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Bioavailability of trace elements

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The concept of trace element bioavailability is discussed. Methods of assessing bioavailability are described including chemical balance, rate of repletion, plasma appearance, isotopic methods (radioisotopes and stable isotopes), and in-vitro techniques. A brief summary is given of factors determining the bioavailability of iron, zinc, copper, manganese, selenium and other trace elements, with references to more detailed reviews where applicable.

INTRODUCTION

The study of the interrelationship between diet and the metabolism of trace elements poses a particular problem to nutritional scientists because many such elements are not well absorbed by the body. Thus a knowledge of trace element intakes is of very little use when assessing the nutritional adequacy of different diets. There are a large number of dietary and host-related factors that affect the absorption of minerals, and many of the physiological variables undergo temporal fluctuations and changes in response to homeostatic adaptive mechanisms. The complexity of the situation is the reason why this area of scientific research has progressed slowly over the past few decades and still has a long way to go. This paper briefly reviews the current state of knowledge with respect to trace element bioavailability in humans.

DEFINITION OF BIOAVAILABILITY

The concept of bioavailability is fairly simple; the problems arise in its determination. Bioavailability can be defined as the proportion of the total mineral in a food, meal or diet that is utilised for normal body functions. This involves various stages, each of which is affected by different dietary and physiological factors, as illustrated in Fig. 1. The amount of a mineral that is available for absorption is dependent upon dietary composition, gastro-intestinal secretions, and luminal interactions (Mills, 1985). The proportion that is taken up by the mucosal cells depends upon a number of host-related factors, and the degree of utilisation in the body depends again upon physiological factors as modified by the chemical form of the mineral.

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Trace elements can be broadly divided into one of three categories, high, medium and low bioavailability, depending upon how well the human body is able to absorb them from the diet. Iron is particularly poorly absorbed from the diet, and because iron deficiency is the commonest nutritional deficiency disorder in the world much of the research into trace element bioavailability has focused on iron. Despite our lack of understanding of the mechanism of iron absorption, much is known about factors affecting iron bioavailability. Zinc, copper and selenium have also received attention, and to a lesser extent manganese.

METHODS OF DETERMINING BIOAVAILABILITY

Chemical balance

A number of methods have been employed to assess trace element bioavailability, as shown in Table 2. Chemical (metabolic) balance, in which trace element intake and excretion is quantitatively measured over a fixed period of time (days or weeks), was the first method to be used but has various drawbacks: (1) it can only be used to study the whole diet, not individual foods or meals, (2) with elements that are not well absorbed, small errors in estimating intake or excretion can lead to large errors in calculating the balance figures, and (3) when introducing a dietary change sufficient time must be allowed for the body to adapt to the new diet. The efficiency of absorption plays a key role in maintaining the correct balance of certain trace elements, notably iron and zinc, but it is in fact part of the bioavailability equation. Given time, the body should adapt to high or low availability for absorption by increasing or decreasing its efficiency of absorption thereby maintaining homeostasis; when there is no physiological need to accrue a mineral, balance may

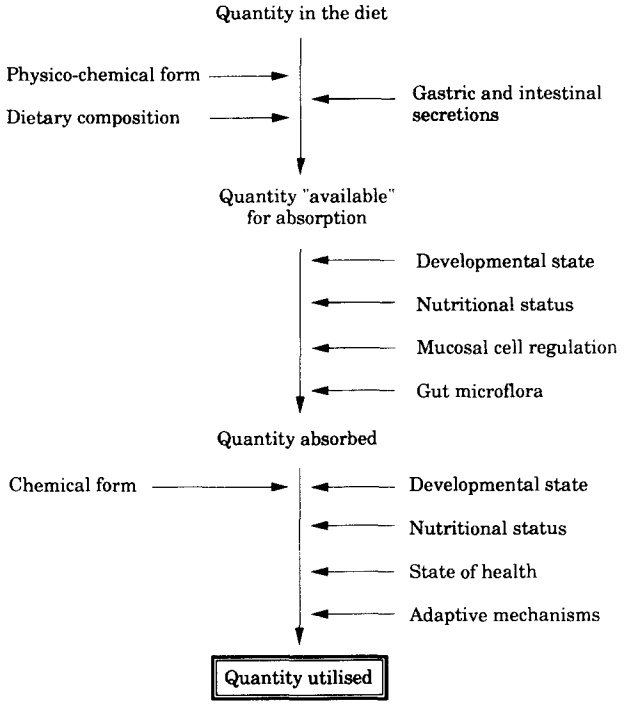

Fig. 1. The different stages of bioavailability.

