

Supplements: questions to ask to reduce confusion¹⁻³

Peggy R Borum

ABSTRACT Written and oral statements concerning supplements are delivered daily to audiences that span the full spectrum of demographics. Yet the common reaction of these audiences to these statements is that they are receiving mixed messages. One source of this confusion could be greatly reduced if each statement concerning supplements always defined the specific parameters of the studies on which the statement is based. Those receiving information about supplements must be made aware that extrapolation of data for one form of a supplement to predict the result of another form may be harmful to one's health. If a statement concerning a supplement does not clearly define the route of delivery, its matrix, the quantity of compound, the purity of compound, and the physiologic condition of the recipient, the statement should be disregarded by all audiences. If the creators of all types of supplement information define these parameters, and if audiences critically review the information provided, confusion concerning supplements will be reduced. *Am J Clin Nutr* 2000;72(suppl):538S-40S.

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INTRODUCTION

Although not the legal definition (1), the term *dietary supplement* is applied by practitioners and the public to a wide variety of products, including food, special formulas, pills, and intravenous infusions. Broadcast media, printed media, the Internet, product information, and scientific literature often make statements concerning supplements. The audiences, or recipients, of these statements span the full spectrum of demographics. Yet the common reaction of these recipients is that they are receiving mixed messages.

One source of confusion that requires great effort and time to eliminate is the lack of the data needed to address dietary supplementation. However, if each statement concerning supplements always defines the specific parameters of the studies on which the statement is based, one current source of confusion will be eliminated. Unfortunately, some reports of studies in the scientific literature do not clearly define all of these parameters. To eliminate this source of confusion, the creators of all types of supplement information must define these specific parameters, or audiences must ignore information that does not include the needed parameters.

Every time scientists or consumers evaluate supplement information or apply it to themselves, they must ask some simple questions. These are as follows: what is the route, matrix,

quantity, and purity of the supplement, and what is the physiologic status of the recipient?

COMPOUNDS, NUTRIENTS, AND MEDICATIONS

For the purposes of this discussion, the components of dietary supplements are termed *compounds*. The same chemical compound may be both a nutrient and a drug. For example, niacin has been long recognized as an important nutrient in the diet, has been added to fortified flour, has been a component of daily vitamin pills, and has been used as a medication in many patients (2). Although all of these uses of niacin are termed *supplementation*, their effects on the recipient are not the same. The manners in which these compounds are presented to the body are various, as shown in **Table 1**.

At the beginning of this century, these compounds were presented to the body in the form of food. After the discovery of the critical role of micronutrients in metabolism, and the occurrence of devastating deficiency diseases that resulted when the diet did not contain these micronutrients in adequate quantities, vitamin supplements began to be widely distributed. Complete liquid formulas for infants who were not receiving breast milk and complete liquid, low-residue formulas for the space program were later developed. Using this technology, scientists developed complete formulas and new enteral methods of delivery with tubes for patients who for medical reasons could not consume a diet in the usual manner. Today, messages from the public media suggest benefits for many healthy adults who consume some of these complete liquid formulas as a supplement to their usual diet. During the last third of the 20th century, special formulas and administration techniques were developed to permit total parenteral nutrition. Individuals whose gastrointestinal tract is either non-functional or has been surgically removed are maintained on total parenteral nutrition. Thus, dietary components, compounds, or nutrients are delivered to the body in a variety of ways.

A growing body of data suggests that a compound required in the diet in a quantity sufficient to prevent well-described deficiency

¹From the Department of Food Sciences and Human Nutrition, University of Florida, Gainesville.

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³Address reprint requests to PR Borum, 409 Food Sciences and Human Nutrition Building, University of Florida, Gainesville, FL 32611-0370. E-mail: prb@gnv.ifas.ufl.edu.

TABLE 1
Delivery of compounds to the body

Delivery form	Route	Matrix	Quantity
Food	Enteral	Very complex	Dietary quantities
Daily vitamins	Enteral	Simple	Dietary quantities
Complete liquid formulas	Enteral	Complex	Dietary quantities
Parenteral nutrition solutions	Parenteral	Simple	Dietary quantities
Fortified food or functional food	Enteral	Very complex	> Dietary quantities
Megadose vitamins or oral drugs	Enteral	Simple	> Dietary quantities
Complete formulas for specific diseases	Enteral	Complex	> Dietary quantities
Intravenous drugs	Parenteral	Simple	> Dietary quantities

diseases may be delivered to the body in higher quantities to prevent or to treat other undesired conditions. For example, folic acid requirements were recently reevaluated and some have concluded that the recommended dietary allowances (RDAs), now referred to as the daily reference intakes (DRIs), should be changed (3). Various compounds have been added (sometimes in quantities greater than those typically consumed in the diet) to products known as fortified foods, functional foods, megadose vitamins, oral drugs, complete formulas for specific diseases, or intravenous drugs.

