Netherlands
The Journal of Medicine

REVIEW

Alcohol-induced Cushing syndrome

Hypercortisolism caused by alcohol abuse

F. Besemer*, A.M. Pereira, J.W.A. Smit

Department of Internal Medicine and Endocrinology, C4-R, Leiden University Medical Center, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)71-52 63 082

ABSTRACT

Background: Cushing's syndrome (CS), a rare syndrome caused by overexposure to glucocorticoids, is difficult to diagnose. The underlying causes of CS include pituitary and ectopic adrenocorticotropic hormone (ACTH) producing tumours and adrenal adenomas or hyperplasia. Alcoholism, however, can cause similar symptoms, giving rise to a so-called pseudo-Cushing state, which aggravates the differential diagnostic dilemmas of CS.

Aim: To document any specific clinical or biochemical features of alcohol-induced CS.

Methods: A Medline computer-aided search was performed to identify studies that have attempted to differentiate between alcohol-induced pseudo-Cushing and CS. Only original articles, not reviews, written in English were included. A total of 62 articles were included.

Results: Clinical and biochemical abnormalities mimicking increased hypothalamus-pituitary-adrenal (HPA) axis activity were found in the majority of the patients, although the severity of the changes varied widely. The most frequently occurring abnormalities were: insufficient suppression after low-dose dexamethasone or increased 24-hour urinary free cortisol (UFC). After alcohol withdrawal, cortisol decreased and dexamethasone-induced suppression of cortisol increased. No differences were noted between alcoholic and control subjects after an ACTH stimulation test, insulin tolerance test or metyrapone test. Differences were found after a naloxone test and hexarelin test. Studies using corticotropin-releasing hormone stimulation and tests after ethanol ingestion revealed inconclusive results.

Conclusion: There is no clear definition for the alcohol-induced pseudo-Cushing state, and hitherto studies fail to provide clues to differentiate between pseudo-Cushing and Cushing's syndrome. Only cessation of alcohol can normalise biochemical abnormalities and regress hypercortisolic symptoms.

KEYWORDS

Alcohol, cortisol, Cushing's syndrome

INTRODUCTION

Cushing's syndrome (CS) is an extremely rare clinical syndrome characterised by overexposure to glucocorticoids with an annual incidence of two to three per million.[1,2] CS is caused by uncontrolled overexposure of the body, including the central nervous system, to corticosteroids. This results in a phenotype characterised by psychopathology (mainly depression), features of the metabolic syndrome (such as insulin resistance, hypertension, and abdominal fat accumulation), but also proximal muscle wasting, and easy bruisability.[3,4] This uncontrolled exposure to endogenous cortisol is caused by tumours, which overproduce corticotropin-releasing hormone (CRH, in very rare cases), adrenocorticotropic hormone (ACTH, by pituitary adenomas or ectopic tumours), or cortisol (by adrenal tumours). Cushing's syndrome is a fatal condition in the absence of adequate treatment. Although the severe classical phenotype is not difficult to diagnose, some frequently occurring illnesses such as depression, obesity, physical stress, and chronic alcoholism can induce a phenotype that largely overlaps with CS and is also accompanied with increased cortisol exposure, and as a consequence, is called a pseudo-Cushing state. The discrimination between CS and these frequently occurring pseudo-Cushing states is difficult because many symptoms of CS, such as overweight, depressed mood, hypertension and irregular menses, are also prevalent in pseudo-CS, and therefore, biochemical tests often provide equivocal results resulting in a low specificity.[5] This review aims to focus on the diagnosis and therapy for alcohol-induced pseudo-Cushing's syndrome.

METHODS

A computer-aided search was performed in Medline using the search terms "alcohol AND hypercortisolism", "alcohol AND cushing", "alcoholic AND cortisol" and "alcoholic AND cushing". Only articles written in English with an abstract were included. The search was performed on 9 September 2010 and resulted in a total of 423 articles. Based on title and abstracts, 352 were excluded; the remaining 71 articles were retrieved for further evaluation. One article was not available[6] and another eight were excluded after complete evaluation, because they did not present original data[7] or were not relevant for the aim of the present study.[8-14] Finally, a total of 62 articles were included for detailed analysis.

