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Fasting Gastrinemia and Elevated Supersaturation with Hydroxyapatite of Fasting Urine – Observations in Renal Calcium Stone Patients and Controls

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Summary. We evaluated serum gastrin, acid-base status, variables of mineral metabolism in fasting blood, as well as pH, relative supersaturation of stone forming constituents, and crystalluria in the associated fasting urine, of control subjects ($n = 12$), and in age- and weight-matched male normocalciuric ($n = 12$) and hypercalciuric ($n = 12$) patients with idiopathic recurrent calcium urolithiasis (RCU). In RCU, mineral metabolism and acid-base data are unchanged, whereas mean serum gastrin is only insignificantly higher as compared to controls. Subclassification of all participants into categories with either high-normal or low-normal gastrin reveals that in RCU with low-normal gastrin there is a higher-than-normal urinary pH and significantly elevated supersaturation of urine with hydroxyapatite. Crystalluria and stone analysis support the assumption that the physicochemical environment accompanied by low gastrin levels predisposes to urinary precipitation of calcium phosphate with subsequent formation of a stone nidus. pH in fasting urine and integrated fasting serum gastrin correlate significantly, suggesting that low fasting serum gastrin in RCU patients may be considered a risk factor for calcium phosphate stone formation.

Key words: Recurrent calcium urolithiasis, Fasting serum gastrin, Mineral metabolism, Urinary supersaturation, Hydroxyapatite, Crystalluria, Stone analysis.

Introduction

Urinary crystal and stone formation is generally attributed to periods of high urinary supersaturation with stone-forming constituents, either alone or in combination with a deficiency of inhibitors of stone-forming processes. Present stone research has difficulty in identifying such periods of high risk of precipitation within the daily urinary cycle of renal stone formers. Following ingestion of test meals, the postprandial urine of patients with recurrent calcium urolithiasis (RCU) exhibits a more marked tendency towards precipitation of calcium-containing mineral phases than the urine of healthy subjects [9, 10, 15]. On the contrary, more systematic studies are lacking for fasting urine.

For a long while, we have been observing that the fasting urine in a number of RCU patients was less acidic than that of control subjects, although signs of renal tubular acidosis were absent [unpublished data]. On the other hand we have repeatedly observed mild hypergastrinemia in these patients [8, 14]. Gastrin, the hormone of gastrointestinal G-cells, stimulates gastric H^+ generation. While a hypocalcemic action has been attributed to gastrin [4], renal tubular action related to acidification of urine has so far not been reported for this hormone. The urinary ion-activity product of calcium phosphate rises dramatically above a urinary pH of 6–6.5, thereby implying the risk to form calcium phosphate crystals [18]. We hypothesized, therefore, that there might be correlations between fasting gastrinemia and the pH, composition and the state of supersaturation of fasting urine. In the present work we report on these data as well as on variables of mineral metabolism and acid-base status in blood. Although the number of data is yet limited we can show that especially hypercalciuric stone formers with low-normal fasting gastrin exhibit elevated supersaturation of urine with respect to hydroxyapatite, whereas patients with high-normal gastrin are uneventful in this regard.

Participants and Methods

All participants were studied under outpatient conditions while on their home diet, according to a standardized program [13]. All had normal renal function (serum creatinine <1.4 mg/dl) and were free

Abbreviations used in this paper: RCU, Recurrent calcium urolithiasis; NC, Normocalciuria; I-HC, Idiopathic hypercalciuria; HAP, Hydroxyapatite; cAMP, cyclic AMP.

of urinary tract infections. None of them suffered from disorders with the symptom hypergastrinemia (in particular Zollinger-Ellison syndrome, antral G-cell hyperplasia, pyloric obstruction, hypergastrinemic duodenal ulcer disease, atrophic gastritis, post-vagotomy status) as well as from disturbances of metabolism such as diabetes mellitus (types I, II), renal tubular acidosis, primary hyperparathyroidism, etc.

Male RCU patients ($n = 24$) were subdivided into the categories normocalciuria (NC; $n = 12$) and idiopathic hypercalciuria (I-HC; $n = 12$), on the basis of either normal calcium (NC) or elevated calcium (I-HC; 3 patients with fasting hypercalciuria) in the 24 h-urine [13].

During the preceding 12 months all patients had either spontaneously passed stones or had been operated on for stones. At the time of the laboratory investigation X-ray positive kidney stones were demonstrable in 3 of the 12 NC- and in 5 of the 12 I-HC patients. Drug intake had been stopped one week before the investigation.