The same compound may be delivered by different routes, in different matrices, and in different quantities to recipients who are in different physiologic states. However, each of these forms of the compound have been termed *supplementation*. Not surprisingly, statements concerning supplementation, based on these various delivery methods of the same compound and the accompanying different effects on the recipient, do indeed give their audiences mixed messages.

CARNITINE: NUTRIENT AND DRUG

This discussion is applicable to many compounds, but carnitine will be used for illustrative purposes. Carnitine biosynthesis in the body requires 2 essential amino acids and several micronutrients. Dietary carnitine is found predominantly in animal products and is known to facilitate β -oxidation of long-chain fatty acids by transporting the fatty acids into the mitochondrial matrix, where the enzymes of β -oxidation are located (4).

Many other functions of carnitine are being investigated and some of these functions may be more critical to the recipients of carnitine supplementation than carnitine's role in facilitating fatty acid oxidation. Exogenous carnitine is not required by healthy adults to maintain health and thus it is not considered an essential nutrient. However, carnitine is being vigorously investigated as a conditionally essential nutrient because exogenous carnitine appears to be required during certain physiologic conditions, such as during the newborn period and during a variety of pathologies (5). The evidence that carnitine is a conditionally essential nutrient for newborns led manufacturers of infant formula more than a decade ago to add carnitine at concentrations found in breast milk to formulas not containing endogenous carnitine. Currently, however, none of the parenteral nutrition solutions available in the United States and frequently used to maintain preterm neonates contain carnitine (5).

Vegan diets contain little or no carnitine. The typical US diet provides $<5\text{mg}\cdot\text{kg}\cdot\text{d}$ of carnitine, but many patients receive carnitine at a dosage of $\geq 100\text{mg}\cdot\text{kg}\cdot\text{d}$. Pharmaceutical-grade carnitine is commercially available in the United States for both enteral and parenteral administration.

The Internet and the print media currently advertise a multitude of products that contain carnitine and suggest that carnitine supplementation is beneficial to many different types of people. Many of these advertisements suggest that carnitine will enable the recipient to either lose weight or improve physical performance.

ROUTE, MATRIX, AND QUANTITY OF COMPOUND

As listed in Table 1, when a compound is delivered to the body in food, the compound is supplied by an enteral route, in a complex matrix, and at dietary quantities. When the compound is delivered in the form of daily vitamins, it is provided by an enteral route, in a simple matrix, and at dietary quantities. When the same compound is delivered in complete formulas, it is provided by an enteral route, in a complex matrix and in dietary quantities. When the same compound is delivered by parenteral nutrition, it is provided by a parenteral route, in a simple matrix, and in dietary quantities.

When the compound is presented in functional foods, it is supplied by an enteral route, in a very complex matrix, and in greater than dietary quantities. When the same compound is delivered in megadose vitamins or oral drugs, it is provided by an enteral route, in a simple matrix, and in greater than dietary quantities. When the same compound is delivered in complete formulas for specific disease groups, it is provided by an enteral route, in a complex matrix, and in greater than dietary quantities. When that same compound is delivered in intravenous drugs, it is provided by a parenteral route, in a simple matrix, and in greater than dietary quantities.

A compound delivered to the body via the gastrointestinal tract is absorbed by a completely different mechanism than is one that is delivered to the body intravenously. However, other differences in metabolism of the compound may occur if the orally ingested compound is metabolized by enterocytes or is metabolized by the first pass through the liver. Several amino acids that are not essential in an oral diet become essential during parenteral nutrition. Drugs administered orally or intravenously do not have the same pharmacokinetics with both routes of administration. Examples of differences in route of administration are foods compared with parenteral nutrition and oral drugs compared with intravenous drugs.

