CAUSES AND MECHANISMS OF HYPERCALCIURIA

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The estimation of urinary calcium is carried out with increasing frequency in many spheres of medical practice. It is, however, in departments dealing with renal stone that the investigation is most often performed and patients with so-called hypercalciuria detected. If the term is to be of any value in clinical work, it should in the first instance be clearly understood what is meant by hypercalciuria.

The term hypercalciuria implies an amount of calcium excreted daily in the urine above the values normally found. An upper limit of normal has therefore to be established and amounts in excess of this are regarded as constituting hypercalciuria. In routine work it is not practical to determine the 24-hour urinary output of calcium under standard conditions of diet, and the normal excretion is therefore defined as the amount excreted in 24 hours on an ordinary dietary regime. The normal, as in many biochemical estimations, will be a range of values, and the upper limit of normality under ordinary conditions of diet is the figure to be decided on.

Samson Wright[1] states that the amount of calcium excreted in the 24-hour urine varies from 50 to 250 mg. Cottet and Vittu[2] regarded the upper limit of normal as 200 mg. Ca in the 24-hour urine. Their upper limit of normality would appear to be too low, since 31% of their patients excreted amounts above this figure and were regarded as hypercalciurics. In a series of 162 normal patients investigated by Pyrah and Raper[3] under ordinary conditions of diet, the urinary calcium varied considerably; in 90·8% the 24-hour figure was below 250 mg.

It thus seems reasonable to conclude that the upper limit of normal urinary excretion of calcium is in the vicinity of 250 mg. per 24 hours, and that hypercalciuria may be arbitrarily defined as the excretion of more than 250 mg. of calcium in the 24-hour urine, under ordinary conditions of diet and in more than one 24-hour period. A finding of hypercalciuria, as thus defined, should stimulate further investigation of the patient. The causes are many and varied.

CAUSES OF HYPERCALCIURIA

The causes have been classified in the following manner:

EXTRA-RENAL

Metabolic
- Excessive ingestion of calcium
- Excessive ingestion of vitamin D
- Acidosis
- Recumbency
- Osteoporosis

Hormonal
- Cushing's disease
- Hyperparathyroidism

Systemic
- Sarcoidosis
- Multiple myelomatosis
- Paget's disease
- Metastatic osseous malignancy

RENAL

Secondary
- Infection
- Fanconi syndrome
- Hyperchloraemic acidosis

Primary
- Idiopathic hypercalciuria

Excessive Ingestion of Calcium

This implies a diet excessively rich in calcium-containing foods such as milk and cheese, or an abnormal addition

to the diet of excessive amounts of calcium, e.g. calcium-containing alkali powders. In such cases a reduction of the calcium-containing items in the diet will correct the hypercalciuria.

Excessive Ingestion of Vitamin D

The mechanism here is thought to be an increase in the absorption of calcium from the intestinal canal as a result of the excessive intake of vitamin D. This may occur in the treatment with large amounts of vitamin D of such conditions as resistant rickets, osteomalacia, arthritis, lupus vulgaris and hypoparathyroidism.

Acidosis

A common instance of this is the hypercalciuria which occurs during the administration of large amounts of ammonium chloride. The calcium is excreted in the urine as base to assist in the excretion of the excess of acid.

Recumbency

There is a marked increase in calcium excretion during periods of immobilization.[4] This increase commences a few days after recumbency begins and continues over a long period. It is thought to be due to a decrease in bone formation while bone resorption continues unabated. Hypercalciuria occurs more readily in the presence of sudden causes of cessation of bone formation such as immobilization for a fracture or poliomyelitis with loss of muscle action.[5] The degree of hypercalciuria depends on the discrepancy between bone destruction and bone formation.

Osteoporosis

This may be either senile or post-menopausal in type. Hypercalciuria may be present in the early stages of this condition but will no longer occur after the skeleton is demineralized.

