CALCIUM ABSORPTION

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Abstract

The methods most commonly used to measure the absorption and retention of orally administered calcium are reviewed. Nearly all make use of calcium radioisotopes. The magnitude of calcium absorption and retention depends upon the chemical form and amount of calcium administered, and the clinical and nutritional status of the subject; these influences are briefly surveyed.

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1. INTRODUCTION

The intestinal absorption of calcium has clinical interest primarily in the investigation of nutrition and of certain diseases. In nutritional studies the chief point at issue is the absorbability of calcium from different foods (including drinking water), either singly or in combination. Numerous diseases are associated with an abnormal calcium status. In clinical studies where there is a suspicion of calcium deficiency, such as in secondary nutritional hyperparathyroidism, primary hyperparathyrodism, or acromegaly, increased retention of a standard oral dose of radiocalcium has diagnostic significance. Alternatively, in the presence of intestinal malabsorption, Cushing's disease, corticosteroid therapy, oral calcium therapy, and certain other conditions, decreased absorption is revealing. Calcium absorption and retention are also of interest in population studies of osteopenia[1,2] and possibly of cardiovascular disease.

In all these investigations, simple and reliable tests of calcium absorption and/or retention would be helpful. The objective of this paper is to give a brief review of the tests, most of which make use of radioisotopes, that have been developed for these purposes. It must be recognized that not all such tests measure the same physiological processes. In particular, one must distinguish between the amount of administered calcium absorbed (i.e., that which passes from the intestinal lumen into the body), the net amount absorbed (that which passes from the intestinal lumen into the body and does not return to the lumen), and the amount retained (that remaining in the body). Furthermore, all of these quantities depend upon the time after administration at which the observation is made.

2. METHODS

2.1 Calcium excretion vs. intake

The classical method for measuring the amount of administered calcium that is retained, or the net amount absorbed, is the calcium-balance study based on chemical analyses. In such studies the subject is usually equilibrated for a period of many days on a diet of constant calcium content. Retention is the difference between the amount ingested and the amount excreted, by all routes (including in principal the dermal route), during a period of several days. Net absorption is the difference between the amount ingested and the amount excreted in the faeces during this period. The time is ambiguous, since the interval between ingestion and excretion cannot be known without the use of tracers, but the results would normally reflect an average behavior over many days. An extensive review of this method has been published by Reifenstein et al.[3]. In practice the validity of the method may be compromised[4] by low accuracy in estimating calcium consumption, by incomplete collection of excreta, and by losses of calcium via the skin.

2.2 Radiocalcium excretion vs. intake

When interest focuses upon the percentage of a particular dose of calcium that is retained or absorbed, the results are much less ambiguous if radiocalcium is added to the dose to identify it uniquely and radiocalcium excretion is measured. Retention may be found if radiocalcium excretion by all routes is observed, and net absorption is deduced from measurements of faecal excretion alone[5,6,7]. This method is vulnerable to the previously mentioned sources of error, except ambiguity as to the administered dose. The use of non-absorbable markers along with the calcium isotope has increased the reliability of the faecal excretion data, but the method remains quite laborious if used in the clinical routine.

2.3 Plasma radioactivity

Attempts have been made[1,8,9,10] to estimate calcium absorption by measuring radiocalcium concentration in plasma after oral administration of the isotope. However, since the quantitative relationship between absorption and plasma concentration is influenced both by the volume of the plasma and by the comparative rates of absorption and clearance, the results can best be described as providing an index rather than a measure of absorption. A more nearly quantitative value can be calculated by comparing the plasma activity

after a subsequent intravenous dose, thereby cancelling out some of these influences[11,12,13].

2.4 Double-isotope methods

The plasma radioactivity test can be made to yield a much more accurate value of absorption by use of a second calcium isotope, namely by injecting this isotope intravenously shortly after the first isotope has been administered orally. An absorption figure is obtained from the ratio between the plasma concentrations of the two isotopes, relative to the respective amounts administered[5,10,14,15,16,17]. Due to the different rates at which the two isotopes reach the plasma, and to the possibly different fractions cleared in the intervals between administration and sampling, corrections to the raw ratio by means of kinetic analysis may allow a useful increase of accuracy[16,21]. The magnitude of the correction decreases as the time between administration and sample collection increases.

De Grazia et al.[5] found that even the isotopic ratio in the urine can be used to calculate the absorption, provided that the first 24-hour collection is discarded. They claim that the results with the urinary double-isotope method depend little upon the mass of carrier accompanying the oral dose.

