

Serum Oxalic Acid in Uremia: Effect of a Low-Protein Diet Supplemented with Essential Amino Acids and Ketoanalogues

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Abstract. Serum oxalic acid (sOx) was determined with a new, specific enzymatic method in 73 uremic patients and the values were plotted against serum creatinine. 41 patients received a free mixed diet, and 32 similar patients were given a low-nitrogen diet supplemented with essential amino acids, ketoanalogues, and calcium carbonate (AD). A significant correlation was found between serum creatinine and sOx levels in patients following a free mixed diet, while no correlation appeared in patients on AD: The sOx concentrations were significantly lower and even normal in this group, and a significant reduction of sOx occurred in 10 patients with chronic renal failure, who changed from a free mixed diet to the AD. The lowering of sOx concentration in patients following AD is attributed both to low intake of its metabolic precursors and to the oral calcium carbonate supplementation.

Introduction

The oxalate that is absorbed by the bowel and that which is metabolically produced is almost entirely excreted as an end product by the kidney and, when renal function is impaired, oxalate is retained in body fluids and secondary oxalosis results [Williams, 1978; Zarembsky et al., 1966; Salyer and Keren, 1973]. Calcium oxalate crystals have been found in many tissues of patients who have died from uremia: myocardium [Bennett and Rosenblum, 1961; Salyer and Keren, 1973], kidney interstitium [Salyer and Keren, 1973], bone [Milgram and Salyer, 1974], synovia [Hoffman et al., 1982], metastatic calcification [Hoffman et al., 1982], arterial and arteriolar media [Op De Hoek et al., 1980].

Since the methods used up to now for the determination of serum oxalate (sOx) were not accurate, the sOx levels in patients with chronic renal failure have not yet been well established. In the present study, a new, highly specific, enzymatic-colorimetric method has been employed for sOx determination [Kohlbecker and Butz, 1981]. In patients with chronic renal failure on free mixed diet we investigated if a correlation exists between sOx and the degree of impairment of renal function as indicated by serum creatinine (sCr) levels. We also investigat-

ed if a very low-protein diet supplemented with essential amino acids and ketoanalogues, and with calcium carbonate (AD) that is poor in oxalate precursors (i.e. serine, glycine and hydroxyproline) [Williams, 1978; Ribaya and Gushoff, 1982], would induce lower sOx levels in patients with steady-state chronic renal failure.

Patients and Methods

In 20 normal volunteers (10 males and 10 females) four fasting blood samples were withdrawn on different days for the measurement of sOx.

Fasting blood samples for sOx were also obtained from 73 patients with chronic renal failure due to various renal diseases (50 CGN, 20 CPN, 3 PKD). Patients with primary oxalosis were excluded. 41 patients (29 males and 12 females), with sCr ranging between 1.9 and 25 mg/dl (mean = 8.7 mg/dl), were following a free mixed diet; 32 patients (15 males and 17 females), with sCr ranging from 5.9 to 13.1 mg/dl (mean = 8.1 mg/dl), were following the AD for 6-36 months (mean = 12 months). The effect of a 6-month AD on sOx levels was also evaluated in 10 patients who had previously followed a free mixed diet.

The AD, previously described [Barsotti et al., 1981], is a vegetarian diet supplying daily per kilogram body weight approximately 0.2 g of unselected protein and 35 kcal furnished mostly by starch and fat (60 and 30%, approximately). A daily supplementation of

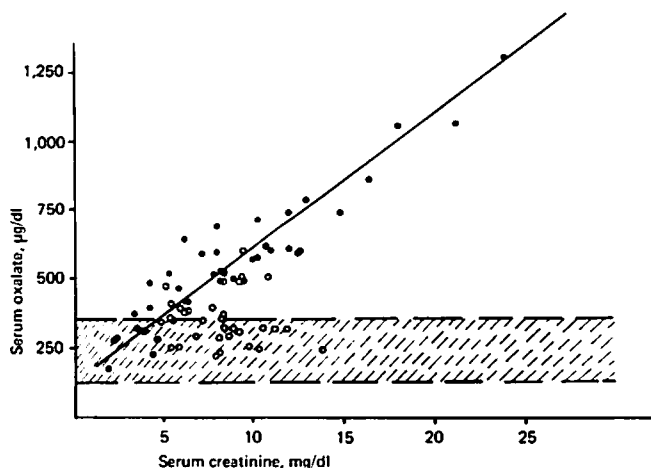


Fig. 1. Relationship between sOx and sCr in patients with chronic renal failure on a free mixed diet (●) or the AD (○). Patients on free mixed diet: $n = 41$, $r = 0.9396$, $p < 0.001$; patients on AD: $n = 32$, $r = -0.0546$, p NS.

tablets of essential amino acids, ketoanalogues and of calcium carbonate (1.5–3.0 g) is given. The hydroxyproline, glycine and serine supply is extremely low.