12 healthy male subjects with normal calcium in 24 h-, 2 h-fastings- and 3 h postprandial urine served as controls. Upper limits of urinary calcium on which the classification is based are: <300 mg (24 h-urine), <0.12 mg/mg creatinine (2 h-fasting urine), <0.28 mg/mg creatinine (3 h-postprandial urine). The distribution of age was as following: 18–40, mean 30.9 years (NC); 18–40, 29.4 (I-HC); 19–41, 30.5 (controls).

From the investigation program [13] the following constituents were chosen for the present study: 2 h-fasting urine (8 to 10 a.m.), 2 blood samples taken from a forearm vein without using a tourniquet (8 a.m. and 10 a.m.; samples 0 and A, see Table 1) and capillary blood from the lobe of the ear (8 a.m.). A 12–15 h overnight fasting period preceded these measures. In the capillary blood, pH and bicarbonate were measured immediately. Serum and urine were stored at −30 °C until analysed.

Analyses

Serum gastrin was determined using an established radioimmunoassay [9]: rabbit antibody, final dilution $1:10^6$, synthetic human gastrin-17 (Bachem, Bubendorf; Switzerland) served as standard and for iodination (Chloramin-T); the assay recognizes all presently known molecular species of gastrin, and recognition of gastrin-17 and gastrin-34 is roughly equal on a molar basis. The intra- and interassay variation coefficients are <10 and <15 per cent, respectively. Concentrations are given as equivalents per ml of gastrin-17.

Serum total and ultrafilterable calcium were determined by complexometry, ionized calcium in the ultrafiltrate by colorimetry (tetramethylmurexide; 22), total protein by refractometry. Other determinations in serum, capillary blood and urine employed routine methods, cyclic AMP (cAMP, kit Amersham-Buchler, Braunschweig; FRG) included. Crystalluria was evaluated using a filter technique [20] and polarization microscopy (for details, see [11]), stone analysis was performed using the latter method.

Calculations, Presentation of Data, Statistics

Since the fasting gastrin levels often vary, the integrated hormone output between 8 a.m. and 10 a.m. was calculated and log-transformed. Serum calcium fractions, phosphate threshold (Tm-Pi), pH, bicarbonate were measured only at 8 a.m. The relative supersaturation products (RSP) of urine with stone forming phases were calculated using EQUIL (courtesy of Drs. L. H. Smith, Rochester/Minnesota; B. Finlayson, Gainesville/Florida; USA) [1], in the modification of Werness et al. [21]. Gastrin in the stone patients revealed a tendency towards higher-than-normal, but not significantly elevated values (Table 1). In order to be able to compare possible influences of either high-normal or low-normal gastrin the data were stratified. The arithmetic mean of the integrated gastrin response of the control subjects served as cut-off point. Although a gaussian distribution is not always present, results are means ± 1 SEM, unless otherwise indicated. The U test or the t test for unpaired data were used, as appropriate, to test for significance ($p < 0.05$) of differences. Regression analysis was performed using the least square procedure.

Results

I. Measured Gastrin and Integrated Gastrin Response

Gastrin in the sample taken at 8 a.m. (sample 0) was as following ($n = 12$ per group): Controls 56 ± 12, NC 78 ± 23, and I-HC 78 ± 18 pg-equiv/ml; the corresponding medians were 40, 62, and 41, respectively. The values in the sample taken at 10 a.m. (sample A) were: Controls 42 ± 7, NC 60 ± 14, I-HC 71 ± 22 pg-equiv/ml; the corresponding medians were 33, 47, and 42, respectively. The values for integrated gastrin output were ($\log_{10}$ area): 3.71 ± 0.07 (controls), 3.81 ± 0.08 (NC), and 3.82 ± 0.09 (I-HC), respectively. The differences between controls and stone patient groups are not significant. The order of magnitude of measured gastrin agrees with reported data for healthy controls [19].

II. Influence of Stratification for High-Normal and Low-Normal Gastrin

1. Data in Blood (Table 1). On the basis of this classification two smaller subgroups with highly significantly different gastrin (comparison between high-normal and low-normal gastrin) emerge from each of the groups (controls, NC, I-HC).

The indicators of the acid-base status (pH, bicarbonate) are not significantly changed when the corresponding groups with either high- or low-normal gastrin are considered. These data are not shown. The same holds for ultrafilterable and ionized calcium, and total protein, which are unchanged. However, the Tm-Pi is markedly lower in NC and I-HC than in controls (differences within a given gastrin protocol not tested), but an influence of either high- or low-normal gastrin is not recognizable.

