Impaired renal tubular function in chronic alcoholics

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Summary

Despite the well known effects of chronic alcohol abuse on the gastrointestinal, cardiovascular, nervous and endocrine systems, little information is available on its effect on renal function. To assess renal function we measured urinary excretion of albumin, α_1 microglobulin and retinol binding protein in 30 chronic alcoholic patients. Our data shows that 40% of chronic alcoholic patients have impaired renal tubular function.

Introduction

Alcohol abuse may produce pathological changes in almost every organ of the body[1]. The effects of chronic alcohol abuse on the gastrointestinal, cardiovascular, nervous and endocrine systems are all well recognized. Little information is, however, available on its effect on renal function. Recent evidence suggests that chronic alcohol abuse can cause tubular damage: it has been reported, for example, that 54% of alcoholic patients with liver cirrhosis[2], and 22% of those without cirrhosis[3] have impaired renal tubular phosphate reabsorption. Fractional urinary excretion of β_2 microglobulin, sodium, potassium, calcium and phosphorus has also been shown to be significantly increased in one-third of chronic alcoholics indicating a complex tubular dysfunction[4]. We have recently reported severe hypophosphataemic osteomalacia in a chronic alcoholic patient with impaired renal tubular phosphate reabsorption and increased α_1 microglobulin excretion suggesting the presence of renal tubular damage[5].

Analysis of the individual proteins in the urine provides a sensitive and specific index of renal damage: albumin has been established as a sensitive indicator of renal glomerular damage[6] whereas increases in smaller molecular weight proteins, such as retinol binding protein, β_2 microglobulin and α_1 microglobulin, indicate tubular damage[6,7]. Recently, however, β_2 microglobulin (molecular weight 11 800) has been shown to be unstable in acid urine[8] and its measurement has been superseded as a test of renal tubular integrity by the measurement of α_1 microglobulin (molecular weight 27 000) and retinol binding protein (molecular weight 21 000)[9]. We have measured urinary excretion of albumin, α_1 microglobulin and retinol binding protein in a group of chronic alcoholic patients in order to assess the effects of chronic alcohol abuse on glomerular and tubular functions.

Patients and methods

Patients

Thirty patients (24 men and 6 women) aged 20-65 years (mean 43.9±10.5) who were enrolled in a psychiatric rehabilitation programme for chronic alcoholism at the Regional Drug and Addiction Unit at Birmingham, UK were investigated. They had been abstinent from alcohol for between 1 and 60 days. All had previously consumed alcohol at a rate of 700-4000 g per week (mean 2160±1030 g per week) for a period ranging from 1½ to 30 years (15.8±9.9 years). No patient had clinical evidence of liver or renal dysfunction.

Controls

Thirty subjects matched for age and sex were studied. None admitted to alcohol consumption of more than 200 g per week.

Methods

Venous blood was collected after an overnight fast for measurement of plasma creatinine, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and albumin. A urine sample was also collected for the measurement of creatinine, albumin, α_1 microglobulin and retinol binding protein. Creatinine, GGT and AST were measured using standard laboratory techniques. Urinary albumin and α_1 microglobulin were measured by electroimmunoassay and retinol binding protein by ELISA. The inter-assay and intra-assay coefficients of variation for the urinary assays were as follows: albumin (ALB) 4% and 2%, α_1 microglobulin (α_1M) 6% and 2%, and retinol binding protein (RBP) 10% and 6% respectively.

Normality test and statistical analysis of the results using linear regression and Student's *t*-test were performed on an Apple Macintosh microcomputer.

Results

Mean urinary albumin (ALB/Cr), α_1 microglobulin (α_1M/Cr) and retinol binding protein (RBP/Cr) excretion rates were all significantly higher in the alcoholic patients than in the control subjects (Table 1).

Table 1. Urinary excretions of albumin (ALB), α_1 microglobulin (α_1M) and retinol binding protein (RPB) in patients and controls (mean±SD)

Analyte	*Alcoholics*	*Controls*	*Significance*
ALB/creatinine (mg/mmol)	1.70± 2.3	0.83±0.43	$P<0.05$
α_1 M/creatinine (mg/mmol)	0.80± 0.7	0.41±0.2	$P<0.005$
RBP/creatinine (μg/mmol)	13.70±10.2	9.50±4.8	$P<0.05$