The enzymatic-spectrophotometric method employed in the present study is highly accurate for levels exceeding $20 \mu\text{g/dl}$ (with a recovery in serum of $99 \pm 4\%$) and highly reproducible (coefficient of variation = 3.1%) [Kohlbecker and Butz, 1981]. The sCr levels were measured with a Beckman Autoanalyzer. The statistical analysis was made with the Student's t test for paired and unpaired data. The linear regression coefficient was calculated with a desk minicomputer (Texas Instrument TI 59C).

Results

Normal volunteers had mean sOx levels of $220.3 \pm 59.3 \mu\text{g/dl}$, which is not significantly different from the values reported by Kohlbecker and Butz [1981]. In the uremic patients following a free mixed diet, sOx was $547.4 \pm 231.14 \mu\text{g/dl}$, and in patients following the AD for a mean of 12 months sOx was $349.03 \pm 94.7 \mu\text{g/dl}$ ($p < 0.001$).

A highly significant correlation ($p < 0.001$) between sCr and sOx levels was found in the uremic patients on free mixed diet (fig. 1). In the uremics on AD no relationship was found between these two parameters, and for comparable values of sCr the sOx levels were significantly lower than those of the patients on free mixed diet (fig. 1). In the 20 subjects on AD (64.4%) normal sOx levels were found, in spite of the renal failure, after 6–36 months of this regimen (fig. 1).

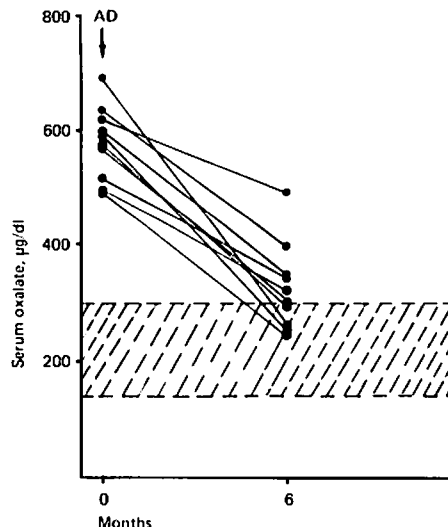


Fig. 2. The changes in sOx concentration that occurred in 10 patients with chronic renal failure 6 months after they had changed from a free mixed diet to the AD.

A decrease in sOx levels (from 576.8 ± 64.1 to $323.4 \pm 77.3 \mu\text{g/dl}$; $p < 0.001$) occurred in 10 uremics, 6 months after they had changed from a free mixed diet to the AD. 5 (50%) out of these patients achieved normal levels of sOx (fig. 2). During the study period renal function did not change significantly (sCr decreased from $9.1 \pm 1.7 \text{ mg/dl}$ at the beginning to $8.1 \pm 2.2 \text{ mg/dl}$ at the end; $p = \text{NS}$).

Discussion

These results show that sOx levels in patients with chronic renal failure receiving a free mixed diet are directly proportional to the severity of the renal failure as indicated by the sCr levels. This relationship is not present in the patients following the AD, who have lower and even normal levels of sOx in spite of renal failure. The lowering effect of AD on the sOx levels in uremics is confirmed by the decrease observed in 10 patients who followed this diet for 6 months.

The AD supplies very low amounts of the metabolic precursors of oxalate (hydroxyproline, glycine and serine), and, moreover, the intestinal absorption of oxalate contained in food is inhibited by the calcium carbonate supplementation. It is known, indeed, that intestinal absorption of oxalate is inversely related to the calcium content of diet [Bataille et al., 1983]. These two factors – low intake of metabolic precursors and low intestinal

absorption – clearly account for the low sOx levels in patients treated with AD.

In our previous work [Barsotti et al., 1981] we have shown that AD slows the rate of decline of renal function in chronic renal failure patients, but the mechanism(s) of this protective effect is not yet well understood. It is known that oxalic acid forms insoluble calcium salts at the pH values of body fluids [Williams, 1978]. It is therefore reasonable to argue that the elevated sOx levels promote the formation of calcium oxalate crystals and their precipitation in tissues. The reduction of plasma oxalate levels obtained with the AD (even to normal values) may prevent the deposition of calcium oxalate in tissues, including kidney. This might be one of the factors that slow the progressive deterioration of the residual renal function in chronic uremics on AD. A similar protective effect (prevention of calcium phosphate precipitation in kidneys) was postulated to explain the protection of renal function exerted by a low-phosphorus diet in rats with experimental renal failure [Ibels et al., 1978; Karlinsky et al., 1980].

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