well be zero, but under anabolic conditions or where storage is possible the balance may be positive. Thus the measured bioavailability of some trace elements is a constantly shifting variable. Although the metabolic balance technique provides an important basis for the characterisation of the state of mineral metabolism, it has limited use in the study of trace element bioavailability. For a general review of methods of studying intestinal absorption in man readers are referred to Sladen (1975).

Rate of repletion

Another approach to estimating bioavailability, particularly applicable to iron, is to measure the rate at which a depleted organism is repleted given different food sources of the element under study. In order to standardise results from different experiments the test materials are usually compared with a well-absorbed reference salt and the results expressed as the ratio between the two. As far as human subjects go, it is not easy to organise studies of this nature. However, this method could be usefully employed to investigate the efficiency of different sources (food and non-food) of an element in treating trace element deficiency.

Plasma appearance

Measurements of plasma appearance of an element following oral ingestion have been used with some success for highly concentrated sources of elements, such as zinc in oysters, or inorganic salts. The oral dose must be great enough to create an observable plasma tolerance curve, that is plasma appearance must exceed disappearance over the period of absorption from the gut. However, the results are at best only semi-quantitative and without giving pharmacological doses the method is not applicable to most food sources of trace elements.

Methods using radioisotopes

The advent of radioisotopes for research purposes enabled considerable progress to be made in the field of trace element bioavailability. It became possible to study individual foods by biosynthetically labelling them with a radioisotope of the element under investigation, as for example employed by Moore and Dubach (1951) to study iron absorption. A significant advance was made in the early 1970s when the use of extrinsic radiolabels was shown to be a valid technique for the measurement of food iron bioavailability (Cook *et al.*, 1972). The radioisotope is assumed to mix completely with the endogenous element and by following the fate of the isotope the absorption and metabolism of the element in the food can be measured. The application of this method for studies of other trace elements such as zinc requires further investigation.

The absorption of the isotope can be measured using the balance technique, i.e. by deducting faecal and urinary excretion from the administered dose over the appropriate time period. Alternatively, where it is convenient to give a γ-radioisotope and a whole body counting facility is available, retention in the body can be measured directly, which has obvious advantages over the balance-type method. However, measures of retention can only be equated with absorption when there is negligible excretion of absorbed isotope over

Table 1. Relative ease of absorption of trace elements

Low (<25%)	Medium (25–75%)	High (>75%)
Fe	Zn	F
Si	Cu	I
Mn	Se	Selenomethionine
V	Mo	B
Ni		Co
Cr		

Table 2. Methods used to assess trace element bioavailability

Chemical balance	
Rate of repletion following depletion	
Plasma appearance	
Radioisotopes	(a) balance technique
	(b) whole body retention (γ-isotopes)
	(c) plasma appearance
	(d) Hb incorporation (Fe)
Stable isotopes	
In-vitro techniques	

the experimental period. This is certainly true for iron, but for elements such as zinc measures of retention always underestimate absorption, especially when subjects are consuming a high-zinc diet and hence excreting quite large quantities of endogenous zinc in the faeces (King & Turnland, 1989).

Plasma appearance of an isotope from a labelled food or meal can be used to indicate trace element bioavailability; the main advantage of using radioisotopes is that the isotope is used as a tracer for normal food and dietary levels of trace elements. Before using this type of approach to study bioavailability it is important to establish that the isotope follows the same metabolic behaviour as the trace element in the food or meal. In comparative bioavailability studies the characteristics of radioisotope absorption kinetics may be useful for determining relative differences in absorption rates between different sources of the trace element under study (Gibaldi & Perrier, 1982).

