EDITORIAL REVIEW

Hypercalciuria

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Key words: calcium absorption, 1,25-dihydroxy vitamin D₃, parathormone, plasma phosphate, renal stone, risk factors.

Abbreviations: 1,25-(OH)₂D₃, 1,25-dihydroxy vitamin D₃; GFR, glomerular filtration rate.

As variety is the spice of life, so controversy is the spice of science; a Guest Editorial allows review of a subject which appears to become more rather than less controversial with the passage of time. Hypercalciuria is controversial, for excellent reasons. There is no agreement on its definition; its pathogenesis is uncertain; and its clinical significance is debatable.

Definition

Flocks (1939) first noted an association between renal stone disease and increased calcium excretion in the urine, but it was not until 1953 that Albright, Henneman, Benedict & Forbes coined the term 'idiopathic hypercalciuria' to describe the disorder, suggested that it might be tubular in origin, and drew attention to the hypophosphataemia which frequently accompanies it. A few years later Henneman, Benedict, Forbes & Dudley (1958) showed that idiopathic hypercalciuria was associated with a high absorption of calcium, and subsequently Jackson & Doncaster (1959) suggested that this hyperabsorption was an adaptation to the increased urinary loss of calcium.

None of these authors was able to define hypercalciuria precisely. Several attempts were made to determine the upper normal limit of calcium excretion, but different workers in different countries under different conditions defined a variety of different ranges. However, it soon became apparent that the conventional Gaussian statistics were not applicable, as the urinary calcium data were skewed to the right. In 1958 Hodgkinson & Pyrah suggested the most practical definition of hypercalciuria up to that time, noting that 90% of 24 h calcium excretion values fell below 7.5 mmol (300 mg)/24 h in normal men, and below 6.25 mmol (250 mg)/24 h in normal women on free diets. They suggested that higher values should be regarded as hypercalciuric. These limits were widely used during the next decade, but can now be replaced by less arbitrary limits (Robertson & Morgan, 1972; Morgan & Robertson, 1974).

These workers have shown by means of a probit transformation that the abnormal distributions of urinary calcium values in normal and stone-forming subjects is not due to an excess of high values but to a deficiency of low values. They suggest that this arises from the overriding need to maintain a normal plasma calcium concentration, which in turn sets a lower limit to the excretion of calcium. Since the upper part of the frequency distributions is Gaussian, simple statistical analysis of this part of the data, which is of greatest interest in this context, shows that the median calcium output of normal men on a free diet in the series is 6.0 mmol (240 mg)/24 h with SD 2.7 mmol (108 mg). Thus the conventional upper normal limit (median + 2 SD) would be 11.4 mmol (456 mg)/24 h, with 3 SD extending to 14.1 mmol (564 mg)/24 h.

This analysis is an advance on earlier attempts.

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to define the normal range of urinary calcium, but still gives a great overlap between normal subjects and stone-formers. The median value in Morgan & Robertson's (1974) idiopathic male stone-formers is significantly raised [7.5 mmol (300 mg)/day; so 3.2 mmol (128 mg)], but most values fall within the normal range, however this is defined. Urinary calcium is continuously distributed and it is likely that the values above the normal median, which are found in 68% of the stone-formers, are relevant to their stone disease and should not be ignored because they fall within a so-called normal range. When distributions overlap in this way, the use of percentiles is more appropriate than the absolute normal range. In Leeds the normal 75th percentile is 7.8 mmol (312 mg)/24 h, the 90th percentile 9.5 mmol (380 mg)/24 h and the 95th percentile is 10.5 mmol (420 mg)/24 h. The use of these percentiles indicates to what extent calcium excretion is above the normal median in any given case. Corresponding percentiles need to be defined for other centres; even within the U.K. there is a large variation in calcium excretion, which may be related to the hardness of the water (Bulusu, Hodgkinson, Nordin & Peacock, 1970; Davis, Morgan & Rivlin, 1970; Watson & Dale, 1966).