Cushing's Disease

In this condition there is over-production of adrenal corticoid hormone causing osteoporosis and consequent hypercalciuria.

Hyperparathyroidism

This condition is an important cause of hypercalciuria.

There are two main theories on the mode of action of the excess of parathyroid hormone. Thomson and Collip[6] believe that the hormone stimulates osteoclastic activity, leading to widespread lacunar absorption, the liberated calcium and phosphate being absorbed into the circulation and the excess excreted by the kidneys. Jahan and Pitts[7] carried out animal experiments to test this theory and state that the hypercalcaemia (and resultant hypercalciuria), produced by the administration of parathormone are dependant on its extrarenal action of mobilizing calcium from the body stores, and not on any specific depression of renal tubular reabsorption of either calcium or phosphorus. Milne,[8] after experimental observations on human calcium metabolism, supports this theory, and further experimental work has been done by Stewart and Bowen[9] and Talmage *et al.*[10] to substantiate it.

The second theory is that of Albright,[5] who states that the excess of parathyroid hormone affects the renal threshold of the serum phosphates so that an excess is excreted in the urine. The fall in serum phosphate ions results in mobilization of calcium from the bones in order to maintain the solubility product at a constant level. The serum calcium is thus raised and any excess is excreted in the urine.

In both theories the mode of production of the hypercalciuria is explained in the same manner viz. by the excretion of the excess of serum calcium in the urine.

Sarcoidosis

Hypercalciuria is an occasional finding in sarcoidosis. In this condition there is no generalized bone decalcification, and the bone lesions, when present, are in the nature of circumscribed lesions of coarse trabeculation and sharply punched-out small cyst-like areas, chiefly in the hands and feet. Harrell and Fisher[11] found an elevated serum calcium in sarcoidosis, which was not confined to cases with bone disease, in 6 out of 11 cases investigated by them. Albright[5] reported a case with hypercalciuria, and Henneman, Carroll and Dempsey[12] investigated 2 such cases and state that the hypercalciuria is due to the endogenous production of a substance resembling vitamin D. Studies in their cases of sarcoidosis with hypercalciuria showed low calcium output in the faeces. This state could be reversed by giving cortisone. This effect of cortisone has been demonstrated by Dent[13] in cases of idiopathic hypercalcaemia of infancy, sarcoidosis, and ordinary vitamin D intoxication, and it forms the basis of his cortisone test. In this test 150 mg. of cortisone are given for 10 days and serum-calcium levels are estimated on the 5th, 8th and 10th days. The hypercalcaemia of sarcoidosis will rapidly fall during this time, usually to normal levels.

Multiple Myelomatosis

The serum calcium may be raised in multiple myelomatosis and then the amount of calcium in the urine is also high. These findings were present in a case of multiple myelomatosis described by Caylor and Nichol[14] and in a case of solitary myeloma reported by Nassim and Crawford.[15] These findings may give rise to difficulty in the differential diagnosis between multiple myelomatosis and hyperparathyroidism. The serum phosphorus is usually normal or raised in multiple myelomatosis but Snapper[16] reported a case with low serum phosphorus. Bence-Jones protein has been found in the urine in less than half of the cases of myeloma and when it occurs it may be continuous or periodic, and in scanty or large amounts. Bence-Jones proteinuria may also occur in myxoedema, leukaemia and carcinoma. The serum alkaline phosphatase however is usually normal in multiple myelomatosis and a rise, if present, is insignificant compared with that found in advanced hyperparathyroidism.[17] The mechanism of the hypercalcaemia is still unknown. It may be absent in the presence of widespread bone lesions and osteoporosis,[18] or it may be present in the absence of demonstrable bone lesions.[19]

Paget's Disease

Hypercalciuria may occur in this condition when the disease is advancing or when a patient with the disease is immobilized. In the active stage of Paget's bone absorption occurs with somewhat haphazard new bone formation, and calcification of the new bone is incomplete. There is thus a discrepancy between bone destruction and bone formation. As a rule there is no difficulty in establishing the diagnosis.

