Plasma 25-Hydroxyvitamin D and Urinary Cyclic AMP in German Patients with Subtotal Gastrectomy (Billroth II)

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In an attempt to clarify the pathogenesis of the disturbed calcium metabolism which sometimes follows partial gastrectomy, we determined plasma 25-hydroxyvitamin D (25-OH-D) concentrations and urinary cyclic 3',5'-adenosine monophosphate (cAMP) excretion in patients who had previously undergone Billroth II gastrectomy and who were without clinical evidence of bone disease. In 17 Billroth II patients plasma 25-OH-D concentrations were reduced (12.6 ± 4.6 ng/ml, mean ± SD) compared to values in 17 control patients with diseases not affecting calcium metabolism (31.6 ± 12.9 ng/ml, P < 0.001). Urinary cAMP excretion, in part reflecting parathyroid function, was higher in 17 Billroth II patients (5.0 ± 2.5 μmol/day) than in the control patients (2.6 ± 1.3 μmol/day, P < 0.001). These results suggest impaired nutrition of vitamin D and secondary hyperparathyroidism in Billroth II patients. While the cause of this phenomenon is unclear, it may contribute to the disturbance of calcium metabolism in patients who have had subtotal gastrectomy.

Partial gastrectomy may be followed by disturbance of calcium metabolism (1–4). In European adults presenting with osteomalacia, 41% have had previous gastric surgery (5); on the other hand, osteomalacia has been reported in 3–25% of postgastrectomy patients (6, 7). From these studies there is no agreement about the role of vitamin D in postgastrectomy bone disease. Therefore, in patients with Billroth II gastrectomy (BII), without overt bone disease, we measured plasma 25-hydroxyvitamin D (25-OH-D) concentrations [which are reported to be low in vitamin D deficiency (8, 9)], and urinary excretion of cyclic 3',5'-adenosine monophosphate (cAMP). Urinary cAMP excretion, in part reflecting parathyroid function, is found elevated in patients with primary hyperparathyroidism (10) and can therefore be used to indicate secondary hyperparathyroidism accompanying vitamin D deficiency (8).

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MATERIALS AND METHODS

Twenty-two patients (2 females, 20 males) with an age of 63.7 ± 9.8 (mean ± SD) who had BII a mean of 11.7 years ago (range, 4–24) were studied. Only patients who had no postgastrectomy syndrome, abdominal pain, or clinical signs of intestinal malfunction were included in the study. For comparison we studied 17 patients (4 females, 13 males) with an age of 60.2 ± 8.9 without diseases known to influence calcium metabolism. They were matched in age (same decade) and—because of seasonal variations of plasma 25-OH-D (11)—in the month of study with 17 of the BII patients.

Plasma 25-OH-D was measured according to Haddad (12, 13) in a receptor-binding assay, using rat kidney cytosol after silicic acid chromatography of a plasma ether extract, in these 17 BII patients and in the controls. A 24-hr urine specimen obtained on the same day as the plasma sample was analyzed for cAMP content using a radioreceptor assay according to Brown et al (14, 15) in the

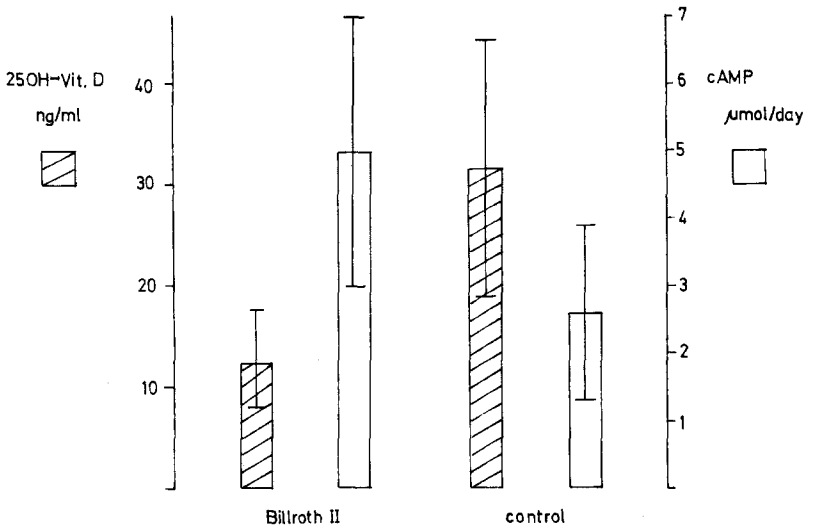

Fig 1. 25-OH-D concentration of plasma and urinary cAMP excretion in patients after partial gastrectomy (Billroth II) and a group of patients without diseases known to influence calcium metabolism (mean ± SD).