Measures of absorption or retention are often used to assess trace element bioavailability because of the lack of reliable and sensitive methods to determine the utilisation of the element in the body. Iron, however, is an exception. Since about 80% of absorbed iron is used for haemoglobin production, the enrichment of red cells with radio-iron 14 days after oral administration can be used to assess dietary iron bioavailability. The exact percentage incorporation of absorbed radio-iron into red cells can be determined by using two different radioisotopes (^{55}Fe and ^{59}Fe), one administered orally and the other intravenously (Bothwell *et al.*, 1979).

Stable isotopes

There are limitations to the use of radioisotopes in human studies which relate to the hazards associated with exposure to ionising radiation. There is no consensus with regard to the ethical considerations involved in the use of radioisotopes for nutritional research. Both between and within countries, different ethics committees will view the same issue differently. However, it is generally agreed that radioisotopes should not be administered to pregnant or lactating women, or to babies and children. Thus, scientists have turned to stable isotopes as a safe alternative to radioisotopes (Turnland & Johnson, 1984). For a review of isotopic tracer methodology see Weaver (1988).

Stable isotopes are naturally occurring nuclides of an element with the same atomic number but differing numbers of neutrons. They have similar chemical properties, but differ in mass and, unlike radioisotopes, pose no known hazards to experimental subjects. Apart from ethical considerations they do have another advantage over radioisotopes, namely a greater potential for multi-isotope studies; some elements such as zinc and selenium have several useful stable isotopes. Conversely, however, some trace elements are monoisotopic, including aluminium, manganese, and cobalt and cannot be studied by means of stable isotopic techniques. The measurement of stable isotopes is more difficult than that of radioisotopes and generally requires more extensive sample preparation. Mass spectrometry and neutron activation analysis are the two methods used, both of which are highly specialised and comparatively expensive analytical techniques. Stable isotopes can be used in exactly the same way as radioisotopes, but larger doses need to be administered, so they are rarely if ever used in true 'tracer' quantities. Thus the validity of using them as extrinsic labels for bioavailability studies needs addressing (Fairweather-Tait *et al.* 1991). Metabolic balances, plasma appearance and, for iron, Hb incorporation are appropriate techniques, but obviously whole body counting is not possible.

In-vitro techniques

The determination of trace element bioavailability is an arduous task, and many attempts have been made to devise a quick and easy way to assess the bioavailability of different foods and diets. For example, they have been subjected to simulated digestion and the amount of soluble, ionisable or dialysable iron has been measured as an index of bioavailability (Lock & Bender, 1980; Hazell & Johnson, 1987; Miller *et al.*, 1981). Attempts have been made to calculate available dietary iron by employing various factors to take into account the presence of enhancers of absorption, namely haem iron and ascorbic acid (Monsen *et al.*, 1978).

Animal models, particularly pigs, can be a useful indicator of the in-vivo situation; and rodents are often used in the first instance, followed later by studies in humans. But the use of animal models may not be possible or even appropriate, and therefore various attempts have been made to develop an in-vitro system for evaluating trace element bioavailability (see relevant papers in Southgate *et al.*, 1989). As with other techniques, iron has received the most attention, but as yet no method has been developed that accurately represents the in-vivo situation. In any case, it would only be possible to determine the proportion of the trace element that is available for absorption, because the in-vitro methods do not include any of the physiological determinants of bioavailability, some of which greatly modify the absorption and subsequent metabolism of trace elements.

ABSORPTION OF DIFFERENT ELEMENTS

Iron

Iron is absorbed by two separate pathways (1) haem iron (derived mainly from haemoglobin), and (2) non-

Table 3. Factors affecting non-haem iron absorption

Positive	Negative
Dietary	
Ascorbic acid	Phytate
Citric acid	Wheat bran
Succinic acid	Polyphenols
Animal protein	Tea
Alcohol	Coffee
Some amino acids (e.g. cystein)	Eggs
Fructose	Calcium
	Trace elements (Cu, Zn, Mn. Co)
Physiological	
Iron deficiency	Iron overload
Gastric acidity	Achlorhydria
Previous low-iron diet	Previous high-iron diet
Anabolic conditions (e.g. pregnancy, childhood)	Malabsorption syndromes

haem iron. Haem iron is taken up into the intestinal mucosal cells as the intact iron-porphyrin complex, and its absorption is not influenced to any great extent by dietary factors, nor by the iron status of the subject. On the other hand, non-haem iron, which is probably taken up into the mucosal cells by a transferrin-like receptor, is markedly influenced by a great number of dietary and physiological factors (Hallberg, 1981). Some of these are shown in Table 3. Haem iron is absorbed more efficiently than non-haem iron, but even in diets with a high meat content it only accounts for about 10–15% of the total iron intake.