For the lower limit of urinary calcium, Morgan & Robertson (1974) identified a normal mean lower limit of about 3.75 mmol (150 mg) with a range of 1.25–6.25 mmol (50–250 mg). Examination of the normal relationship between plasma and urinary calcium (Peacock, Robertson & Nordin, 1969) shows that the mean normal calcium excretion at the lower normal limit of plasma calcium of 2.25 mmol/l (0.025 mmol/l (0-1 mg/100 ml) of glomerular filtrate, equivalent to a urinary excretion of 3.7 mmol (144 mg)/24 h at a glom-
erular filtration rate of 100 ml/min (Fig. 1). Thus when the plasma calcium is maintained at this concentration by the parathyroid feedback mechanism, the urine calcium is also maintained. The range of calcium excretion at this plasma calcium is also very similar to the range of lower limits defined by Morgan & Robertson. This lower limit of calcium excretion, governed by the lower limit of plasma calcium concentration, contrasts with magnesium and phosphate, where plasma concentrations are more labile, and the excretion can fall to very low values in deple-
tional states by reduction in plasma concentra-
tions (Marshall, Nordin & Speed, 1976).

Another factor complicating the recognition of hypercalciuria is the great intraindividual variation in urinary calcium. Although the relationship between urinary and dietary calcium in normal subjects is relatively flat (regression coefficient 0.06: Nordin, 1976), owing to the rather low absorption of dietary calcium, the corresponding slope in idiopathic male calcium stone-formers is much steeper (mean regression coefficient 0.20: Peacock, Hodgkinson & Nordin, 1967), so that diet plays a critical role in the calcium excretion of this group of calcium stone-formers, where recognition of hypercalciuria is particularly important. The intraindividual coefficient of variation of urinary calcium in normal subjects on a free diet is 11.2%, and of stone-formers 19%, whereas the corresponding values on fixed diets are 10.2 and 10.6% respectively (unpub-
lished results). Thus the intraindividual variation of urinary calcium in stone-formers on a free diet is much greater than that on a fixed diet, and also much greater than in normal subjects on a free diet. Some of this variation may also be seasonal, as there is significant seasonal variation in calcium excretion (Robertson, Gallagher, Marshall, Peacock & Nordin, 1974) in both normal subjects and stone-formers. The distinction that has been drawn by Coe, Canterbury, Firpo & Reiss (1973) between persistent and intermittent hypercalciuria is therefore a distinction without a difference, except insofar as hypercalciuria due to high

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**Fig. 1.** Normal relationship between mean plasma and urinary calcium concentrations, established by calcium infusions. The interrupted line indicates the normal lower limit.
calcium absorption is more likely to be 'inter-
mittent' than is hypercalciuria due to increased
bone resorption.

Classification

However hypercalciuria is defined, it is clear
that an absolute increase in urinary calcium can
only come from the diet or the skeleton, or both,
giving a classification into dietary, absorptive,
resorptive and absorptive plus resorptive
hypercalciuria (Nordin, Peacock & Wilkinson,
1972a, b).

Dietary hypercalciuria, due to a high dietary
calcium, is rare because the calcium intake has to
be extremely high (about 2 g daily) to produce
hypercalciuria when calcium absorption is
normal.

Absorptive hypercalciuria is characterized by
a raised urinary calcium on a normal intake
which falls towards or into the normal range as
the calcium intake is reduced; the fasting
urinary calcium/creatinine ratio is normal, as is
the fasting urine hydroxyproline/creatinine
ratio (Nordin, 1976b); calcium absorption is,
of course, increased, and tubular reabsorption
of calcium is normal (Peacock & Nordin, 1968).
This is the condition known as 'idiopathic
hypercalciuria', seen in many male idiopathic
calcium stone-formers.

Resorptive hypercalciuria is characterized by
a raised urinary calcium which is relatively
independent of dietary intake, that is present in
the fasting state and which is associated with a
raised fasting urinary hydroxyproline/creatinine
ratio. Calcium absorption may be normal or
low. It occurs in some cases of hyperpara-
throidism, in myelomatosis, hyperthyroidism
and in bone cancer.

The resorptive plus absorptive type combines
the features of both the above. Calcium absorp-
tion and the fasting calcium/creatinine ratio are
high, but the 24 h calcium excretion is even
higher; calcium excretion falls on a low calcium
diet but not into the normal range. The fasting
hydroxyproline/creatinine ratio is also raised.
This type of hypercalciuria is seen in many cases
of primary hyperparathyroidism and probably
in sarcoidosis.

