SERUM GASTRIN AND SERUM CALCITONIN
IN PATIENTS
WITH CHRONIC RENAL FAILURE

By

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ABSTRACT

The interrelationship between serum gastrin and serum calcitonin concentrations was studied in 73 patients with chronic renal failure. In both haemodialyzed and non-dialyzed patients increased serum concentrations of these hormones were found compared with normal controls. In non-dialyzed patients with creatinine clearance above 10 ml/min a highly significant correlation between serum gastrin and creatinine clearance was found, whereas no correlation was found in patients with creatinine clearance below 10 ml/min. Between serum gastrin and serum calcitonin, a significant positive correlation was found in non-dialyzed patients, whereas no correlation could be demonstrated in haemodialyzed patients. These findings may be explained by a relationship between the two hormones or be secondary to a decreased elimination due to the reduced renal function.

In patients with chronic renal failure increased serum gastrin and serum calcitonin concentrations have been reported (Korman et al. 1972; Feldman & Singer 1975; Heynen & Franchimont 1974; Silva et al. 1977). In chronic renal failure the degradation of gastrin is decreased and this may explain the elevated gastrin concentration (Glendinnen et al. 1973; Feldman & Singer 1975).

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1975). The cause of the increased serum calcitonin in these patients is unknown. In a previous study, however, we have found significant correlation between serum calcitonin and creatinine clearance and between calcitonin and serum phosphorus (Nielsen et al., in press). This suggests that decreased elimination and/or increased production due to stimulation by serum phosphorus may explain the increased serum calcitonin.

Pentagastrin has a strong stimulating effect on the secretion of calcitonin in patients with medullary thyroid cancer (Hennesy et al. 1973; Franchimont & Heynen 1976). Thus, increased serum calcitonin in patients with chronic renal failure might be due to increased serum gastrin.

The present study was carried out to elucidate the relationship between serum gastrin and serum calcitonin and between serum gastrin and renal function in patients with chronic renal failure.

**Patients and Methods**

*Patients.* — The study comprised 73 patients, 32 men and 41 women, with chronic renal disease. The mean age was 47.1 years (range 13–72 years). 28 patients had creatinine clearance between 10 and 70 ml/min, 27 patients had creatinine clearance between 5 and 10 ml/min and 18 patients had creatinine clearance below 5 ml/min (chronic haemodialysis patients). Patients with symptoms of peptic ulcer were excluded from the study. Haemodialysis was performed for 6–9 h, 2–3 times weekly using a 1 m² 13.5 μm thick cuprophane membrane (Rhône-Poulenc, RP 5). The dialyze contained 3.0 mEq/l of calcium.

*Methods.* — Serum concentrations of calcium, phosphorus, creatinine, protein, gastrin and calcitonin were measured after an overnight fast. Creatinine clearance was measured using 24 h urine periods. In haemodialyzed patients the blood samples were taken before the start of dialysis. After clotting, the blood samples were centrifuged at 4°C and stored at –20°C until analysis.

Serum concentrations of calcium, phosphorus and creatinine were measured by autoanalyzer methods.

*Gastrin.* — Gastrin was measured by radioimmunoassay as described previously (Brandsborg et al. 1975a,b; Stadil & Rehfeld 1973). The antiserum employed (4562) was kindly donated by professor J. F. Rehfeld, Aarhus, Denmark. The specificity was investigated as described by Rehfeld et al. (1972) and corresponded to the specificity of antiserum 2604. Furthermore no cross reactivity was found with synthetic human monomer calcitonin (Ciba, Switzerland). The antiserum reacts with component I, II and III with equivmolar potency.

*Calcitonin.* — Calcitonin was determined by radioimmunoassay using a commercial antibody to human calcitonin (Calbiochem, USA) and synthetic human monomer calcitonin (Ciba, Switzerland) for standards and iodination. [125I]calcitonin was prepared by the chloramin-T method (Tashjian 1969). The labelled antigen was purified by absorption to and elution from a microfine precipitated silicate Quso G 82 (Philadelphia Quartz Co., Philadelphia, USA) (Tashjian 1969). More than 90% of the labelled, purified antigen could be bound by the antibody. Assay conditions were
modified from Dietrich et al. (1975). Two hundred µl serum and 250 µl antibody dilution in 0.1 M tris – 0.25% human serum albumin pH = 7.3 was pre-incubated for two days at 4°C. Fifty µl [125I]calcitonin dilution giving about 5000 cpm was added followed by two days incubation at 4°C. Antibody-bound calcitonin was precipitated by polyethylene glycol (PEG 6000). Standards were prepared in serum from totally thyroidectomized patients. Each serum in duplicate together with a tube without antibody to correct for incubation damage and non-specific binding of the tracer. The lowest detectable concentration was 20 pg/ml. The precision of double determinations was 10 pg/ml. Reproducibility was determined using a control serum with a calcitonin level of 140 pg/ml. Over 9 assays the coefficient of variation was 14%.

No cross reactivity was found with synthetic human gastrin I (Imperial Chemical Industries Ltd., Cheshire, England) in a range of 100–1000 pg/ml, highly purified bovine parathyroid hormone (Wilson Laboratories, Chicago, Ill., USA) in a range of 100–4000 pg/ml, highly purified porcine cholecystokinin and synthetic cholecystokinin - like octapeptide (SQ 19.844) (kindly provided by professor J. F. Rehfeld, Aarhus, Denmark) in ranges of 250–2000 pg/ml, synthetic cyclic human somatostatin (kindly supplied by dr. S. Engkjær Christensen, Aarhus, Denmark) in range of 125–1000 ng/ml, synthetic pentagastrin (Imperial Chemical Industries Ltd., Cheshire, England) in a range of 125–1000 pg/ml or porcine monocomponent insulin (Novo, Denmark) in a range of 100–4000 µU/ml. No interference with creatinine (0.03–0.20 mg/ml), urea (0.9–3.4 mg/ml), human albumin (2.5–100 mg/ml or sodium chloride (120–150 mEq/l) was found in the range examined.