2.5 Whole-body counting

Direct measurement of calcium retention can be made by whole-body counting. The first studies related to health were published in 1962 by Bohr et al.[22] and North et al.[23] using orally administered ^{47}Ca, and more systematic studies have been reported by Sjöberg et al.[24,25,26]. A suitable procedure for the test is to administer ^{47}Ca orally after an overnight fast and after a background measurement on the patient. A measurement 1 to 3 hours after administration is often used to obtain a so-called 100% value, namely the counting rate when 100% of the administered dose is in the body. Measurement is repeated 10 to 14 days later and the retained activity, expressed as a fraction of the administered dose, is taken as the ratio of the latter counting rate to the 100% value.

The reproducibility of the whole-body counting technique is good. Typically errors caused by counting statistics and by the effects of changes in the spatial distribution of the radionuclide between the initial and final measurements (altered location within body, changes in body position, etc.) total only a few percent. Measurements of retention after replicate administrations of ^{47}Ca to the same subjects by Sjöberg et al.[30] showed discrepancies

of about 15% of the mean retention value, these discrepancies being attributable not only to the afore-mentioned errors in technique but also to the biological variations of retention from day to day.

To deduce absorption values from the retention values directly measured by whole-body counting requires certain precautions and additional measurements. The presence in the intestine of unabsorbed tracer (e.g., 13% at 6 days[27], 0 - 2% at 10 days) requires that the whole-body count be made not earlier than 10 to 14 days after administration. During this period considerable excretion of previously absorbed tracer occurs, e.g., 20% of the administered dose in the urine (half of which may appear within the first 4 days[26]), and a comparable amount in the faeces[28,29]. That in the urine can be determined by collecting and measuring the urine, and a lower limit of absorption (sometimes called a "minimum absorption" value) can be calculated as the sum of the retention and urinary excretion. Reexcretion into the faeces cannot be directly observed. If its magnitude is about the same in health and disease, the "minimum absorption" value is well correlated with tracer absorption, and is clinically relevant. However, were an unrecognized elevation of faecal reexcretion present in certain diseases, the "minimum absorption" figure might depart so abnormally from the true absorption as to be clinically misleading.

2.6 Partial-body counting

Estimation of ^{47}Ca absorption has also been attempted from external measurements not of the whole body but of a part of it. A primary consideration has been to eliminate the long delay that is inevitably entailed if the intestines are in the detector's field of view and must therefore be cleared of unabsorbed tracer before a meaningful measurement becomes possible. Such measurements have most often been performed on an arm[18,19,20]. However, because many factors other than absorption influence the activity of the arm (or any other part of the body), several assumptions are required. Curtis et al.[19] were able to deduce a quantitative result by calibration with an intravenous injection: the counting rate of the arm was first measured after a small intravenous dose which was followed 3 hours later by the oral test dose.

3. EFFECT OF DOSE PARAMETERS ON ABSORPTION

Both the quantity and the chemical form of the calcium in the administered dose affect absorption. Most investigations have shown a somewhat higher absorption of calcium from the chloride than from the gluconate or lactate, or from milk[16,31,32]. The percentage absorbed decreases as the mass of

administered calcium increases, but the absolute amount absorbed increases at the same time[30,33].

Table 1 shows results of "absorption" tests obtained in control subjects by various authors using various quantities and chemical forms of calcium as the administered dose and various methods of assessing absorption, net absorption, or retention.

4. EFFECT OF CLINICAL PARAMETERS ON ABSORPTION

The scope of this paper allows only brief mention of the influence of clinical conditions upon absorption. For more comprehensive information readers are referred to earlier literature[26,34,35,36].

4.1 Nutritional factors affect the absorption of calcium both from test administrations in the laboratory and from food[37,38]. The percentage absorption of test doses of calcium is generally inversely related to the level of calcium in the diet. The absorption of calcium from the food is affected by, among other things, the phytate, phosphate, and fat content of the food.

4.2 Gastrointestinal disease also affects calcium absorption and retention. In idopathic and pancreatogenic steatorrhea, calcium absorption is inhibited[26]. A similar situation may prevail in some other forms of malabsorption. On the other hand, patients with the postgastrectomy syndrome (dumping syndrome), or with other conditions following partial gastrectomy, usually show no inhibition of the absorption of test doses of calcium salts, although calcium in food may be less well absorbed because of the maldigestion frequently seen in such patients.

4.3 Endocrine disease influences calcium absorption, which is stimulated by parathormone. In primary and secondary hyperparathyroidism, and in acromegaly, the absorption of calcium salts is thus increased[26]. However, in situations with hypercalcaemia, such as myeloma, where parathormone secretion could be expected to be inhibited, calcium retention remains normal (Table 2).

There are some indications that corticosteroids may inhibit calcium absorption[26,34]. Absorption may be moderately decreased in Cushing's disease and in patients being treated with corticosteroids. However, alternative explanations of this decrease also exist.