Relative hypercalciuria arises when calcium
excretion is normal in absolute terms but too
high relative to (a) the diet or (b) the filtered
load of calcium. The former occurs when an
absorptive hypercalciuric subject has a restricted
calcium intake; the calcium output may fall
within the normal absolute range and yet be
higher than normal relative to the intake. In the
latter, calcium excretion may be normal in
absolute terms but too high relative to the
filtered load because tubular reabsorption of
calcium is reduced. This is seen in hypopara-
throidism and in some cases of renal failure
with hypocaemia (Cochran & Nordin, 1971).
If reduced tubular reabsorption of calcium ever
produces an absolute hypercalciuria, it can only
be because the calcium loss in the urine has
activated some mechanism which increases the
absorption and/or resorption of calcium, and
the hypercalciuria is then in the final analysis
absorptive or resorptive or both. No condition
in which this occurs is known, with the possible
exception of renal tubular acidosis; the sugges-
tion that this may be the mechanism of
idiopathic hypercalciuria will be discussed
below.

Pathogenesis

The above classification of hypercalciuria into
absorptive and resorptive types has now been
applied by Pak, Ohata, Lawrence & Snyder
(1974), by Pak, Kaplan, Bone, Townsend &
Waters (1975) and subsequently by other Ameri-
can groups. Pak et al. (1975) reported that six
out of thirty stone-formers had raised fasting
calium/creatinine ratios and attributed this to
tubular hypercalciuria. Polypchuk, Harrison &
Wilson (1976) reported seven cases of renal
hypercalciuria in a series of thirty-one stone-
formers and then used the data to prove, by a
somewhat circular argument, that the fasting
urine calcium cannot be used to distinguish be-
tween absorptive and renal hypercalciuria.
This reasoning results from an inadequate
understanding of the underlying mechanisms.
The relation between filtered and excreted
calcium is such that very small changes in the
former can produce relatively large changes in
the latter. This was shown by MacFadyen,
Nordin, Smith, Wayne & Rae (1965), who
measured plasma and urinary calcium in forty
subjects on normal and low calcium diets and
showed that the daily decrease of some 1–2
mmol (40–80 mg) that occurred in urinary
calcium could be explained by the reduction of
less than 0.05 mmol/l (0.2 mg/100 ml) which
occurred in the plasma calcium. Fig. 1 shows
why this should be so. In the normal range of
plasma calcium concentration, a rise of only 0.1 mmol/l (0.4 mg/100 ml) is beyond analytical resolution in any individual case, and would normally produce an increase in calcium excretion of some 0.025 mmol/l (0.1 mg/100 ml) of glomerular filtrate, which represents a doubling of the normal fasting urinary calcium excretion. An elevated fasting calcium/creatinine ratio associated with a plasma calcium value 'within the normal range' cannot therefore be attributed to tubular dysfunction without more exhaustive investigation, for it could arise from an undetectable increase in the fasting plasma calcium after incomplete elimination of the previous day's dietary load. Although we have shown that the absorption of calcium after an average meal is completed in about 6 h, and the elimination in a further 6 h (Nordin, Marshall, Peacock & Robertson, 1974), it cannot be assumed that this will invariably be the case in very high absorbers; some spill-over from the previous day's absorbed calcium may be seen, particularly if the fast has been less than 12 h. An occasional high fasting calcium/creatinine ratio in stone-forming cases was noted by Peacock, Knowles & Nordin (1968), who showed that a few hours of additional fasting brought these stray values into the normal range. Calcium infusion, with the measurement of calcium excretion at different levels of filtered load, is necessary to study the tubular handling of calcium in cases where the initial plasma calcium is within the normal range. When such infusions were performed by Peacock & Nordin (1968), the unequivocal conclusion was that tubular reabsorption of calcium was normal in idiopathic hypercalciuria. Any explanation of idiopathic hypercalciuria must account for an increased calcium absorption, normal tubular reabsorption of calcium (as judged by calcium infusions), normal fasting urinary calcium (or the calcium becomes normal if the fast is long enough) and for the calcium excretion approaching or falling within the normal range when the dietary calcium is sufficiently low. This evidence leaves little doubt that idiopathic hypercalciuria is absorptive in origin. Thus parathyroid hormone levels are more likely to be normal or low (Pak et al., 1974; Shen, Baylink, Nielsen, Hughes & Haussler, 1975; Peacock, Marshall, Robertson & Varnavides, 1976) than high (Coe et al., 1973). The tendency to low levels of the hormone (if correct) might produce a marginal reduction in tubular reabsorption of calcium but this would be secondary to suppression of parathyroid hormone and associated with high-normal plasma calcium levels, rather than a cause of stimulation of the hormone and associated with low-normal plasma calcium concentrations as Coe & Kavalach (1974) suggest. The mechanism of this hyperabsorption has not been understood until recently, but Haussler, Baylink, Hughes, Brumbaugh, Wergedal, Shen, Nielsen, Counts, Bursac & McCain (1976) have reported that plasma 1,25-(OH)2D3 is significantly raised in idiopathic hypercalciuria and suggest that this is the cause of the high calcium absorption. They attribute the raised mean concentrations of this active vitamin D metabolite to the significantly reduced mean plasma phosphate in their hypercalciuric patients, which then activates the renal 1-hydroxylase, raises the plasma concentration of 1,25-(OH)2D3, increases calcium absorption and (directly or indirectly) reduces the plasma level of parathyroid hormone (Shen et al., 1975). It should be noted that the slightly reduced plasma levels of parathyroid hormone reported by this group are compatible with some reduction in tubular reabsorption of calcium, but this would be regarded as secondary to suppression of the hormone rather than the cause of its stimulation as implied by Coe & Kavalach (1974). In all these data it is important to note that the abnormalities reported in idiopathic stone-formers are based entirely on mean values; all the variables studied show a large overlap between the normal and stone-forming populations. This is true of calcium excretion, of calcium absorption (Nordin, 1976b), of 1,25-(OH)2D3, of plasma phosphate concentrations (Haussler et al., 1976) and of levels of parathyroid hormone (Shen et al., 1975), and this remains true even if the hypercalciuric cases are considered separately. This suggests that these are not specific abnormalities but simply abnormal mean values due to selection by stone disease of individuals in the upper or lower parts of the various normal ranges. Clearly, if the risk of calcium stone disease were proportional to the urinary calcium, the mean calcium excretion of stone-formers would be high; if this excretion resulted from high absorption, the mean absorption would be
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high, and if this was due to 1,25-(OH)₂D₃, the mean high plasma level of this hormone would result from selection by stone disease of a certain part of the general population.