RESULTS

Clinical presentation

Case reports were identified on patients who had symptoms compatible with CS, which eventually proved to be the result of alcoholic addiction, which illustrates that symptoms of the diseases resemble each other.[15-21]

Details on physical examination were reported in all 16 cases; 87.5% had a moon face, 69% hypertension, 81% muscle weakness or tiredness, 12.5% striae and 75% truncal obesity. In Cushing's syndrome, moon face is reported in 82 to 90%, hypertension in 68 to 75%, weakness in 60 to 64%, and obesity in 95% of cases, respectively.[3,4]

Clinical symptoms were reported in 10 out of 16 cases: 50% had weight gain, 30% easy bruisability, 30% sleepiness, 20% headache and only one person suffered from depression. In CS easy bruisability is reported in 65%, whereas headache and sleepiness are not reported.[3,4]

BIOCHEMICAL PRESENTATION

Circulating cortisol concentrations

In the case reports cortisol was elevated in 12 out of 13 patients, which normalised after alcohol abstinence in all patients.[15,16,19-21] Twelve studies investigated plasma cortisol concentrations in alcoholic patients. Six studies found no differences with control subjects, while six other studies found elevated cortisol levels in alcoholics.[28-33] A decrease in mean cortisol after abstinence (7-30 days) was seen in three other studies.[31,34,35] Three studies measured cortisol during 24 hours and observed no differences in circadian rhythms in alcoholics compared with controls,[36-38] although mean cortisol decreased in one study after approximately 30 days of abstinence.[37] Coiro, *et al.* measured cortisol in ten women with alcohol-induced pseudo-Cushing and found a higher fasting cortisol at 8.30 am compared with controls.[39] Frias *et al.* evaluated teenagers and adolescents during acute alcohol intoxication and found elevated cortisol levels, which was more pronounced in females.[40,41] In the study by Bannan and colleagues, 20% of alcoholics were found to have hypercortisolism that appeared to be positively correlated to withdrawal symptoms.[42]

Stalder *et al.* detected higher cortisol in the hair of subjects who had recently stopped drinking alcohol compared with both controls and subjects who had a longer abstinence period.[43]

Salivary cortisol

Salivary cortisol was measured in only two studies: The first (Adinoff *et al.*) reported higher salivary cortisol concentrations at daytime in intoxicated alcoholics and non-intoxicated withdrawal subjects than controls,[44] whereas Beresford noted a higher salivary cortisol in heavy drinking than light drinking alcohol-dependent subjects at awaking and 30 minutes thereafter.[45]

Urinary free cortisol (UFC) excretion

Five studies measured 24-hour UFC.[33,39,46-48] Coiro *et al.* reported higher fasting mean cortisol than control subjects but no difference between pseudo-Cushing and Cushing patients.[39] Stewart *et al.* and Wand *et al.* noted a higher mean 24-hour UFC in 28 alcoholics *vs* 32 controls.[33,47] In contrast Rosman *et al.* reported a lower cortisol in alcoholic subjects, which was to be expected since all his subjects had proven cirrhosis or compelling clinical evidence for it.[46] Willenbring observed normal urinary cortisol that decreased even further after three weeks of alcohol abstinence.[48] Urinary cortisol or corticoids were elevated in three subjects presented in case reports,[16,21] slightly elevated in two[17,18] but not different compared with controls in seven subjects.[15,20]

Dynamic tests to evaluate the HPA axis

Low-dose (1 mg) oral dexamethasone suppression: The dexamethasone suppression test (DST) can be used to demonstrate hypercortisolism. The Endocrine Society advises giving 1 mg dexamethasone orally at 11 pm and taking blood samples the next day at 8 am for determination of plasma cortisol, which should be suppressed to below 50 nmol/l to obtain a specificity greater than 95%.[49] Nine studies took blood samples in alcoholics as recommended, and their results are presented in *table 1*.[27,39,46,50-55] Insufficient suppression was reported in 0 to 75%. Three studies performed the test at admission for alcohol detoxification and found inadequate suppression in 50% (35/70) of patients. After an average of four weeks of alcohol withdrawal, cortisol suppression was still inadequate in seven out of 59 patients.[27,50,53]. In another study,[56] patients also underwent a DST at different periods

Table 1. *Studies reporting the results of a 1 mg dexamethasone suppression test*

