Inpatient alcohol detoxification and plasma calcitonin (with original findings)

To the Editor: Calcitonin is secreted mainly by the parafollicular cells of the thyroid; the assay of calcitonin is used in the management of thyroid nodules [1, 2] and for the diagnosis of medullary thyroid cancer [2, 3]. It has been reported that acute alcohol ingestion leads to increase in plasma calcitonin [4], whereas the study of the effect of chronic alcohol ingestion on calcitonin has led to controversial results [5]. More in detail, in the above mentioned paper mostly normal blood levels of calcitonin were found in alcohol-dependent subjects and no changes in its levels were noted after weaning from alcohol. The caveat is that few subjects were studied (n=20), that the inclusion criteria were not standardized and that the alcohol detoxification program was not detailed. Thus, we aimed to study the relationship between calcitonin levels and alcohol consumption in a substantial number of alcohol-dependent subjects admitted to a rigorous alcohol detoxification program. On these points we consider the present paper as original.

We assessed changes of plasma calcitonin, in chronic alcohol-dependent subjects (all patients fulfilled the DSM-IV diagnostic criteria for alcohol abuse/dependence) [6] upon admission and after 4-5 weeks of strictly inpatient detoxification. The assay used was the IRMA-hCT assay (CIS bio international, Gif-sur-Yvette, France; inter assay CV: 6.7%, intra assay CV: 5.2%). Gender, age, body mass index (BMI), smoking, elevated liver enzymes (AST > 35IU/L and/or ALT > 35IU/L and/or γGT > 50IU/L) and timing of alcohol use before admission, within 6h or more than 6h were noted. The subjects were given a regular hospital diet of about 1800-1900 kcal/day with 2 servings of vegetables and 3 servings of fruit per day. The protocol included vitamin replacement (vitamins C, E and B complex) and oral diazepam (30-60mg in divided doses), with gradual taper-off over a week. Statistical analyses were done with Fisher's exact test, McNemar's test and the Kruskall Wallis test. We considered calcitonin levels<12pg/mL for men and <7pg/mL for women, to be normal [7, 8].

Sixty-four men and 29 women (mean age±SD: 46±11 years, mean BMI±SD: 24.0±3.3kg/m^2) were included in the study. Most were smokers of at least 10 cigarettes per day (n=89), with no change in their smoking habits during inpatient detoxification. Two thirds of the subjects had no alcoholic drink for at least six hours before admission (62%), the remaining had ingested alcohol closer to admission. The six-hour limit was chosen taking into account the half life of ethanol-approximately 3 to 6h [9]. Slight elevations in at least one hepatic enzyme were noted in 74% of subjects upon admission but persisted in 48% of subjects after 4-5 weeks of alcohol detoxification. Overall calcitonin was within normal limits upon admission (Q1/median/Q3: 1.9/2.7/6.0pg/mL) and remained so after 4-5 weeks of abstinence (Q1/median/Q3: 2.5/3.1/5.9pg/mL) for most subjects (P=0.37, Kruskal-Wallis) (Fig. 1). Three and 5 subjects had higher than normal calcitonin upon admission and after 4-5 weeks of detoxification, respectively (P<0.001, McNemar). More in detail, 3 men had higher than normal calcitonin upon admission (at 12.4, 21.8 and 21.8pg/mL). The "albeit moderate" increase in calcitonin persisted only in one man after inpatient alcohol detoxification (at 21.8pg/mL), whereas it showed an increase from a previously normal value in another man (at 17.7pg/mL); the remaining 3 higher than normal values were *de novo* findings in women (at 30.8, 7.6 and 7.1pg/mL). Overall, this slight increase in the total number of subjects with higher than normal calcitonin after detoxification remained significant irrespective of gender, BMI, hepatic enzymes' elevation or timing of last drink (Fisher's exact test and McNemar's test).

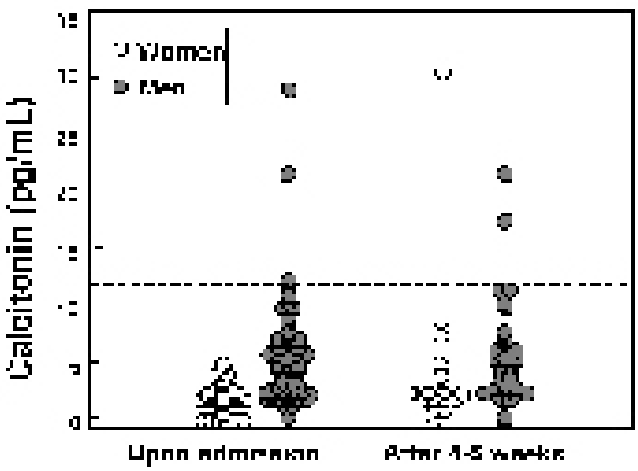

Figure 1. Calcitonin levels upon admission and after alcohol detoxification. Dashed lines denote upper normal levels (*<12pg/mL for men and <7pg/mL for women*)

We do not have a concrete explanation for the increase in number of subjects with higher than normal calcitonin levels after detoxification from alcohol since subsequent evaluation for thyroid-parafollicular cell pathology was negative (nevertheless the values with one exception were not exceedingly high). Smoking is known to affect calcitonin levels [8], but most subjects were smokers and their smoking habits did not change during the hospital stay. Maybe acute alcohol ingestion leads to higher calcitonin levels whereas chronic alcohol consumption lowers calcitonin; alcohol withdrawal thus leads to rebound elevation in calcitonin's levels in some subjects. Interestingly, a potential protective role of alcohol consumption on differentiated thyroid cancer risk has been suggested by various epidemiological studies via unknown mechanisms. No studies have focused however on calcitonin-secreting medullary thyroid cancer, which is often hereditary and of vastly different origin and pathologic characteristics compared to differentiated thyroid cancer [10].