2. Data in Urine (Table 1; Fig. 1). Urine volume is lowest in controls with low gastrin, and no influence of gastrin is recognizable in the two stone patient groups. However, in the presence of low-normal gastrin the urinary pH of the controls tends to fall ($p < 0.10$), whereas in I-HC the pH rises markedly. NC reveals the highest pH values which, however, do not differ significantly owing to the already high values of the corresponding group with high gastrin levels. When the groupwise-pooled data for pH and gastrin from the two protocols (high- and low-normal gastrin, respectively) are submitted to regression analysis there is a

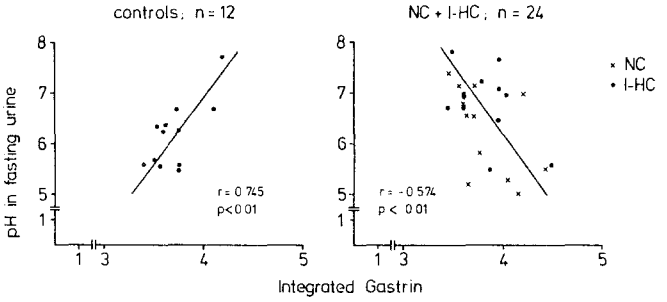

Fig. 1. Relationship between integrated gastrin in fasting serum and pH in the associated urine. Lines are eye-fitted

positive correlation in controls (Fig. 1). A negative correlation emerges in NC ($r = -0.504, p < 0.10, n = 12$) and I-HC ($r = -0.663, p < 0.05, n = 12$). For the combined group of patients (NC + I-HC) the correlation is highly significant (Fig. 1). No other correlations were found.

In the I-HC group, calcium is higher than in NC and controls, a finding reflecting the existence of fasting hypercalciuria in three patients (see Participants and Methods). Citrate, magnesium, oxalate are normal and uninfluenced by gastrin (data not shown), as is the case for cAMP, an indirect indicator of the bioactivity of circulating parathyroid hormone, and phosphate. Pyrophosphate is highest in controls within high gastrin levels, but is strongly decreased in the presence of low gastrin levels (approx. 30 per cent of the value observed with high gastrin levels). In NC, pyrophosphate appears lowered independent of gastrin (approx. 43 per cent of the value of the controls with high gastrin levels), whereas in I-HC it is statistically unchanged.

3. Supersaturation of Urine (Fig. 2). Relative supersaturation [21] of the stone-forming phases or substances varies considerably (see range of individual values as foot-notes to the columns). The medians for brushite and uric acid are in the undersaturation range (negative values; not shown) in all groups, while for hydroxyapatite (HAP), sodium acid urate and calcium oxalate there is a tendency towards precipitation (positive values). For these latter phases there is significantly higher supersaturation in the presence of low gastrin, and this is most marked in I-HC and the pooled group NC + I-HC (HAP and sodium acid urate).

4. Crystalluria (Table 2). The total number of positive crystalluria findings is 12 out of 18 individuals designed to have high gastrin, 17 out of 18 of those designed to have low gastrin. Accordingly, the median score is higher in this latter moiety (not statistically tested). The contribution of calcium oxalate to crystalluria appears independent of gastrin (6 and 7; high versus low gastrin, respectively), whereas calcium phosphate appears to predominate in subjects with low gastrin (6 and 10; high versus low gastrin, respectively). A clear distinction between controls and stone patients in terms of crystalluria is, however, not recognizable.

Table 1. Influence of classification according to high-normal or low-normal integrated $\int_0^A$ fasting serum gastrin levels in control subjects, upon associated variables in the same serum sample and fasting urine, respectively