Study	N	Age (yrs)	Duration alcoholism (yrs)	Amount alcohol	Time since last drink	Cortisol > 5 μg/dl after DST	Cortisol > 5 μg/dl after abstinence
Bailly	10	27-47	15.8	258	?	60%	10%
Coiro 2000	8	35.7	≥ 5	189.1 g/day	?	75%	
Coiro 2004	10	31.7	≥ 5	240 g/wk	?	60%	
Emsley	36	41-60 30-58	22/22	?	40/6 months	0%	
Oszoy	30	43.03	21.83	330.4 g/day	≥ 4 weeks	22.22%	13.6%
Ravi	30	40	9.6	≥ 15 whiskey on ≥ 3 days	0	63.3%	11.1%
Rosman	17	31-53	10-30	?	?	12.5%	
Swartz 1982	43	44.4/40.8	12.6/9.5	391/326 ml/day	?	4.65%	
Szucs	22	53	?	?	≥ 2weeks	?	

N = number of subjects, DST = dexamethasone suppression test.
Emsley: 19 korsakoff and 17 non-amnesic alcoholists. Swartz: means were reported for non-suppressors and suppressors respectively.

after withdrawal with cortisol measurements at 3 pm. The longer the period of abstinence, the more patients had normalised suppression. In three case reports, abnormal dexamethasone suppression test in alcoholic patients normalised after abstinence.[17,19,21]

Other cortisol suppression tests

Many studies used Carroll's concept for psychiatric research to measure cortisol at 4 and 11 pm after a dexamethasone test.[57] All 11 studies that measured cortisol at 4 pm noticed no suppression in some of the alcoholics, ranging from 6 to 63.3%.[27,48,50,53,54,58-62] Most patients were tested during alcohol withdrawal. Five studies measured cortisol at 11 pm; one of them found normal suppression,[52] the others did not.[27,50,53,61]

Majumdar (1988) observed a non-suppressed cortisol at 4 pm in two out of 20 detoxicated alcoholics after a 2 mg DST.[63] In six of 30 alcoholics who had just stopped drinking non-suppressed cortisol levels were found whereas after abstinence this number decreased to two. Rees also measured a high cortisol after a 2 mg DST in one out of two persons, which normalised after 16 days alcohol abstinence.[21] Proto performed a DST with 2 mg dexamethasone a day for three days and noted normal suppression of cortisol in all six subjects.[20]

Hundt did a DST with 1.5 mg dexamethasone with measurements at 8 am and detected abnormal suppression in four out of 19 alcoholic patients (21%) during alcohol withdrawal.[64]

Fink recruited ten alcoholic patients who were subjected to an intravenous DST with 1 mg/hour of dexamethasone for two hours with subsequent cortisol measurements at 1/2, 1,1 1/2 and 2 hours.[65] Four patients showed abnormal cortisol values.

Combined suppression and stimulation tests

Three studies found no differences in cortisol between alcoholics and controls using the 250 μg ACTH stimulation test.[29,47,55] One of these studies noticed that normal subjects had a cortisol response after a 0.25 μg ACTH stimulation test, which was absent in alcoholics.[47] Another study observed that two out of 13 tested alcoholics did not meet criteria for normal responsiveness; however, four alcoholics had higher levels than normal subjects.[46]

A CRH test (100 μg or 1 μg/kg bolus) was performed in seven studies and three observed no differences in cortisol response in alcoholics and controls,[25,30,50] although two of them found a blunted ACTH response.[25,30] Two others observed a blunted cortisol response[22,47] and two noticed a higher cortisol.[64,66] Three studies retested the subjects after withdrawal, one reported a lower cortisol response,[50] while the others detected no differences between controls and alcoholics anymore.[22,64] Two studies reported no differences in cortisol after an insulin tolerance test (ITT) between non-intoxicated alcoholics and controls,[24,67] yet one noted a blunted ACTH response in alcoholics.[67] ACTH was too high in the subject that underwent an ITT presented by Lamberts.[19] Coiro 2000 performed a hexarelin test in 25 subjects and registered an increase in ACTH and cortisol in controls and subjects with Cushing, but not in alcoholics.[51] Wand performed a metyrapone test in 14 alcoholics and 13 volunteers, and found similar decrements in cortisol in alcoholics and controls.[47] Although the ACTH response and 11 deoxycortisol levels were much lower than in controls and thus 50% of alcoholics met criteria for adrenal insufficiency. Lamberts described a woman with a metyrapone test compatible with Cushing's syndrome.[19] Inder infused 20 mg naloxone in nine alcoholics and nine controls and showed a blunted rise followed by a slower fall to normal values in alcoholics.[25] The controls demonstrated positive correlations between basal cortisol and cortisol increment and ACTH increment, which were not present in the alcoholic subjects.