Metastatic Osseous Malignancy

Malignant secondary invasion of bone may give rise to hypercalcaemia and hypercalciuria. A primary source should be sought for in the common sites, viz. breast, prostate, kidneys, bronchus and thyroid.

Renal Infection

Acute pyelonephritis has been stated by Albright[5] to be an occasional cause of hypercalciuria. The mechanism by which this might occur is tubular damage and resultant faulty tubular reabsorption of calcium, leading to excessive excretion in the urine. This view is supported by a case of hypoparathyroidism described by Albright in which there was no calcium in the urine, but when a severe staphylococcal renal infection supervened the patient started excreting large amounts of calcium and as the condition responded to treatment with antibiotics the urinary calcium gradually returned to zero.

Renal Hyperchloraemic Acidosis

In this condition there is primarily a tubular dysfunction with no glomerular insufficiency. The nature of the primary pathological renal lesion in these cases varies, being either infective or degenerative.

The metabolic breakdown of the foodstuffs of a normal diet leads to a slight excess of fixed anions. These patients are unable to keep in proper acid-base balance and develop a metabolic acidosis with low plasma bicarbonate and high plasma chloride. The tubular defect may be considered to be a partial failure of sodium-hydrogen exchange leading to decreased excretion of ammonia and titratable acid and increased excretion of bicarbonate. Since sodium-hydrogen exchange is a mechanism of sodium reabsorption, one might expect that these patients would become depleted of sodium. This, however, does not occur to a significant degree because the urinary sodium is replaced by other fixed cations, mostly calcium and potassium. The exact tubular mechanisms responsible for the hypercalciuria are not well understood.

The diagnosis is made on the biochemical findings and the administration of base will correct the acidosis and the hypercalciuria.

Fanconi Syndrome

In addition to the other well-known manifestations of this condition, such as glycosuria and amino-aciduria, hypercalciuria may also be present, since the increased excretion of organic acids causes a secondary increase in the urinary excretion of base. Milne *et al.*[20] suggest that there may in addition be defective reabsorption of $NaHCO_3$. If this is correct it would be an added factor in the production of hypercalciuria.

Primary Renal Hypercalciuria

After all the known causes have been excluded, there still remain cases in which the urinary output of calcium is above normal. These patients excrete a large amount of calcium in the urine for any given serum-calcium level and independent of the dietary calcium. It is patients in this group that have been labelled idiopathic hypercalciuria. It has been suggested that these patients have had staphylococcal pyelonephritis in the past.[5] It is possible to theorize along these lines and postulate resultant permanent tubular damage leading to defective reabsorption of calcium as an isolated phenomenon. There is, however, no evidence to support this view, nor has it been possible up to now to demonstrate any pathological lesion of the kidneys in these cases, either by means of renal-function studies or histologically.

A wide variety of single or multiple biochemical abnormalities have been described as a result of disordered function of the proximal renal tubule. In the classical Fanconi syndrome the triple resorptive defect of glucose, phosphate and amino acids occurs and the best-known single resorptive defect is renal glycosuria.

It seems possible that hypercalciuria exists within this group of conditions as a further example of a single resorptive defect and that patients exhibiting this abnormality are the ones now referred to as idiopathic hypercalciuria. With this concept of the underlying cause this term should be discarded and the term primary renal hypercalciuria applied to these cases instead. If used in its intended sense within the above classification, a clearer picture of the causes of hypercalciuria will emerge. Further investigation is required to substantiate this concept.

SUMMARY

In this article hypercalciuria is defined, a classification of the causes is presented, and observations are made on the diagnosis of the various causal conditions and the mode of production of hypercalciuria in these. The use of the term 'primary renal hypercalciuria' is suggested to replace 'idiopathic hypercalciuria'.

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