

Correction by Dietary Therapy of the Endocrinological Abnormalities of Chronic Renal Failure: Possible Effects on Protein Metabolism

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In chronic renal failure (CRF), protein malnutrition, due to an increase of protein catabolic rate [1], is a common finding, having a multifactorial cause. Secondary hyperparathyroidism (HPTH) [2, 3], hypogonadism with elevated circulating estradiol (E_2) in the males [4, 5], low T_3 in the presence of high reverse T_3 (rT_3) levels [6] are also common findings.

Previous experience with CRF patients showed that a low-protein, low-phosphorus, supplemented diet (SD) can correct HPTH [7], male hypogonadism [8] and improve metabolic derangements involving carbohydrate [9], lipid [10] and, overall, protein turnover [1].

In this investigation we evaluated the E_2 changes in male uremics and re-examined the endocrine abnormalities previously studied and the effects of dietary therapy on all of them.

Material and Methods

A group of 13 male CRF patients (18-41 years) was studied. Underlying diseases were chronic glomerulonephritis (7 cases) and interstitial nephropathy (6 cases). The mean value of creatinine clearance (Cl_{cr}) in the pretreatment stage was 13.4 ± 2 ml/min. During a first period of 15 days these patients followed a conventional low nitrogen diet

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(CLND) (0.6 g/kg/day protein), and then changed to the SD. The SD supplies daily 0.3 g/kg/day of proteins of vegetable origin and is supplemented with a mixture of amino acids and ketoanalogues as previously described [1]. Calcium carbonate (2–4 g/day), iron, and B-complex vitamins were also supplied. Antihypertensive drugs were given, when required, after excluding any possible neuroendocrine interference. No aluminum-containing PO_4 binders, nor vitamin D_3 or derivatives were given.

At the end of the follow-up period on CLND, and subsequently, in the course of SD every second month blood samples were taken for biochemical measurements and urine was also collected: the figures reported are those obtained at the end of the study period (2–4 months). Blood specimens were examined for the following assays: serum creatinine (sCr), PTH middle molecule (PTH-MM), E_2 , LH, FSH, testosterone (T), T_3 , T_4 and rT_3 .

Cl_{cr} was determined on the 24-hour urine collection. sCr and urinary creatinine were measured by means of autoanalyzer. Hormonal assays were performed as follows: heparinized blood samples for hormonal evaluations were centrifuged within 5 min after withdrawal and plasma was stored at -20 C° until radioimmunoassay was performed. E_2 , T, LH, FSH and rT_3 were measured by kits from Biodata (Italy), PTH-MM by kits from Immuno-Nuclear (USA), T_3 and T_4 by Lepetit (France). Normal values for hormonal determinations were the following: E_2 , 10–35 pg/ml; LH, 7–15 mIU/ml; FSH, 4.5–20 mIU/ml; T, 3–10 ng/ml (these data referred to male subjects); rT_3 , 90–350 pg/ml; T_3 , 80–200 ng/ml; T_4 , 4.5–12.5 $\mu\text{g}/\text{dl}$; PTH-MM, 0.29–0.85 ng/ml.

The statistical analysis of the collected data was performed by means of Student's *t* test for paired data. All results are expressed as mean \pm SD values.

Results

After the SD treatment period Cl_{cr} was not significantly modified (from 13.4 ± 2 to 12.9 ± 1 ml/min. In the course of the SD treatment period, endocrine consistent changes occurred: PTH fell from very high values (2.5 ± 1.4 to 1.2 ± 0.6 ng/ml, $p < 0.001$); 4 out of 13 studied patients, who had elevated PTH levels, were completely corrected (<0.85 ng/ml). Serum T was low-normal and increased (3.2 ± 1.3 to 5.9 ± 1.2 ng/ml, $p < 0.001$); 5 out of 13 studied patients presented basally T values below the normal range; 4 of these were corrected completely by the SD treatment (fig. 1).