Nine studies measured cortisol response after alcohol intake. The studies all used different designs. Three of

them found no or a slight change in HPA hormones in alcoholics compared with controls,[29,68,69] three described a higher response[65-67,70-72] and two others observed a lower response.[73,74] One study noticed only changes in cortisol and ACTH in subjects who had gastrointestinal symptoms after drinking alcohol.[75]

The last two studies pointed towards an altered cortisol feedback mechanism in alcoholics. Lovallo measured cortisol after public speaking and detected no cortisol response in alcohol-dependent subjects, but did find this in controls.[76]

Coiro 2007 measured cortisol after an exercise test in alcoholics after four, six and eight weeks of abstinence.[77] After four weeks abstinence, exercise induced no change in cortisol and ACTH in contrast to in controls; after eight weeks the difference between controls and alcoholic had disappeared.

BEST TREATMENT OF ALCOHOL-INDUCED CUSHING

The search did not find any articles about treatment of alcohol-induced Cushing's syndrome. Nevertheless, case reports invariably demonstrated that resolution of symptoms and biochemical disturbances occurs after alcohol withdrawal.[15-21]

DISCUSSION

This review demonstrates that the clinical and biochemical features of the alcohol-induced pseudo-Cushing syndrome vary widely, and that no criteria are available to distinguish between CS and alcohol-induced CS. No stringent criteria were found for the definition of pseudo-Cushing syndrome. Different biochemical tests that evaluate different properties of the HPA axis yielded different results. In addition, standardisation of tests and test criteria varied widely precluding simple generalisations of test results. No laboratory tests yielded sufficient discriminatory power to detect alcohol-induced pseudo-Cushing syndrome. Signs and symptoms tend to normalise after cessation of alcoholism for at least a month. At end of the 1970s the first case reports appeared on patients with symptoms mimicking Cushing's syndrome, caused by alcoholism.[15-21] Tests that were characteristic for hypercortisolism normalised after cessation of alcohol abuse.

Plasma cortisol levels were higher in alcoholics in nine studies[28-33,40-42] and normal in six other studies.[22-27] This discrepancy can be explained by the different study designs: four of six studies that observed no differences in cortisol[22,24,25,27] were done in subjects who had stopped drinking alcohol for at least ten days. In contrast, seven of nine studies that reported a higher cortisol used subjects who stopped drinking for less than one day.[28,30,31,33,40-42] Consequently, the observed higher cortisol could either be provoked by alcohol or by the stress during the first days of abstinence.

Furthermore, blood samples of five out of six studies that observed no difference were taken between 8 and 9 am,[22,24-27] while this was the case in only two out of nine studies that observed differences.(32,33) Other studies did not reveal time or took samples late in the morning, afternoon or night. Since cortisol secretion has a circadian rhythm, time of sampling has a great influence on cortisol level.

Inadequate suppression was measured in 0 to 75% of alcoholics[27,39,46,50-55] during a 1 mg dexamethasone suppression test. However, the studies all used different designs. In the study that observed an appropriate suppression, tests were performed in subjects that were abstinent for at least 12 weeks.[52] One study only stated that there was no difference in plasma cortisol between controls and alcoholics.[55]

After one month of abstinence more suppression was observed using a 1 mg dexamethasone suppression test.[27,50,53] However, these three studies measured cortisol at three different moments and classified suppression as abnormal if at any of these moments suppression was abnormal. Also, they did not mention at which time the suppression was abnormal.

In conclusion, the literature does not provide any evidence for clinical symptoms or laboratory investigations suitable for diagnosing hypercortisolism caused by alcoholism. However, the number of patients studied was limited, different study designs, diverse definitions for alcoholism and pseudo-Cushing were used and tests were performed in various populations. Additionally, most studies were performed during alcoholic withdrawal, which is likely to induce stress and thus hypercortisolism.