The absorption and metabolism of a compound may be significantly altered by the presence of other compounds. There are many well-documented examples of the absorption of a compound being decreased or increased by the chemical composition of the matrix or even of the liquid consumed with the micronutrient. For example, the iron in a serving of liver will be absorbed quite differently from the iron in a vegan diet. Also, the iron in an iron supplement capsule

will be absorbed quite differently if it is taken at breakfast with a cup of tea or with a glass of orange juice (6). Food, complete formulas for specific disease states, and oral pills clearly present a compound to the body in very different matrices. However, the data from one of these delivery forms are frequently and incorrectly used to suggest what should be expected from one of the other forms.

Examples of the differences in matrix of delivery of a compound include food compared with daily vitamins and complete formula for specific disease states compared with oral drugs. Carnitine is transported across the gastrointestinal tract by both active and passive processes, and the percentage of carnitine absorbed compared with that excreted is greatly modified by the quantity being presented to the gastrointestinal tract. In addition, the metabolism of carnitine by the enterocyte may be altered by the quantity of carnitine being presented. Many studies have evaluated the potential beneficial effect of carnitine on symptoms such as anemia and exercise tolerance in renal patients on hemodialysis (7). Many questions remain unanswered, however, including what quantity of carnitine should be presented. Some investigators have administered quantities of carnitine to patients on hemodialysis greater than those consumed in the diet of most populations, with what they consider to be very beneficial effects. Other investigators have found that quantities closer to those consumed in the diet by many healthy populations give more beneficial effects. However, the data from one of these delivery methods are frequently and incorrectly used to suggest what would be expected from one of the other delivery methods. Examples of differences in quantity of a compound in its delivery include food compared with fortified food, daily vitamin compared with oral drug, complete formula compared with formula for specific disease, and parenteral nutrition compared with intravenous drug.

Thus, supplemented compounds are delivered to the body in many different ways. Sometimes the process is termed *nutrition* and sometimes it is termed *drug treatment*. In no case, however, can one assume that the effects seen with one delivery of the compound will occur if the compound is delivered in a different way.

PURITY

The purity of a compound is also very important. If a 1-g capsule of carnitine is not pure, there are 2 potential problems: the recipient is not receiving the 1 g of carnitine that he or she supposedly needs, and he or she is also receiving an unknown compound that may cause harm.

Most recipients assume that any compound being administered to them is pure. For pharmaceutical-grade compounds, documented quality-control checks are required to support that assumption. However, these checks are not required for compounds that are not drugs. As with many other compounds, non-pharmaceutical-grade carnitine products have been shown to vary widely in their purity, from 100% pure to undetectable concentrations (8). With some products, the capsules within a single bottle actually vary in purity. However, statements on the bottle often do not include any reference to the purity of the compound.

PHYSIOLOGIC STATE OF THE RECIPIENT


One reason compounds are delivered to recipients in different quantities, in different matrices, and by different routes is

that the physiologic states of the recipients differ and therefore so do their needs. Even if one assumes that the preterm neonate, the child with an inborn error of metabolism, the renal patient on hemodialysis, and the weekend athlete would all benefit from exogenous carnitine, their needs or their metabolism of the supplemented carnitine would not be the same. However, data from a recipient in one physiologic state are frequently and incorrectly used to suggest what should be expected from supplementation of a recipient in a very different physiologic state.

CONCLUSIONS AND RECOMMENDATIONS

Supplement information is confusing to many audiences. On the basis of current knowledge, the following recommendation could be implemented today by the creators of all information concerning supplements: Any statement concerning supplementation of a compound should define its route of delivery, its matrix, the quantity of the compound, the purity of the compound, and the physiologic condition of the recipient. Users of supplement information should ask the following simple questions and when evaluating supplement statements should disregard statements that do not address these questions:

- What is the route of delivery of the supplement?
- What is the matrix of the supplement?
- What is the quantity of the supplement?
- What is the purity of the supplement?
- What is the physiologic condition of the recipient?

All users of supplements should be aware that extrapolation of data from one delivery form of the supplement to predict the result of another delivery form may be harmful to their health. All users of supplement information and all creators of supplement information, whether they are scientists designing a new experimental study, individuals considering policy recommendations affecting large numbers of people, or health-conscious individuals hoping to improve a healthy lifestyle, should always ask questions about route, matrix, quantity, purity, and the physiologic status of the recipient who will use the supplement. 

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