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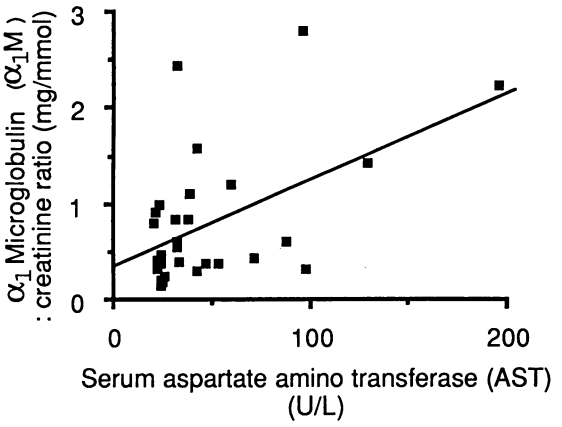

Figure 1. Relationship of urinary α_1M excretion and serum AST in alcoholic patients

The upper limits of normal, defined as the mean+2SD of the urinary concentrations observed in the control group were 1.7 mg albumin per mmol creatinine; 0.79 mg α_1M/mmol creatinine and 19 μg RBP/mmol creatinine.

Fifteen patients (50%) showed one or more abnormal results: 12 patients (40%) had increased α_1M excretion rate, 6 patients (20%) had an increased albumin excretion rate and 4 patients (13%) an increased RBP excretion rate.

Urinary α_1M and RBP concentrations were well correlated ($r=0.65$, $P<0.001$), as were the α_1M and albumin concentrations ($r=0.5$, $P<0.005$) and the RBP and albumin concentrations ($r=0.48$, $P<0.01$).

There was a negative trend between urinary albumin, α_1M and RBP concentrations and time lapsed since stopping drinking which was, however, not statistically significant.

Similarly, no correlation could be discerned between urinary albumin, α_1M or RBP concentrations and the length of drinking history or the average daily amount of alcohol consumed. There was, however, a significant positive correlation between urinary albumin excretion and serum GGT, AST and ALP concentrations ($P<0.05$, $P<0.001$ and $P<0.01$ respectively). Urinary α_1M (Figure 1) correlated positively with serum AST ($r=0.51$, $P<0.005$), but not with GGT or ALP and there was no correlation between urinary RBP and any of the liver enzymes.

Mean serum albumin concentration (36.7±5.1 g/l) was significantly lower in the 12 patients with increased urinary α_1M excretion than in the 18 patients in whom it was normal (40.9±4.2 g/l, $P<0.02$).

Discussion

Ethanol is inherently toxic to biological tissue and virtually every cell in the body is liable to damage when repeatedly subjected to it. Acetaldehyde, its main intermediate metabolite, is even more toxic on a molar basis than the parent compound. It is therefore surprising that the damaging effects of chronic ethanol abuse on the kidneys and on kidney function have until recently largely gone unrecognized.

The present study shows that some 40% of chronic alcoholic patients admitted to an alcohol rehabilitation centre exhibited tubular proteinuria. Urinary α_1M seemed to be the more sensitive of the two markers of tubular damage employed. Each of the 4 patients who excreted increased amounts of RBP also had increased urinary α_1M. Renal tubular dysfunction would not therefore have been missed if α_1M alone had been used as a test of renal functional integrity in these patients. The difference in sensitivity between these two proteins can partly be explained by difference in their sizes, molecular weights and normal urinary excretion rates. α_1M has a slightly higher molecular weight than RBP (27 000 vs 21 000) and its urinary concentration is normally some 100-150 times that of RBP. Recent evidence suggests that tubular uptake of low molecular weight proteins is a selective process[10], determined by their physicochemical properties such as net electrical charge, type of positively charged groups and the size of the proteins themselves.

The increase in albumin excretion shown by 6 of the patients (20%) was mild and not necessarily indicative of glomerular damage since tubular damage can impair the tubular reabsorption of albumin sufficiently to permit its appearance in the urine in greater than normal amounts.

The positive correlation between the urinary excretion of proteins (albumin and α_1M) and the concentration of certain plasma enzymes (GGT, AST and ALP) in the alcoholic patients, coupled with the finding that patients with abnormal α_1M levels had lower than normal serum albumin concentrations suggests that liver damage may contribute to or even cause renal impairment. It is well recognized that renal tubular damage can occur in patients with liver cirrhosis[2,11], although it does not appear to be related to its severity[11,12].

Rhabdomyolysis is a recognized complication of alcohol abuse[13,14] and the resultant myoglobinuria may cause tubular damage[13]. Urine testing in our patients for 'haemoglobin' by Ames Multistix - which are equally sensitive to myoglobulin - was uniformly negative. Serum creatine kinase activity, which was measured in 24 of the 30 patients (results not shown), was also normal. The tubular damage in our patients cannot, therefore, have been caused by rhabdomyolysis.