Therefore, alcoholic patients diagnosed with CS should have repeat clinical and biochemical work-up after cessation of alcohol before subsequent (radiological) investigations can be performed.

REFERENCES

1. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf). 1994;40(4):479-84.
2. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001;86(1):117-23.
3. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. Lancet. 2001;357(9258):783-91.
4. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367(9522):1605-17.

5. Ross EJ, Linch DC. Cushing's syndrome--killing disease: discriminatory value of signs and symptoms aiding early diagnosis. Lancet. 1982;2(8299):646-9.

6. Loosen PT, Chambliss B, Ekhator N, Burns D, Geracioti TD, Orth DN. Thyroid and adrenal dysfunction in abstinent alcoholic men: locus of disturbance. Neuropsychopharmacology. 1993 Dec;9(4):255-66.

7. Jenkins RM. Alcohol-induced Cushingoid syndrome. Biomedicine. 1981;34(4):169-70.

8. Ahmed A, Saksena S, Sherlock M, Olliff SP, Elias E, Stewart PM. Induction of hepatic 11beta-hydroxysteroid dehydrogenase type 1 in patients with alcoholic liver disease. Clin Endocrinol (Oxf). 2008;68(6):898-903.

9. Cobb CF, Van Thiel DH, Gavaler JS, Lester R. Effects of ethanol and acetaldehyde on the rat adrenal. Metabolism. 1981;30(6):537-43.

10. Jeffcoate WJ, Silverstone JT, Edwards CR, Besser GM. Psychiatric manifestations of Cushing's syndrome: response to lowering of plasma cortisol. Q J Med. 1979;48(191):465-72.

11. Nava F, Premi S, Manzato E, Campagnola W, Lucchini A, Gessa GL. Gamma-hydroxybutyrate reduces both withdrawal syndrome and hypercortisolism in severe abstinent alcoholics: an open study vs. diazepam. Am J Drug Alcohol Abuse. 2007;33(3):379-92.

12. Rouach H, Ribiere C, Nordmann J, Nordmann R. Acute ethanol effects on rat liver tryptophan oxygenase and tyrosine aminotransferase. Pharmacol Biochem Behav. 1980;13(Suppl 1):139-43.

13. Zimmermann US, Buchmann A, Steffin B, Dieterle C, Uhr M. Alcohol administration acutely inhibits ghrelin secretion in an experiment involving psychosocial stress. Addict Biol. 2007;12(1):17-21.

14. Hu J, Xia Y, Wu Z, Liu L, Tang C. Fluoxetine might alleviate brain damage and hypercortisolemia related to chronic alcohol in rats. J Stud Alcohol Drugs. 2010;71(2):290-4.

15. Aron DC, Tyrrell JB, Fitzgerald PA, Findling JW, Forsham PH. Cushing's syndrome: problems in diagnosis. Medicine (Baltimore). 1981;60(1):25-35.

16. Endo Y, Chuhbachi A. Hyperlipemia in alcohol-induced pseudo-Cushing's syndrome. Jpn J Med. 1986;25(2):184-5.

17. Jordan RM, Jacobson JM, Young RL. Alcohol-induced Cushingoid syndrome. South Med J. 1979;72(10):1347-8.

18. Kapcala LP. Alcohol-induced pseudo-Cushing's syndrome mimicking Cushing's disease in a patient with an adrenal mass. Am J Med. 1987;82(4):849-56.

19. Lamberts SW, Klijn JG, de Jong FH, Birkenhager JC. Hormone secretion in alcohol-induced pseudo-Cushing's syndrome. Differential diagnosis with Cushing disease. JAMA. 1979;242(15):1640-3.

20. Proto G, Barberi M, Bertolissi F. Pseudo-Cushing's syndrome: an example of alcohol-induced central disorder in corticotropin-releasing factor-ACTH release? Drug Alcohol Depend. 1985;16(2):111-5.

21. Rees LH, Besser GM, Jeffcoate WJ, Goldie DJ, Marks V. Alcohol-induced pseudo-Cushing's syndrome. Lancet. 1977;1(8014):726-8.

22. Adinoff B, Martin PR, Bone GH, Eckardt MJ, Roehrich L, George DT, et al. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. Arch Gen Psychiatry. 1990;47(4):325-30.