Overall it seems that there are slight effects of alcohol abuse on calcitonin's levels per se and alcohol ingestion should not obscure the diagnostic evaluation of thyroid nodular disease [11], as it has been tentatively suggested in the past. Our findings, on a substantial and statistically sound number of subjects fulfilling DSM-IV criteria for alcoholism, agree with and complement the results of the latter research work with the added originality of having subjected submitted the study subjects to a rigorous and time-proven alcohol-weaning protocol [12, 13]. Additionally the timing of last drink before alcohol weaning was taken into consideration.

In conclusion, the effect of alcohol abuse on calcitonin is slight and alcohol ingestion should not obscure the diagnostic evaluation of thyroid nodular disease.

Acknowledgement
This work was conceived in part by the late Dr Panagiotis Kontoleon and is dedicated to him.

The authors declare that they have no conflicts of interest

Bibliography

1. Costante G, Durante C, Francis Z et al. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. *Nat Clin Pract Endocrinol Metab* 2009; 5: 35-44.
2. Elisei R. Routine serum calcitonin measurement in the evaluation of thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 2008; 22: 941-53.
3. Bertagna F,Giubbini R,Savelli G et al. A patient with medullary thyroid carcinoma and right ventricular cardiac metastasis treated by ^{90}Y-Dotatoc. *Hell J Nucl Med* 2009; 12: 161-4.
4. Rico H. Alcohol and bone disease. *Alcohol Alcohol* 1990; 25: 345-52.
5. Vantyghem MC, Danel T, Marcelli-Tourvieille S et al. Calcitonin levels do not decrease with weaning in chronic alcoholism. *Thyroid* 2007; 17: 213-7.
6. Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV). 1994 Washington, D.C.: American Psychiatric Association.
7. Basuyau JP, Mallet E, Leroy M, Brunelle P. Reference Intervals for Serum Calcitonin in Men, Women, and Children. *Clin Chem* 2004; 50: 1828-30.
8. d'Herbomez M, Caron P, Bauters C et al. Reference range of serum calcitonin levels in humans: influence of calcitonin assays, sex, age, and cigarette smoking. *Eur J Endocrinol* 2007; 157: 749-55.
9. Hoiseth G, Morini L, Polettini A et al. Blood kinetics of ethyl glucuronide and ethyl sulphate in heavy drinkers during alcohol detoxification. *Forensic Sci Int* 2009; 188: 52-6.
10. Meinhold CL, Park Y, Stolzenberg-Solomon RZ et al. Alcohol intake and risk of thyroid cancer in the NIH-AARP Diet and Health Study. *Br J Cancer* 2009; 101: 1630-4.
11. Herrmann BL, Schmid KW, Goerges R et al. Calcitonin screening and pentagastrin testing: predictive value for the diagnosis of medullary carcinoma in nodular thyroid disease. *Eur J Endocrinol* 2010; 162: 1141-5.
12. Liappas J, Paparrigopoulos T, Tzavellas E, Christodoulou G. Impact of alcohol detoxification on anxiety and depressive symptoms. *Drug Alcohol Depend* 2002; 68: 215-20.
13. Chatzipanagiotou S, Kalykaki M, Tzavellas E et al Alteration of biological markers in alcohol-dependent individuals without liver disease during the detoxification therapy. *In Vivo* 2010; 24: 325-8.

Ioannis Ilias[1] MD, PhD, Thomas Paparrigopoulos[2] MD, PhD, Elias Tzavellas[2] MD,PhD, Dimitris Karaiskos[2] MD, Georgios Meristoudis[3] MD, Alexandros Liappas[4] MSc, Ioannis Liappas[2] MD, PhD

1. Department of Endocrinology, Diabetes and Metabolism, Elena Venizelou Hospital, 2, Elena Venizelou Square, GR-11521, Athens, Greece
2. First Department of Psychiatry, Athens University Medical School, Eginition Hospital, 74, Vassilisis Sofias Avenue, GR-11528, Athens, Greece
3. Department of Nuclear Medicine, Henri Dunant Hospital, Athens GR-11526, Greece
4. School of Pharmacy and Biological Sciences, University of Central Lancashire, PR1 2HE, Preston, UK

Ioannis Ilias MD, PhD
Department of Endocrinology, Diabetes and Metabolism, Elena Venizelou Hospital, 2, Elena Venizelou Square, GR-11521, Athens, Greece, E-mail: iiliasmd@yahoo.com, Fax: +30 210 6411156

Hell J Nucl Med 2011:14(2): *Published on line: 16 June 2011*