the TRH response was shown in most of these studies, only 20-35% of all assessed patients showed blunting of the TRH response.^[18-21,29,36] It is not currently known as to why only some alcoholics have TRH response abnormality. Loosen *et al.* in 1993^[39] classified patients with TRH abnormality according to the classification of Cloninger (1987), but failed to show association with Type II alcoholism, a subtype of alcoholism with a high hereditary component.^[40] Other studies too explored the possible genetic contribution for altered TRH tests by focusing on patients with a positive family history of alcoholism or on high-risk children of alcoholic fathers.^[41,42] However, none of these studies found a possible genetic contribution.

Co-occurring liver cirrhosis in alcoholism was also considered as a possible contributor for the altered TRH response by its effect on the HPT axis. But a review by Loosen *et al.* in 1992, looking into this issue, found that while 26% patients without liver disease showed a reduced TRH response, only one of the six studies on alcohol-dependent patient with liver disease reported abnormality in TSH response. The authors, therefore,

suggested that TRH response dysfunction in alcoholism cannot be attributed simply to liver cirrhosis.^[6,43]

ALCOHOL AND THYROID VOLUME

Alcohol is known to have a direct toxic effect on thyroid cells, which is used therapeutically in ethanol ablation therapy of thyroid nodules.^[35,44] Alcohol-induced direct toxicity may account for the reduction in the thyroid volume in alcohol-dependent patients (as compared to healthy controls) as seen in multiple ultrasound studies.^[22,24,45] The severity of thyroid fibrosis in alcoholics correlates with the duration and total dose of alcohol use rather than peak blood levels, as studies show chronic alcohol users to have more fibrosis than acute binge drinkers. The reduced thyroid size is accompanied by a reduction in T3 and fT3 concentrations with normal T4, fT4, and TSH values in most studies. Although alcohol causes similar hepatic fibrosis by direct toxicity, liver damage does not seem to be a contributor to the thyroid fibrosis. A significant reduction in thyroid volume has been reported in ultrasound studies in alcohol-dependent patients without liver cirrhosis when compared to healthy controls. Additionally, patients with non-alcoholic liver cirrhosis show no differences in thyroid volume when compared to controls. Thus, the toxic effect of alcohol on thyroid appears to happen independent of liver damage.^[22]

The toxic effect of alcohol on the thyroid may also confer some benefit and it has been suggested that alcohol consumption may be protective for the development of goiter. Knudsen *et al.* in 2001, studying 4649 healthy subjects, found association of smaller thyroid volume and lower prevalence of solitary nodules with increasing levels of alcohol consumption.^[45] In contrast, a recent study found an increase in thyroid volume in chronic alcohol users.^[16] The thyroid volume increase was dependent on the dose of alcohol consumed and independent of the associated smoking habits. The authors, however, did not postulate any biological basis for their divergent report.^[16]

HYPOTHESIS ON THE MECHANISM OF THE EFFECT OF ALCOHOL ON THYROID

The fact that alcohol causes direct cellular toxicity on thyroid cells thereby producing thyroid suppression and reducing thyroid volume is well established. However, the mechanism of alcohol-induced reduction in TSH secretion to TRH stimulation is open to speculation. One hypothesis for this phenomenon is a possible down-regulation of the TRH receptors in the pituitary due to chronically high TRH concentrations. Physiologically, TRH levels increase when there is a decrease in peripheral concentration of thyroid

hormones or where there is more demand for T3 and T4. In chronic alcoholism and in early alcohol abstinence, T3 and T4 levels are reported to be low. This pattern of peripheral low thyroid hormones in various stages of alcoholism can chronically induce a slightly elevated TRH release.^[6] The increased TRH can subsequently cause feedback suppression of the TRH receptors, thereby blunting the downstream TSH secretion.