23. del Arbol JL, Aguirre JC, Raya J, Rico J, Ruiz-Requena ME, Miranda MT. Plasma concentrations of beta-endorphin, adrenocorticotropic hormone, and cortisol in drinking and abstinent chronic alcoholics. Alcohol. 1995;12(6):525-9.

24. Eisenhofer G, Johnson RH, Lambie DG. Growth hormone, vasopressin, cortisol, and catecholamine responses to insulin hypoglycemia in alcoholics. Alcohol Clin Exp Res. 1984;8(1):33-6.

25. Inder WJ, Joyce PR, Ellis MJ, Evans MJ, Livesey JH, Donald RA. The effects of alcoholism on the hypothalamic-pituitary-adrenal axis: interaction with endogenous opioid peptides. Clin Endocrinol (Oxf). 1995;43(3):283-90.

26. Leggio L, Malandrino N, Ferrulli A, Cardone S, Miceli A, Gasbarrini G, et al. Is cortisol involved in the alcohol-related fat mass impairment? A longitudinal clinical study. Alcohol Alcohol. 2009;44(2):211-5.

27. Ozsoy S, Esel E. Hypothalamic-pituitary-adrenal axis activity, dehydroepiandrosterone sulphate and their relationships with aggression in early and late alcohol withdrawal. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(2):340-7.

28. Burra P, Franklyn JA, Ramsden DB, Elias E, Sheppard MC. Severity of alcoholic liver disease and markers of thyroid and steroid status. Postgrad Med J. 1992;68(804):804-10.

29. Elias AN, Meshkinpour H, Valenta LJ, Grossman MK. Pseudo-Cushing's syndrome: the role of alcohol. J Clin Gastroenterol. 1982 Apr;4(2):137-9.

30. Heuser I, von Bardeleben U, Boll E, Holsboer F. Response of ACTH and cortisol to human corticotropin-releasing hormone after short-term abstention from alcohol abuse. Biol Psychiatry 1988;24(3):316-21.

31. Kutscher S, Heise DJ, Banger M, Saller B, Michel MC, Gastpar M, et al. Concomitant endocrine and immune alterations during alcohol intoxication and acute withdrawal in alcohol-dependent subjects. Neuropsychobiology. 2002;45(3):144-9.

32. Stewart A, Johnston DG, Alberti KG, Nattrass M, Wright R. Hormone and metabolite profiles in alcoholic liver disease. Eur J Clin Invest. 1983;13(5):397-403.

33. Stewart PM, Burra P, Shackleton CH, Sheppard MC, Elias E. 11 beta-Hydroxysteroid dehydrogenase deficiency and glucocorticoid status in patients with alcoholic and non-alcoholic chronic liver disease. J Clin Endocrinol Metab. 1993;76(3):748-51.

34. Majumdar SK, Shaw GK, Bridges PK. Relationship between plasma adrenocorticotrophic hormone and cortisol concentrations in chronic alcoholic patients with depression. Drug Alcohol Depend. 1989;23(2):111-6.

35. Soardo G, Donnini D, Varutti R, Milocco C, Basan L, Esposito W, et al. Effects of alcohol withdrawal on blood pressure in hypertensive heavy drinkers. J Hypertens. 2006;24(8):1493-8.

36. Bertello P, Agrimonti F, Gurioli L, Frairia R, Fornaro D, Angeli A. Circadian patterns of plasma cortisol and testosterone in chronic male alcoholics. Alcohol Clin Exp Res. 1982;6(4):475-81.

37. Iranmanesh A, Veldhuis JD, Johnson ML, Lizarralde G. 24-hour pulsatile and circadian patterns of cortisol secretion in alcoholic men. J Androl. 1989;10(1):54-63.

38. Mukai M, Uchimura N, Hirano T, Ohshima H, Ohshima M, Nakamura J. Circadian rhythms of hormone concentrations in alcohol withdrawal. Psychiatry Clin Neurosci. 1998;52(2):238-40.

39. Coiro V, Volpi R, Galli P, Manfredi G, Magotti MG, Saccani-Jotti G, et al. Serum total prostate-specific antigen assay in women with Cushing's disease or alcohol-dependent pseudo-Cushing's State. Horm Res. 2004;61(3):148-52.