The efficiency of absorption of iron is dose-dependent; all forms of dietary iron enter one of two common pools, haem and non-haem iron. In general, about 25% of the haem iron in meals containing meat is absorbed, and 10% of the non-haem iron. The latter figure is variable depending on the quantity and mix of enhancers and inhibitors present in the meal. Absorption from individual foods is even more variable, ranging from less than 1% to more than 20% in normal individuals.

Zinc

Zinc is absorbed more efficiently than iron; in Western-type diets about 40% of dietary zinc is absorbed. Unlike iron, the body excretes substantial amounts of zinc via intestinal secretions as part of its homeostatic regulatory mechanism (Matseshe *et al.*, 1980). The efficiency of absorption of zinc is related to body zinc status, being greater in zinc deficiency and lower under conditions of zinc excess (Fairweather-Tait, 1988).

Diet plays an important role in determining zinc bioavailability (Solomons, 1982). Phytate forms an insoluble complex with zinc, thereby reducing its availability for absorption; calcium accentuates this effect by forming complexes that are even less soluble. There is competitive inhibition with other minerals of similar chemical properties (e.g. iron and copper) which if present in sufficient quantities will reduce zinc absorption (Flanagan, 1989). Animal protein has been shown to improve zinc bioavailability, and zinc in human milk is noted for its high bioavailability. The reason for the higher absorption of zinc from human than from cows' milk has not yet been established.

Copper

Copper absorption in humans ranges from 25 to 70% (Davis & Mertz, 1987). The efficiency of intestinal absorption is regulated by both the nutritional status of the individual and a number of dietary factors (August *et al.*, 1989). Since the body is able to excrete copper in bile and via the kidneys, excretion also contributes towards the maintenance of homeostasis. Ascorbic acid, fructose and phytate reduce copper absorption. However, the inhibitory effect of phytate is less pronounced than with zinc. Other trace elements, if present in sufficiently high concentrations, have an antagonistic effect on copper absorption, including zinc, iron and molybdenum. Protein generally increases copper absorption, as do certain amino acids.

Manganese

Only about 3–4% of dietary manganese is absorbed, and the efficiency of absorption appears to be independent of dose and body manganese status (Hurley & Keen, 1987). The form of manganese affects its absorbability; manganese in meat and fish is better absorbed than that in legumes, and human milk better than cows' milk. The manganese in human milk is found mostly in the whey whereas in cows' milk it is present primarily in the casein fraction. Iron inhibits manganese absorption.

Selenium

The chemical form of selenium not only determines its absorption but also its subsequent utilisation in the body, as illustrated by the different tissue distributions observed in animals following the administration of different dietary sources of selenium (Hazell, 1985). Selenomethionine, the predominant form of dietary selenium, is well-absorbed over a reported range of 76 to 100%. Inorganic selenium comprises only a small fraction of the total in foods; selenate is absorbed more efficiently than selenite. Results from animal studies suggest that there are differences in the bioavailability of selenium from different plant and animal foods.

Other trace elements

Inorganic chromium compounds are poorly absorbed

(<3%), regardless of dose or chromium status, but there is some evidence that chromium complexes in the diet are more available than simple chromium salts (Anderson, 1987). Silicon absorption is greatly influenced by its chemical form. Balance studies indicate that about 30–50% of silicon is absorbed, much of which is excreted through the kidney (Nielsen, 1988). Molybdenum is moderately well absorbed (25–80%) and like silicon it is rapidly turned over and eliminated via the kidney. Nickel and vanadium are both very poorly absorbed, and are subsequently excreted via the kidney (Nielsen, 1988).

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