17 controls and in 12 of the BII patients. The study was done during the months June–December. During this time cAMP was measured in the urine of 5 additional BII patients.

Serium calcium (using flame photometry), phosphorus (16), alkaline phosphatase (17), SGOT, SGPT (18), and creatinine (19) were determined in all patients on the day of the study. Systematic x-ray examinations were not done; however, radiographs obtained for clinical purposes showed no evidence of osteomalacia in any of the patients.

RESULTS

None of the patients had clinical signs of bone disease (bone or back pain, skeletal deformities). Serum calcium, phosphorus, alkaline phosphatase, SGOT, SGPT, and creatinine were normal in each studied subject. Plasma 25-OH-D in BII patients was 12.6 ± 4.6 ng/ml (mean ± SD), significantly decreased compared to 31.6 ± 12.9 ng/ml in the control group ($P < 0.001$). Urinary excretion of cAMP in the BII patients was 5.0 ± 2.5 µmol/day, higher than 2.6 ± 1.3 µmol/day measured in the controls ($P < 0.001$) (Figure 1). There was no relationship between plasma 25-OH-D and urinary cAMP excretion in 12 BII patients and controls ($r = 0.46$, $P > 0.05$). No relationship could be found between the number of years following BII and the 25-OH-D concentrations in BII patients ($r = 0.15, P > 0.05$).

DISCUSSION

Measurement of 25-OH-D provides a means of determining the "vitamin D status" of a patient. Although 1,25-dihydroxyvitamin D_3 is thought to be the physiologically active form of vitamin D, 25-OH-D_3 is the major circulating metabolite, synthesized mainly by the liver from vitamin D_3 (from the skin or the diet). Impaired supply of vitamin D may be reflected in low concentrations of 25-OH-D, which are observed to be below 10 ng/ml in osteomalacia (8, 9).

The group of Billroth II patients we investigated showed decreased concentrations of plasma 25-OH-D compared to control patients. This indicates some degree of impaired vitamin D nutrition, although not severe enough to cause known biochemical sequels of vitamin D deficiency, such as hypocalcemia or increased serum alkaline phosphatase. Decreased dietary vitamin D intake or exposure to sunlight in the BII group might account for the dif-

ferences in plasma 25-OH-D we observed. These are, however, probably not the main reasons because the BII patients were of similar age and lived in the same area as the control patients. BII patients and respective controls were studied in the same months to exclude seasonal variation in plasma 25-OH-D (11). Since serum levels of SGOT, SGPT, and alkaline phosphatase are normal in these BII patients, it is unlikely that they have severe liver disease or an impaired ability to hydroxylate vitamin D_3 to 25-OH-D.

A decreased absorption of labeled vitamin D_3 or synthetic 25-OH-D_3 has been reported only in BII patients with osteomalacia (1, 13, 20). However, postgastrectomy patients often have malabsorption of fat (21). This might result in malabsorption of vitamin D and a loss of biliary 25-OH-D, which is known to undergo enterohepatic circulation (22). Although we did not measure stool fat in our patients, one can speculate that this mechanism is the main reason for low plasma 25-OH-D.

The increased urinary cAMP might reflect secondary hyperparathyroidism in these patients. We offer the hypothesis that the low plasma 25-OH-D concentration evokes increased parathyroid hormone levels even when other biochemical parameters of vitamin D action, such as serum calcium concentration and alkaline phosphatase, are still normal.

Although there was no clinically overt disease from vitamin D deficiency in our BII-patients, the finding of diminished circulating 25-OH-D levels and indirect evidence for secondary hyperparathyroidism corresponds well with the high incidence of osteopenic bone disease in these patients in Germany (23), where regular addition of vitamin D to food is prohibited (24). Our findings suggest that low plasma 25-OH-D concentrations may play a role in the disturbed calcium metabolism of BII patients, in addition to other factors, such as calcium deficiency (3, 25) and malabsorption, to which it might be closely related.

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