40. Frias J, Rodriguez R, Torres JM, Ruiz E, Ortega E. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adolescents of both sexes. Life Sci. 2000;67(9):1081-6.

41. Frias J, Torres JM, Miranda MT, Ruiz E, Ortega E. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adults of both sexes. Alcohol Alcohol. 2002 Mar;37(2):169-73.

42. Bannan LT, Potter JF, Beevers DG, Saunders JB, Walters JR, Ingram MC. Effect of alcohol withdrawal on blood pressure, plasma renin activity, aldosterone, cortisol and dopamine beta-hydroxylase. Clin Sci (Lond). 1984;66(6):659-63.

43. Stalder T, Kirschbaum C, Heinze K, Steudte S, Foley P, Tietze A, et al. Use of hair cortisol analysis to detect hypercortisolism during active drinking phases in alcohol-dependent individuals. Biol Psychol. 2010;85:357-60.

44. Adinoff B, Ruether K, Krebaum S, Iranmanesh A, Williams MJ. Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. Alcohol Clin Exp Res. 2003;27(9):1420-7.

45. Beresford TP, Arciniegas DB, Alfers J, Clapp L, Martin B, Beresford HF, et al. Hypercortisolism in alcohol dependence and its relation to hippocampal volume loss. J Stud Alcohol. 2006;67(6):861-7.

46. Rosman PM, Farag A, Benn R, Tito J, Mishik A, Wallace EZ. Modulation of pituitary-adrenocortical function: decreased secretory episodes and blunted circadian rhythmicity in patients with alcoholic liver disease. J Clin Endocrinol Metab. 1982;55(4):709-17.

47. Wand GS, Dobs AS. Alterations in the hypothalamic-pituitary-adrenal axis in actively drinking alcoholics. J Clin Endocrinol Metab. 1991;72(6):1290-5.

48. Willenbring ML, Morley JE, Niewoehner CB, Heilman RO, Carlson CH, Shafer RB. Adrenocortical hyperactivity in newly admitted alcoholics: prevalence, course and associated variables. Psychoneuroendocrinology. 1984;9(4):415-22.

49. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(5):1526-40.

50. Bailly D, Dewailly D, Beuscart R, Couplet G, Dumont P, Racadot A, et al. Adrenocorticotropin and cortisol responses to ovine corticotropin-releasing factor in alcohol dependence disorder. Preliminary report. Horm Res. 1989;31(1-2):72-5.

51. Coiro V, Volpi R, Capretti L, Caffarri G, Chiodera P. Desmopressin and hexarelin tests in alcohol-induced pseudo-Cushing's syndrome. J Intern Med. 2000;247(6):667-73.

52. Emsley RA, Roberts MC, Aalbers C, Taljaard FJ, Kotze TJ. Endocrine function in alcoholic Korsakoff's syndrome. Alcohol Alcohol. 1994;29(2):187-91.

53. Ravi SD, Dorus W, Park YN, Collins MC, Reid RW, Borge GF. The dexamethasone suppression test and depressive symptoms in early and late withdrawal from alcohol. Am J Psychiatry. 1984;141(11):1445-8.

54. Swartz CM, Dunner FJ. Dexamethasone suppression testing of alcoholics. Arch Gen Psychiatry. 1982;39(11):1309-12.

55. Szucs N, Varga I, Patocs A, Toth M, Jakab C, Glaz E, et al. Plasma 6beta-hydroxycortisol measurements for assessing altered hepatic drug metabolizing enzyme activity. Acta Physiol Hung. 2003;90(3):217-23.

56. Balldin J, Berggren U, Bokstrom K, Lindstedt G, Sjoberg J, Wendestam C. Dexamethasone suppression test in alcohol withdrawal: relationship to depression and liver function. Drug Alcohol Depend. 1992;30(2):175-9.

57. Carroll BJ. Dexamethasone suppression test for depression. Adv Biochem Psychopharmacol. 1984;39:179-88.

58. Abou-Saleh MT, Merry J, Coppen A. Dexamethasone suppression test in alcoholism. Acta Psychiatr Scand. 1984;69(2):112-6.

59. Carson SW, Halbreich U, Yeh CM, Galanter M. Liver function, plasma dexamethasone, and DST results in detoxified alcoholics. Psychiatry Res. 1989;30(2):217-21.