On this hypothesis it is possible to calculate the increasing stone risk due to rising urinary calcium from the ratio of the frequency in normal subjects and stone-formers at different calcium outputs. An increase in daily urinary calcium from 7.5 to 15 mmol (300 to 600 mg) increases the risk of calcium stone disease from about 1% in the population as a whole to about 6% in individuals with a urinary calcium over 15 mmol (600 mg)/day. Similarly, from the known distributions of radiocalcium absorption values in normal subjects and stone-formers, one can calculate that an increase in radiocalcium absorption from 0.3 to 2.0 of the dose absorbed/h has the same effect (Fig. 2). This increase in risk with increasing absorption and excretion of calcium does not prove the risk hypothesis, but is of a reasonable order of magnitude. This does not mean that one should not search for the mechanism of hyperabsorption in seeking the cause of idiopathic calcium stone disease, but it does mean that, because the variables under consideration are continuous, a specific abnormality peculiar to calcium stone-formers is unlikely to be found, although it should be possible to find a combination of abnormalities which distinguishes them.

Assuming then that high calcium excretors are more liable to calcium stone disease than normocalciuric individuals, it is legitimate to look at the factors which govern calcium absorption and excretion, and in this connection the data of Haussler et al. (1976) are extremely relevant. Even though they have selected their cases for hypercalciuria, there is still a considerable overlap in plasma concentrations of 1,25-(OH)₂D₃ between patients and control subjects, as expected on the risk hypothesis. The risk of calcium stone disease is increased in individuals with high plasma 1,25-(OH)₂D₃ concentrations because of their high calcium absorption and excretion rates, although the majority of their values fall within the normal range and would therefore be found in a proportion of normal subjects.