Serum E_2 was found to be very high, confirming previous reports [5], and fell significantly during SD (105 ± 91.3 to 66.1 ± 53.4 pg/ml, $p < 0.001$); 12 subjects in the studied group had levels above the upper normal limit before SD treatment and in 3 of these the values were completely corrected by dietary therapy. T_3 was low-normal basally and increased after SD treatment (89.3 ± 30.9 to 135 ± 39.9 ng/dl, $p < 0.001$) (fig. 2). Five patients had values below normal limit before treatment and in 4 of them these were completely corrected (fig. 2). T_4 was normal basally and did not change in the course of SD treatment (7 ± 1.8 to 8.5 ± 2.2 $\mu\text{g}/\text{dl}$); rT_3 decreased from

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Figure 1: A line graph showing data trends over time. The graph has a vertical y-axis and a horizontal x-axis. There are several lines plotted, each representing a different data series. The lines generally show an upward trend, with some fluctuations. The lines are labeled with letters A, B, C, D, and E. The x-axis is labeled with years from 1980 to 2000. The y-axis is labeled with values from 0 to 100. The lines represent different data series, with A and B showing the highest values and C, D, and E showing lower values. The lines are plotted on a grid background.

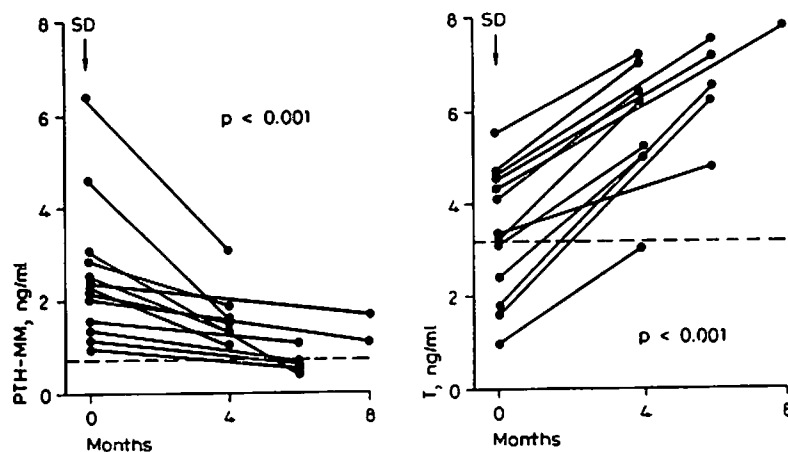


Fig. 1. This figure depicts the behavior of serum PTH and T in a group of 13 male patients with chronic renal failure, during the treatment with a low-protein diet supplemented with amino acids and ketoanalogues (SD). The dotted line indicates the upper limit of the normal range for PTH, and the lower limit for T.

high-normal values (262.1 ± 87.6 to 209.5 ± 76.1 pg/ml, $p < 0.01$). Gonadotropins (LH, 22.6 ± 7.6 to 19.6 ± 7.7 mIU/ml; FSH, 13.5 ± 7.8 to 10.3 ± 6.2 mIU/ml) were all at the upper limit of the normal range, as mean value, and did not change significantly during SD.

Discussion

In agreement with previous observations [11, 12], renal function did not change significantly during the SD period and this permits the exclusion of the theory that the changes of serum hormones might be caused by an improvement of kidney function. The hormonal changes that occurred following the SD treatment are then to be attributed to the diet itself.

Besides the correction of HPTH, T secretion and thyroid hormones, previously reported, the additional finding has been the fall of the elevated E_2 levels. This hormonal derangement, which is probably responsible for gynecomastia, hyperprolactinemia and impotence occurring in male CRF patients [5], is probably also related to protein catabolism [5]. Previous results