Statistical evaluations were carried out by the Mann-Withney U-test and Spearman's rank correlation test.

RESULTS

Non-dialysis patients with chronic renal failure. – In non-dialyzed patients serum concentrations of gastrin and calcitonin were significantly elevated compared with normal controls (Table 1). Fig. 1 shows the relationship between

| Table 1. |
|-----------------|-----------------|-----------------|
| Serum gastrin and serum calcitonin in patients with chronic renal failure compared with normal controls. Medians and range are given. |
| normal controls | creatinine clearance 5–70 ml/min | creatinine clearance < 5 ml/min (chronic haemodialysis) |
| s-gastrin pg/ml  | 20 (12–50) n = 21 | 74 (17–600) n = 55 | 90 (48–600) n = 18 |
| s-calcitonin pg/ml | 20 (10–120) n = 28 | 80 (10–325) n = 38 | 140 (90–220) n = 18 |

\[ P < 0.01 \]
Relationship between serum gastrin and creatinine clearance in non-dialyzed patients with chronic renal failure.

\[ R = -0.40 \]
\[ p < 0.01 \]

**Fig. 1.**

Relationship between serum gastrin and serum calcitonin in non-dialyzed patients with chronic renal failure.

\[ R = 0.34 \]
\[ n = 38 \]
\[ p < 0.05 \]

○ = creatinine clearance \( \geq 10 \) ml/min, ● = creatinine clearance 5–10 ml/min.
serum gastrin and creatinine clearance in non-dialyzed patients. A significant inverse correlation between serum gastrin and creatinine clearance in the total patient group was found ($R = -0.40, n = 55, P < 0.01$). In patients with creatinine clearance higher than 10 ml per min a highly significant inverse correlation was found ($R = -0.72, n = 28, P < 0.001$), whereas no significant correlation was found in patients with creatinine clearance below 10 ml/min.

Fig. 2 shows the relation between serum gastrin and serum calcitonin in non-dialyzed patients with different degree of impairment of kidney function. In the total patient group a low but significant correlation between serum gastrin and serum calcitonin was found ($R = 0.34, n = 38, P < 0.05$).

In patients with creatinine clearance higher than 10 ml/min a more close relation was found ($R = 0.45, n = 20, P < 0.05$). No correlation between serum gastrin and serum calcium was found.

Patients on chronic haemodialysis. In this patient group the serum concentrations of gastrin and calcitonin were increased to the same degree as in the non-dialyzed patients with creatinine clearance below 10 ml/min. The elevation of the hormones was significant compared with normal values ($P < 0.01, P < 0.01$, respectively). A negative, but not significant, correlation between serum concentrations of gastrin and calcitonin was found in this patient group ($R = -0.37, n = 18$). Between serum gastrin and serum calcium and between serum gastrin and serum phosphorus no significant correlation was found.

**DISCUSSION**

In agreement with previous studies we found increased serum gastrin and serum calcitonin concentrations in patients with chronic renal failure (Feldman & Singer 1975; Heynen & Franchimont 1974; Korman et al. 1972; Silva et al. 1977).

The relationship between serum gastrin and creatinine clearance has not been previously described. The present study shows a highly significant inverse correlation between serum gastrin and creatinine clearance in patients with creatinine clearance above 10 ml/min, whereas no correlation could be demonstrated in uraemic patients, i.e. patients with creatinine clearance below 10 ml/min.

The increased serum gastrin concentration in patients with chronic renal failure has been ascribed to a reduced elimination of the hormone due to the reduced renal function at lower metabolic clearance rate of polypeptide hormones such as insulin (Silvers et al. 1969), growth hormone (Cameron et al. 1969), calcitonin (Ardaillou et al. 1970) and parathyroid hormone (Freitag et al. 1978). It has been proposed that the increased serum gastrin in patients with
chronic renal failure is related to the loss of normally functioning renal mass and not a result of the uraemic state per se, as bilateral nephrectomy was followed by increased serum gastrin, whereas no change from normal values was found following bilateral ureteral ligation in laboratory animals (Davidson et al. 1974).

The reason for the elevated serum calcitonin concentration in patients with chronic renal failure might be a decreased elimination due to the reduced renal function as highly significant inverse correlation has been found between serum concentration of calcitonin and creatinine clearance in a previous study (Nielsen et al., in press). Other explanations may be a stimulated calcitonin production caused by hyperphosphataemia (Franchimont & Heynen 1976; Heynen & Franchimont 1974; Nielsen et al., in press) or an increased calcitonin production secondary to the increased serum gastrin concentration in these patients as pentagastrin is a strong calcitonin stimulator in patients with medullary thyroid cancer and may induce calcitonin release in normals (Franchimont & Heynen 1976; Hennesy et al. 1973).

The present study cannot confirm whether an aetiological relationship is present between hypergastrinaemia and hypercalcitoninaemia in patients with chronic renal failure. Further studies are necessary to elucidate the possible relationship between the two hormones in chronic renal failure.

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