Nonetheless, there must be a reason why the plasma 1,25-(OH)₂D₃ concentrations are high even if they fall within the normal range, and Haussler attributes this to the significantly reduced mean plasma phosphate in hypercalciuric stone-formers. This hypophosphataemia is undisputed (Table 1). The evidence that hypophosphataemia activates renal hydroxylase is reviewed by Haussler et al. (1976) and supported by their own data and appears extremely convincing. However, although the mean plasma phosphate of stone-formers is low, most values fall within the normal range, unlike the plasma...
TABLE 1. Plasma phosphate concentrations in normal subjects and stone-formers

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<thead>
<tr>
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<th>Plasma phosphate (mmol/l)</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>1.02±0.13</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single stone-formers</td>
<td>0.85±0.17</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent stone-formers</td>
<td>0.89±0.12</td>
<td>23</td>
<td>&lt;0.001</td>
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phosphate concentrations in hypophosphataemic rickets, which clearly constitute a separate population.

Thus the problem of idiopathic hypercalciuria becomes the problem of why the plasma phosphate is lower in some individuals than others. This is well-trodden ground. The plasma phosphate concentration, like that of other electrolytes, is determined by the relation between flow (i.e. the net rate of input of phosphate into the plasma from the intestine, bone and soft tissues), glomerular filtration rate and tubular reabsorptive capacity (Bijvoet, 1969; Nordin, 1976a, b). The concentration of each of these molecules in plasma is positively related to flow and tubular reabsorption and negatively related to GFR. Thus as low plasma phosphate must result from a low flow, low tubular reabsorption or high GFR, or a combination of these factors, none of them by itself needs to be outside the normal range. The idea that the hypophosphataemia of hypercalciuria is due to low tubular reabsorption is expounded by Haussler et al. (1976) and by Coe & Kavalach (1974), but it is likely that this is an oversimplification. The significantly reduced mean plasma phosphate in stone-formers shown in Table 1 does not have a single cause. In some, low tubular reabsorption of phosphate is the main cause; in others, low flow; in others it seems to be a high GFR; but in most it is simply that the combination of these three variables is such as to produce a plasma phosphate below the normal mean value. Just as there are many ways of skinning a cat so there are many ways of reducing plasma phosphate. The search for the cause of hypophosphataemia in stone-formers is vain. There is no more a single cause for this abnormality than there is for calcium stone disease itself.

The conclusion has to be that the higher the urinary calcium, the greater the risk of calcium stone formation due to the increased risk of oversaturation of the urine with calcium salts (Robertson, Peacock, Marshall, Marshall & Nordin, 1976). The main determinant of urinary calcium in the population is the absorption of calcium (Davis et al., 1970). As far as we know, the main determinant of calcium absorption is 1,25-(OH)2D3, the production of which is regulated by parathyroid hormone and by the plasma phosphate concentration. The latter in turn is determined by the relationship between flow, GFR and tubular reabsorption. The risk hypothesis assumes that there exist normal individuals whose plasma phosphate for one reason or another is low enough to activate the renal hydroxylase sufficiently to produce sufficient calcium absorption to raise the urinary calcium. Perhaps in the final analysis, the Ca/P ratio of the Western diet is at fault. If we ate more phosphorus, our plasma phosphate concentrations would be higher and this chain of events would be less common. Alternatively, if we ate less calcium the effects of hypophosphataemia would perhaps be less important. It is a striking fact that the P/Ca ratio of Western diet is lower than that in most other areas. It is surely not without significance that phosphate feeding is increasingly recommended as the best treatment for calcium stone disease.

Significance

It is beyond the scope of this Editorial to explore in any detail the chain of events which leads from a high urinary calcium to an abnormal risk of stone disease, but it is worth noting that urinary tract stones provide a good example of the risk hypothesis which has been successfully applied to coronary heart disease (Dolder & Oliver, 1975). The cause of renal stones is probably an imbalance between the saturation of urine and its inhibitory activity (Robertson et al., 1976). Saturation with calcium oxalate depends mainly on the calcium and oxalate concentrations in the urine. The urinary calcium depends on the absorbed calcium and the latter (apparently) on the plasma phosphate. In addition to raised calcium and oxalate excretion, other major risk factors which can be identified are low urine volume and low inhibitory activity. Discriminant analysis shows that these are sufficient to separate the stone-formers from control subjects (Robertson et al., 1976), but
other minor factors (such as low urinary sodium and magnesium) are already known, and there are almost bound to be other minor risk factors not as yet identified. It is appropriate combinations of these risk factors which lead to renal stone disease. Future research into other diseases is likely to concentrate more on the identification of risk factors than on the discovery of single causes.

References