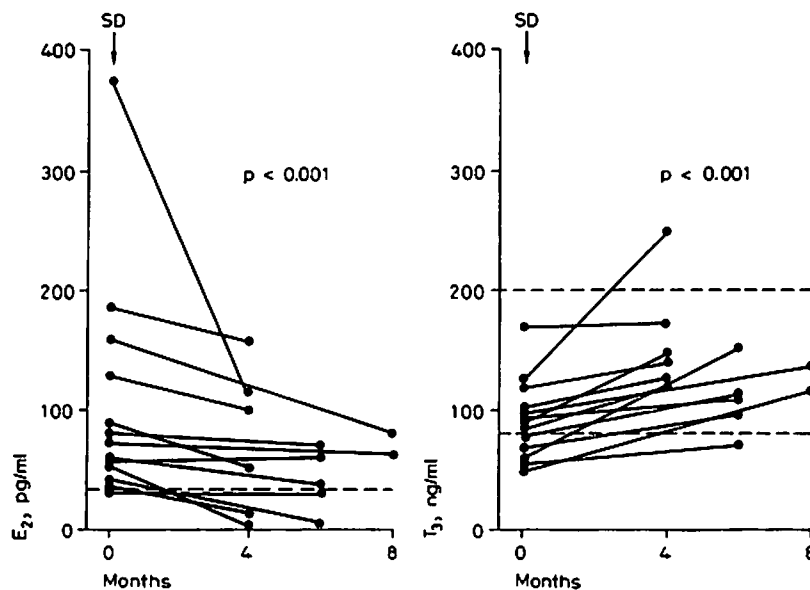


Fig. 2. This figure describes the changes of serum E_2 and T_3 in a group of 13 male patients with chronic renal failure, after a period of SD. The dotted lines indicate the upper limit of the normal range for E_2 , and the two limits of normality for T_3 .

refer to an important anabolic effect of the SD on protein metabolism [1] in CRF. These endocrine changes, altogether, may explain a great part of these results. In figure 3 are summarized the pathophysiological mechanisms through which the SD can influence protein metabolism via endocrine functions. First of all, the reversal of HPTH [13], obtained due to the low phosphorus intake and calcium supplementation. The reversal of HPTH probably causes a fall of serum glucagon levels [13], another powerful catabolic hormone. Glucagon levels also decrease as a consequence of the increase of serum T_3 , which enhances its catabolism [13]. The fall of PTH, together with the decrease of GH and glucagon [14] (due to T_3 and PTH changes), improves insulin peripheral activity, as is also done by the fall of circulating beta-endorphin [13], so explaining the findings on the reversal of hypertriglyceridemia and of glucose intolerance in CRF patients by the SD [13]. Finally, among all the endocrine actions of the SD which counteract protein catabolism, or are indices of an improved balance, we must consider, in these CRF patients, the fall of E_2 in males, accompanied by an increase

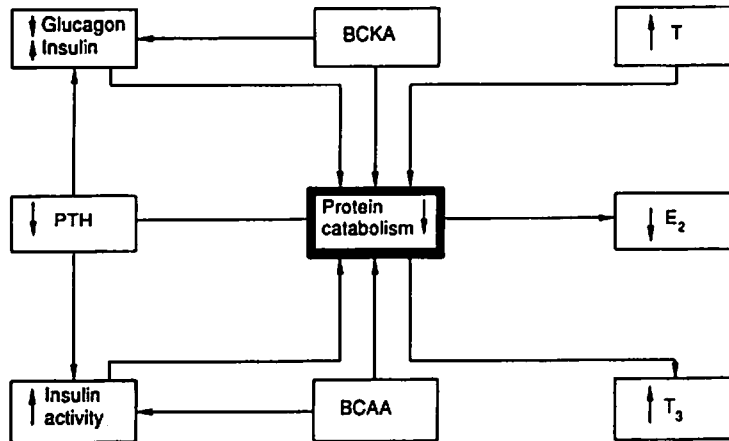


Fig. 3. In this graph are shown all the endocrinological changes due to the SD in chronic renal failure, which can oppose protein catabolism. Also described are the direct effects of the essential amino acids (EAA) and the branched chain ketoanalogues (BCKA), which are given by supplementation in the SD. The referred data are the result of this experience, but previous reports are also included.

of T. The restoration of T secretion [13] exerts a potent anabolic effect. Precursor hormones, as progesterone, are shunted in much lesser amounts to the synthesis of 'ring-A' aromatized steroids, the most powerful of which is E_2 . Concomitantly steroid precursors in endocrine active cells now allow the production in CRF males of more T and androgens. This fact may explain why elevated E_2 levels are considered a sign of protein catabolism, since it increases at the expense of the potent anabolic T which falls in males. In addition, we must consider the effect of the supplementation of the amino acids that must now surely be considered as true and powerful neuromediators, regulating most endocrine functions through neural pathways [15]. Amino acids play an important role in the control of the secretion of PTH, insulin, glucagon, and pituitary-gonadal axis. These effects are obtained by the amino acids directly or may be mediated by an influence on adrenergic, dopaminergic or serotonergic pathways. Ketoanalogues and the branched chain ones, particularly, also exert a direct anabolic effect [16], by reducing protein degradation and enhancing protein synthesis. This effect is probably also mediated by the stimulation of insulin secretion [17].

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