60. Del Porto JA, Monteiro MG, Laranjeira RR, Jorge MR, Masur J. Reversal of abnormal dexamethasone suppression test in alcoholics abstinent for four weeks. Biol Psychiatry. 1985;20(11):1156-60.

61. Khan A, Ciraulo DA, Nelson WH, Becker JT, Nies A, Jaffe JH. Dexamethasone suppression test in recently detoxified alcoholics: clinical implications. J Clin Psychopharmacol. 1984;4(2):94-7.

62. Muller N, Hoehe M, Klein HE, Nieberle G, Kapfhammer HP, May F, et al. Endocrinological studies in alcoholics during withdrawal and after abstinence. Psychoneuroendocrinology. 1989;14(1-2):113-23.

63. Majumdar SK, Shaw GK, Bridges PK. The dexamethasone suppression test in chronic alcoholics with and without depression and its relationship to their hepatic status. Drug Alcohol Depend. 1988;21(3):231-5.

64. Hundt W, Zimmermann U, Pottig M, Spring K, Holsboer F. The combined dexamethasone-suppression/CRH-stimulation test in alcoholics during and after acute withdrawal. Alcohol Clin Exp Res. 2001;25(5):687-91.

65. Fink RS, Short F, Marjot DH, James VH. Abnormal suppression of plasma cortisol during the intravenous infusion of dexamethasone to alcoholic patients. Clin Endocrinol (Oxf). 1981;15(1):97-102.

66. Fonzi S, Solinas GP, Costelli P, Parodi C, Murialdo G, Bo P, et al. Melatonin and cortisol circadian secretion during ethanol withdrawal in chronic alcoholics. Chronobiologia. 1994;21(1-2):109-12.

67. Berman JD, Cook DM, Buchman M, Keith LD. Diminished adrenocorticotropin response to insulin-induced hypoglycemia in nondepressed, actively drinking male alcoholics. J Clin Endocrinol Metab. 1990;71(3):712-7.

68. Danel T, Vantyghem MC, Touitou Y. Responses of the steroid circadian system to alcohol in humans: Importance of the time and duration of intake. Chronobiol Int. 2006;23(5):1025-34.

69. Ida Y, Tsujimaru S, Nakamaura K, Shirao I, Mukasa H, Egami H, et al. Effects of acute and repeated alcohol ingestion on hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal functioning in normal males. Drug Alcohol Depend. 1992;31(1):57-64.

70. Dai X, Thavundayil J, Santella S, Gianoulakis C. Response of the HPA-axis to alcohol and stress as a function of alcohol dependence and family history of alcoholism. Psychoneuroendocrinology. 2007;32(3):293-305.

71. Linkola J, Fyhrquist F, Ylikahri R. Renin, aldosterone and cortisol during ethanol intoxication and hangover. Acta Physiol Scand. 1979;106(1):75-82.

72. Valimaki MJ, Harkonen M, Eriksson CJ, Ylikahri RH. Sex hormones and adrenocortical steroids in men acutely intoxicated with ethanol. Alcohol. 1984;1(1):89-93.

73. Ireland MA, Vandongen R, Davidson L, Beilin LJ, Rouse IL. Acute effects of moderate alcohol consumption on blood pressure and plasma catecholamines. Clin Sci (Lond). 1984;66(6):643-8.

74. Waltman C, Blevins LS, Jr., Boyd G, Wand GS. The effects of mild ethanol intoxication on the hypothalamic-pituitary-adrenal axis in nonalcoholic men. J Clin Endocrinol Metab. 1993;77(2):518-22.

75. Inder WJ, Joyce PR, Wells JE, Evans MJ, Ellis MJ, Mattioli L, et al. The acute effects of oral ethanol on the hypothalamic-pituitary-adrenal axis in normal human subjects. Clin Endocrinol (Oxf). 1995;42(1):65-71.

76. Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol Clin Exp Res. 2000;24(5):651-8.

77. Coiro V, Casti A, Jotti GS, Rubino P, Manfredi G, Maffei ML, et al. Adrenocorticotropic hormone/cortisol response to physical exercise in abstinent alcoholic patients. Alcohol Clin Exp Res. 2007;31(5):901-6.