Vitamin D deficiency with secondary hyperparathyroidism may occur in chronic alcoholics[15] and parathyroid hormone can influence the renal tubular handling of a number of ions[16,17]. Our patients, however, had normal plasma calcium and parathyroid hormone levels (results not shown) and hence their tubular dysfunction cannot be due to this cause.

De Marchi *et al.*[4] found that the increase in fractional urinary β_2 microglobulin excretion in his alcoholic patients was reversed by abstinence for about 30 days. In the present study there was a nonsignificant negative trend between α_1M excretion and the number of days of abstinence from alcohol. Eleven of the 12 patients with increased α_1M had only stopped drinking alcohol for a period between 1 and 10 days. The increase in urinary α_1M may therefore have been due to impaired renal tubular function rather than to tubular injury.

If, however, the proximal renal tubules are repeatedly or chronically subjected to injury, there might be a progressive loss of tubules which, because of the large reserve capacity of the kidney, remains clinically silent until late in the course of the patients illness. Our data suggest that, in addition to the well-known effects of chronic alcohol abuse on the nervous, gastrointestinal and cardiovascular systems, it may also cause renal dysfunction either directly or indirectly through liver damage.

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References

1 West L, Maxwell D, Noble E, Soloman D. Alcoholism. *Ann Intern Med* 1984;**100**:405-16
2 Adler A, Gudis, Berbyne G. Reduced renal phosphate threshold concentration in alcoholic cirrhosis. *Miner Electrolyte Metab* 1984;**10**:63-6
3 De Marchi S, Cecchin E, Grimaldi F. Reduced renal phosphate threshold concentration in chronic alcoholics: one component of a more complex tubule dysfunction? *Miner Electrolyte Metab* 1986;**12**:147-8
4 De Marchi S, Cecchin E, Grimaldi F, Basile A, Dell'Anna L, Tesio F. Reversible tubular dysfunction in alcohol abuse. *Proc EDTA-ERA* 1984;**21**:866-74
5 Labib M, Marks V. Hypophosphataemic osteomalacia and alcoholism: a possible link. *Alcohol Alcohol* 1988;**23**:111-4
6 Peterson PA, Evrin PE, Berggaard I. Differentiation of glomerular, tubular, and normal proteinuria: Determinations of urinary excretion of B_2-microglobulin, albumin and total protein. *J Clin Invest* 1969;**48**:1189-98
7 Yu H, Yanagisawa Y, Forbes M, Cooper E, Crockson R, MacLennan I. Alpha-1-microglobulin: an indicator protein for renal tubular function. *J Clin Pathol* 1983;**36**:253-9
8 Davey P, Gosling P. B_2 microglobulin instability in pathological urine. *Clin Chem* 1982;**28**:1330-33
9 Bernard A, Vyskocil A, Mahieu P, Laurerys R. Assessment of urinary retinol-binding protein as an index of proximal tubular injury. *Clin Chem* 1987; **36**:775-9
10 Sumpis B, Maack T. Kinetics, competition and selectivity of tubular asborption of proteins. *Am J Physiol* 1982;**243**:379-92
11 Wilkinson SP, Porman B, Hurst D, Williams R. Pathogenesis of renal failure in cirrhosis and fulminant hepatic failure. *Postgrad Med J* 1975;**51**:303-5
12 Amodio A, Merkel F, Zuin M, Ruol A. Evaluation of renal tubular damage in liver cirrhosis by urinary enzymes and beta-2-microglobulin excretions. *Eur J Clin Invest* 1981;**11**:293-43
13 Hed R, Lundmark C, Fahlgren H, *et al.* Acute muscular syndrome in chronic alcoholism. *Acta Med Scand* 1962;**171**:585-99
14 Perkoff G, Hardy P, Velez-Garcia E. Reversible acute muscular syndrome in chronic alcoholism. *N Engl J Med* 1966;**274**:1277-85
15 Lalor B, France M, Powell D, *et al.* Bone and mineral metabolism and chronic alcoholic abuse. *Q J Med* 1986;**229**:497-511
16 Barzel U. Parathyroid hormone, blood phosphorus, and acid-base metabolism. *Lancet* 1971;i:1329-31
17 Agus Z, Gardner L, Beck L, Goldman M. Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium and phosphate. *Am J Physiol* 1973; **224**:1143-8

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