5. SUMMARY

Several methods have been developed to measure calcium absorption, or the related quantities net absorption and retention. These include comparison of calcium excretion with intake, comparison of radiocalcium excretion with intake, assay of plasma radioactivity, use of double-isotope techniques, whole-body counting, and partial-body counting. Where appropriate instrumentation is available, whole-body counting is a simple method for measuring retention. Technical errors in this method include those associated with counting statistics and irreproducibility in measurement geometry (a few percent), and incomplete clearance from the intestines of unabsorbed radiocalcium (only 0 - 2% after ten days). An estimate of absorption may be derived from the figure for retention by collecting and assaying the urine (typically containing 10 - 15% of the administered dose) and allowing a comparable amount for faecal reexcretion (which can be measured only by introduction of additional techniques).

The double-isotope plasma measurement method is a relatively simple procedure for directly measuring absorption, but its ability to distinguish between normal and pathological conditions has been studied less extensively than has that of the whole-body counting method.

Dose parameters that influence absorption include the chemical form and the amount of calcium. The percentage absorption normally decreases as the amount of carrier increases.

The clinical conditions that influence absorption include nutritional, gastrointestinal, and endocrinological factors. Absorption is generally decreased by a previous high calcium intake, by gastrointestinal malabsorption, and possibly by corticosteroids. It is increased by primary or secondary hyperparathyroidism and by acromegaly.

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TABLE I

ABSORPTION AND RETENTION OF CALCIUM IN SOLUBLE SUBSTANCES

Reference	Carrier		No. of Subjects	Method	Result					
					Net absorption		Absorption		Retention	
	Type	mg Ca			%	mg Ca	%	mg Ca	%	mg Ca
De Grazia and Rich[40]	Chloride	10	6	Faecal excretion	42	4.2				
Avioli et al.[41]	"	20	10	" "	48.8	9.8				
Kinney et al.[42]	"	30	19	" "	61.2	18.4				
Mautalen et al.[16]	"	200	20	" "	46.7	93.4				
Parsons et al.[43]	Milk	200	12	" "	26.0	52.0				
Jaworski et al.[44]	Lactate	300	8	" "	38.3	114.9				
Iwanovich et al.[45]	Carbonate	800	5	" "	13.8	110.4				
Curtis et al.[46]	Gluconate	200	10	External arm counting			22.9	45.8		
De Grazia et al.[5]	"	10	12	Double isotope urine ratio			67.5	6.8		
"	"	200	16	"			25.6	51.2		
"	"	500	6	"			21.8	109		
Tothill and Dellipani[47]	Milk	-	15	"			26.0	-		
Agnew et al.[48]	Chloride	10	19	Whole-body counting at about 1 week					36 -62	3.6- 6.2
Harris and Heaney[49]	"	20	9	"					38.2-59.1*	7.6- 11.8
Arman and Reizenstein[50]	"	50	12	"					37.6	18.8
Sjöberg et al.[30]	"	135	27	"					35.7	48.2
Sjöberg[26]	"	675	17	"					21.7	146.5
Bohr et al.[22]	Milk	-	2	"					6 - 6.8	-
Deller[51]	"	200	6	"					20 -32	40 - 64
Fischermann et al[52]	"	200	5	"					12 -24	24 - 48
Deller et al.[33]	Lactate	200	7	"					28 -54	56 -108
North et al.[23]	20mEqSr	-	6	"					10.2-16.5*	-
Sabol et al.[53]	-	-	7	"					34.6-42.2**	-

* Measured at six days

** Day of measurement not stated

TABLE 2. CALCIUM ABSORPTION AND RETENTION IN ENDOCRINE AND HAEMATOLOGICAL DISEASES

Disease Condition	No. of Subjects	Carrier		Mean Net Absorption* (%)	Mean Retention** at 2 weeks (%)	Reference
		Type	mg Ca			
Acromegaly	12	$CaCl_2$	135		40	Sjöberg[26]
	2	Milk	200	55		Parsons et al.[43]
Primary hyper-parathyroidism	9	$CaCl_2$	135		40	Sjöberg[26]
	2	Milk	200	67		Parsons et al.[43]
Osteoporosis	7	$CaCl_2$	135		27	Sjöberg[26]
	8	Milk	100	41		Cameron et al.[54]
	17	Milk	200	36		Parsons et al.[43]
Myeloma	14	$CaCl_2$	135		39	Killander et al.[55]
(Controls)	27	$CaCl_2$	135		29	Sjöberg[26]
	12	Milk	200	26		Parsons et al.[43]
	8	Milk	100	28		Cameron et al.[54]

* Derived from cumulative faecal excretion of radiocalcium

** Based upon whole-body counting of radiocalcium