There seems to be fair amount of evidence supporting the feedback TRH receptor suppression by TRH. Chronic ethanol treatment in rats has resulted in an increase in TRH mRNA in neurons in the hypothalamus.^[46,47] Additionally, experimentally increased TRH level has resulted in a down-regulation of pituitary TRH receptors in rats with both TSH secreting tumors^[48,49] as well as in healthy pituitary tissue.^[50] And finally, alcohol-dependent patients in abstinence, who showed a strong blunting of the TRH response, also showed high endogenous TRH levels in the CSF and vice versa,^[17,51] suggesting that increased CSF TRH was the cause of the TRH response blunting.

Another hypothesis regarding thyroid dysfunction in alcoholism suggests that alcoholism results in Euthyroid Sick Syndrome (ESS), a condition characterized by reduced T3 concentrations and elevated concentrations of the thyroid hormone metabolite rT3.^[25] ESS is observed in a variety of other non-thyroidal illnesses like chronic renal failure, liver dysfunction, after stress of surgery and with various medications.^[52,53] However, current evidence does not favor ESS as a cause of thyroid dysfunction in alcoholism. In contrast to elevated rT3 concentrations in the ESS, rT3 concentrations are normal in alcoholics^[18,29-31,37] and reduced T4 concentrations in alcoholism are sometimes accompanied by normal or elevated concentrations of T3, a pattern not seen in ESS.^[28,36,37] Therefore, thyroid abnormality in alcoholism is not fully explained by ESS.

ALCOHOL AND THYROID CANCER

Several studies report a decrease in thyroid cancer risk with alcohol use.^[54-57] A large prospective study following up 1,280,296 women with 421 new cases of thyroid cancer showed a clear reduction in risk of thyroid cancer with greater alcohol consumption,^[58] and two smaller prospective studies^[59,60] similarly reported a small reduction in risk, albeit not reaching statistical significance. Comorbid tobacco use, which also causes a reduction of thyroid cancer, has been a consistent confounding factor in these studies, and in a pooled analysis of 2725 thyroid cancer cases, from 14 case-control studies,^[54] the statistical association of decreased cancer in alcohol consumption disappeared after adjusting for smoking.

The most conclusive evidence to date of the effect of alcohol on thyroid cancer comes from the finding of the large NIH-AARP Diet and Health Study, which prospectively followed up 490,000 participants including 292,000 men over a period of 7½ years during which 170 men and 200 women developed thyroid cancer. The study clearly showed a significant reduction of cancer risk when consuming two or more drinks per day (RR = 0.57) as compared to no drinking. Even consuming one or more drinks of beer per day was associated with a decreased risk when compared with no beer drinking, particularly in men (RR = 0.47), whereas no clear dose – response relationship was found with wine consumption. The inverse association was stronger in males, whereas in females, though trends of decrease were found, it did not reach statistical significance. The strength of the inverse association persisted even when adjusted for smoking and non-smokers had a further reduction in risk (RR = 0.33) when compared to smokers (RR = 0.78). The decrease in risk was seen in all types of thyroid cancer, although the authors observed a clearer inverse association for papillary (RR = 0.58) as compared with follicular thyroid cancer (RR = 0.86).^[61]

A theoretical hypothesis for this protective phenomenon stems from the fact that TSH is known to increase the proliferation of follicular thyroid cells in laboratory studies.^[62,63] Alcohol may prevent the proliferative effect of TSH on the thyroid follicle, thereby reducing the occurrence of cancer.^[61]

ALCOHOL AND AUTOIMMUNE THYROID DISEASES

Alcohol is known to decrease the frequency of autoimmune disorders like rheumatoid arthritis^[64] and systemic lupus erythematosus.^[65] One recent prospective Danish study reported significant protective role of alcohol in preventing autoimmune hypothyroidism. The study diagnosed 140 cases of autoimmune hypothyroid from 2,027,208 person-years of observation and reported a negative association between alcohol consumption and the incidence of overt autoimmune hypothyroidism. One interesting finding of the study was that though modest to high alcohol consumption of 1-20 units/week protects from developing autoimmune overt hypothyroidism, a higher consumption of ≥ 21 units/week did not show the protective effect.^[66]