	High normal gastrin			Low normal gastrin		
	Controls	NC	I-HC	Controls	NC	I-HC
1. Data in serum						
$\int_0^A$ Gastrin: $\log_{10}$ area	3.87 ± 0.08 (6)	4.00 ± 0.09 (7)	4.12 ± 0.11 (5)	3.55 ± 0.04[b] (6)	3.55 ± 0.03[b] (5)	3.61 ± 0.03[b] (7)
Total calcium; mg/dl	9.43 ± 0.10 (6)	9.31 ± 0.14 (7)	9.76 ± 0.08 (5)	9.60 ± 0.09 (6)	9.56 ± 0.13 (5)	9.61 ± 0.11 (7)
Tm-Pi C-Cr^{-1} 100; mg/dl	4.08 ± 0.42 (6)	2.83 ± 0.21 (7)	3.16 ± 0.38 (5)	4.05 ± 0.37 (6)	3.22 ± 0.28 (5)	3.27 ± 0.38 (7)
2. Data in urine						
Volume; ml	187 ± 51 (6)	164 ± 28 (7)	154 ± 42 (5)	70 ± 16[a] (6)	165 ± 66 (5)	144 ± 22 (7)
pH;	6.39 ± 0.34 (6)	6.65 ± 0.31 (7)	5.71 ± 0.35 (5)	5.83 ± 0.15 (6)	7.03 ± 0.21 (5)	6.87 ± 0.14[a] (7)
Pyrophosphate/Creatinine; nM/mg	0.151 ± 0.03 (6)	0.060 ± 0.021 (7)	0.139 ± 0.053 (4)	0.041 ± 0.005[a] (6)	0.066 ± 0.046 (5)	0.097 ± 0.044 (5)
Phosphate/Creatinine; mg/mg	0.23 ± 0.05 (6)	0.22 ± 0.04 (7)	0.24 ± 0.064 (5)	0.20 ± 0.03 (6)	0.19 ± 0.05 (5)	0.21 ± 0.03 (7)
cAMP/Creatinine; nM/mg	2.60 ± 0.29 (6)	2.99 ± 0.17 (7)	2.58 ± 0.12 (5)	2.63 ± 0.15 (6)	2.83 ± 0.08 (5)	2.53 ± 0.19 (7)
Calcium/Creatinine; mg/mg	0.07 ± 0.01 (6)	0.07 ± 0.01 (7)	0.10 ± 0.03 (5)	0.06 ± 0.02 (6)	0.07 ± 0.01 (5)	0.10 ± 0.02 (7)

Tm-Pi C-Cr^{-1} 100: phosphate threshold per 100 ml creatinine clearance. Means ± SEM. ( ): number of observations. For other abbreviations see section Participants and Methods

[a] $p < 0.01$; [b] $p < 0.001$ versus high-normal gastrin

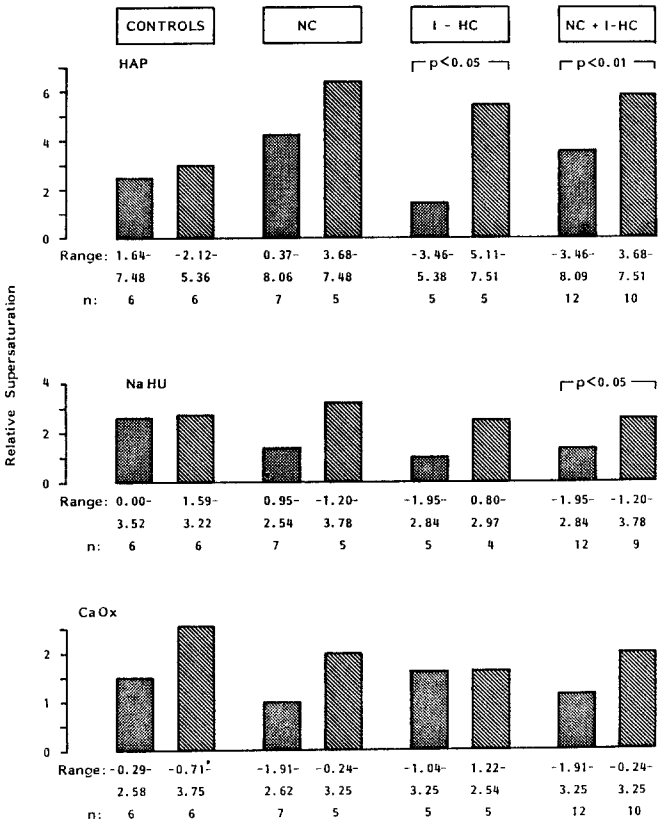

Fig. 2. The degree of relative supersaturation expressed in $\Delta G(1)$, of fasting urine with hydroxypatite (HAP), sodium acid urate (NaHU) and calcium oxalate (CaOx), as a function of the associated integrated gastrin in fasting blood (□: high normal gastrin; □: low-normal gastrin); for details and group symbols see section: Participants and Methods, and Results (Tables 1, 2). Values below 0 indicate undersaturation, positive values a pressure to crystallization (see [22]). *Range:* range of individual values. ( ): number of observations

5. Stone Analysis. Calcium phosphate is the dominant constituent in the stones available from the 18 patients classified as NC or I-HC, in whom the urinary pH was >6.19, whereas calcium oxalate dominates in stones from 6 patients with urinary pH <6.19.

Discussion

This study fails to show that gastrin in fasting blood is statistically elevated in RCU, and this contrasts with our earlier reports [8, 14]. The discrepancy may be explained by the more rigid selection criteria (identical age, body weight) for the participants in the present as opposed to previous communications. For instance, it is known that gastrin increases with age [5]. Moreover, considering the high standard errors especially in RCU, gastrin appears to be non-parametrically distributed, suggesting that sub-groups with possibly clearly elevated gastrin may be hidden among stone patients. Unpublished results from our laboratory indicate that one such sub-group may be characterized by lower than normal pH in fasting urine, when samples from controls and patients with pH below 6.19 are considered. Thus the present work indicates that classification of stone patients into the various calciurias may be an unsatisfactory tool in unmasking anomalous gastrinemia. For this reason stratification was chosen as a tool to elucidate some aspects of the metabolic state marked by high- or low-normal gastrin.

An alkaline tide effect of gastrin (owing to the shift of H^+ form the gastric tissue and blood sites to the gastrointestinal lumen) upon ionized serum calcium and a subsequent constant stimulation of the parathyroid glands has been suggested [3], but cannot be confirmed in the present work.

Normal parathyroid gland function also in the individuals with high-normal gastrin is further substantiated by unchanged ionized calcium (mean values for high- and low-normal gastrin in the combined groups, would be 4.69 and 4.61 mg/dl, respectively), Tm-Pi, and urinary cAMP and phosphate (Table 1).

The stratification for gastrin revealed, however, that particularly in I-HC patients, but also in those from the NC group, the fasting urine pH is elevated in the presence of low circulating gastrin concentrations (right side of Table 1).

Therefore the question arises as to whether gastrin, a hormone stimulating gastric H^+ generation, also participates in the acidification of urine. At present, more specific studies on such renal effects of gastrin and the renal handling

Table 2. Calcium oxalate and calcium phosphate crystalluria, and the crystalluria score in fasting urine after gastrin classifications as in Table 1. ( ): number of individuals

	High-normal gastrin			Low-normal gastrin		
	Controls (6)	NC (7)	I-HC (5)	Controls (6)	NC (5)	I-HC (7)
Calcium oxalate	1/5[a]	2/5	3/2	4/2	1/4	2/5
Calcium phosphate	1/5[a]	3/4	2/3	2/4	3/2	5/2
Score[b]; median/range	0/0–0.5	0.25/0–1	0.5/0–3	0.5/0–2	0.25/0–1	0.5/0.25–1.5

[a] cases with/without crystals
[b] for details of calculation see Ref. 12

of gastrin in health and stone desease are not available. Interestingly, acidification defects located primarily in the proximal tubule have been described in the renal hypercalciuria variety of non-infected RCU patients [17], but these subjects additionally had signs of urinary phosphate wastage which is not encountered in our I-HC series. Moreover, these authors, as we in the present study [unpublished data], could not attribute the resulting elevated urinary pH to parathyroid hormone or vitamin D status, or signs of renal tubular acidosis suggesting that some intrinsic defect may be responsible. The positive correlation of gastrin and urinary pH in controls gives rise to speculation on an indirect coupling of these two variables via an additional factor. This hypothetical factor should be absent in RCU, at least in the I-HC group, since here gastrin and urinary pH are negatively correlated (Fig. 1). Since simple correlations do not prove any cause-and-effect relationship further work is needed focussing more directly on possible renal actions of gastrin.

The stratification for low- and high-normal gastrin levels reveals also that normally there may be a positive relationship between gastrinemia and urinary pyrophosphate, i.e. both substances may move concomitantly. However, a direct interrelation of the two parameters may be unlikely, since pyrophosphate is also low in the NC subgroup with high-normal gastrin (left side of Table 1). Pyrophosphate is a documented inhibitor of growth and aggregation of calcium phosphate crystals [2] and is also discussed as an inhibitor of nucleation. Thus, the combination of higher urinary pH and lower urinary pyrophosphate seems to contribute to the elevated supersaturation of the urine with HAP in RCU (Fig. 2). Consequently low gastrin, if coinciding with this combination, may probably constitute a risk factor for calcium phosphate nucleation, crystalluria and possibly urolithiasis.

If this is so, the type and degree of crystalluria and stone analysis should roughly reflect the accompanying physicochemical environment of urine. Our data on crystalluria may give a hint in the direction that increasing urinary pH in the I-HC group is accompanied by more calcium phosphate crystals (Table 2). A larger series of stone patients is currently under evaluation considering together gastrin, supersaturation products, inhibitory activity, and crystalluria. In contrast to crystalluria the available stone analyses appear to support the above conjecture of the role of urinary pH as a determinant upon stone composition. In non-infectious idiopathic calcium phosphate stone disease (<75 per cent phosphate, 0–25 per cent calcium oxalate) we previously found a urinary pH of 6.75, which agrees favorably with the value found by others [6] and in the present series with a pH of 6.95 for the combined RCU group (NC + I-HC) in the protocol with low-normal gastrin (Table 1).

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