EFFECT OF MATERNAL ALCOHOL CONSUMPTION ON FETAL THYROID HORMONAL STATUS

Though maternal consumption of alcohol results in fetal alcohol syndrome with multiple congenital defects,

thyroid largely seems to remain unharmed by the *in utero* alcohol exposure. Most animal studies report no effect of maternal alcohol administration on neonatal and adult offspring animals,^[67,68] although Hannigan *et al.* in 1990 reported significantly lower serum total thyroxine (T4) concentrations in young rats exposed to alcohol *in utero* than normal and pair-fed control rats.^[69] Human studies have similarly reported that though alcohol consumption during pregnancy is related to multiple alcohol-related birth defects (ARBDs), the level of the neonatal T4 is mostly within normal limits.^[70] Thus, alcohol does not seem to have significant effect on the thyroid axis in the neonate.

TREATMENT OF ALCOHOLISM AND THE THYROID AXIS

Apart from the changes that happen to the thyroid hormones during the time of alcohol withdrawal as well as early and late abstinence, treatment of alcoholism uses medications that may themselves interfere with the thyroid functioning. Benzodiazepines are most commonly used to tide over the acute withdrawal symptoms of alcohol. Chlordiazepoxide, a long-acting benzodiazepine, is the medication of choice though diazepam and clonazepam are often used, as well as lorazepam in cases of hepatic damage. Benzodiazepines as a group appear to be safe with no prominent action on the thyroid axis,^[71] and animal studies report that diazepam did not affect the availability of thyroid hormone in blood circulation.^[72] Conversely, the plasma concentration of diazepam seems to increase in hypothyroid rats, but remains normal in hyperthyroidism.^[73]

For continuation of abstinence, disulfiram, acamprosate, and naltrexone are most commonly used. Disulfiram, an irreversible inhibitor of aldehyde dehydrogenase, is used as a deterrent agent to prevent drinking. It results in accumulation of acetaldehyde in the body subsequent to alcohol consumption, which results in unpleasant effects after drinking. Disulfiram is known to have prominent anti-thyroid action, and as early as in 1954 it was shown to react chemically with iodine forming a complex that creates a state of relative iodine deficiency and hampers the iodine trapping by the thyroid.^[74] With deterrent agents becoming less popular in treatment, the research interest in disulfiram has decreased as evidenced by most papers on the drug being from 1980s.^[75,76]

Of the various anti-craving agents, acamprosate, an N-Methyl-D-aspartate (NMDA) receptor antagonist, does not seem to have any effect on thyroid, whereas naltrexone, an opioid receptor antagonist, might have slight thyroid stimulating effect without any clinical significance.^[77,78] Baclofen, an agonist for the GABA-B receptors and long

used for treatment for spasticity, is now being used as an anti-craving agent. Baclofen does not seem to have any effect on the peripheral thyroid hormones, but can produce a blunting of the TRH-stimulated TSH release in normal persons^[79] though its effect on the already deranged thyroid axis needs to be studied.

CONCLUSION

The effect of alcohol on the HPT axis is significant and alcohol consumption affects almost all aspects of the functioning of the thyroid gland. Given the comorbidity of mood disorders in alcoholism and the relation of mood disorders with hypothyroidism, these findings open up interesting theoretical possibilities to explain the increased occurrence of mood disorders in alcoholism. Although current studies have mostly looked into the effect of alcohol on the neuro-endocrine axis, such associations are rarely unidirectional. The altered thyroid levels in withdrawal may adversely affect alcohol abstinence by changing the hormonal milieu in the brain, increasing withdrawal dysphoria, and increasing craving. At present, such studies are few and upcoming, but it creates the possibility of understanding and treating alcohol use disorders from a whole new perspective.

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Cite this article as: Balhara YP, Deb KS. Impact of alcohol use on thyroid function. *Indian J Endocr Metab* 2013;17:580-7.

Source of Support: Nil, **Conflict of Interest:** None declared.