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Review

Biomarkers of carotenoid bioavailability

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ABSTRACT

The use of biomarkers constitutes an essential tool to assess the bioavailability of carotenoids in humans. The present article aims to review several methodological, host-related and modulating factors relevant on assessing and interpreting carotenoid bioavailability. Markers for carotenoid bioavailability can be broadly divided into direct, biochemical or "analytical" markers and indirect, physiological or "functional" indicators. Analytical markers usually refer to biochemical indicators of intake and/or status (short and long term exposure) while functional measures may be interpreted in terms of cumulative exposure, biological effect (bioactivity) or modification of risk factors. Both types of markers display advantages and limitations but, in general, a relationship exists among the type of marker, the biological specimen needed and the time required for a change. Humans may absorb a wide range of carotenes and xanthophylls and many of them may be found in serum and tissues. However, under physiological conditions, the several classes of dietary carotenoids may behave unequally leading to a different systemic profile and, moreover, they can be selectively accumulated at target tissues. In addition, some carotenoids may be chemically and enzymatically modified generating different oxidative metabolites and apocarotenoids. Quantitatively, the biological response upon carotenoid intervention (assessed by analytical and functional markers) is highly variable but the use of large doses and long-term protocols may lead to saturation effects and the loss of linearity in the response. Also, despite carotenoid exposition is considered to be safe, markers of overexposure include clinical signs (i.e. carotenodermia, corneal rings and retinopathy) and biochemical indicators (hypercarotenemia, xanthophyll esters). Overall, both host-related and methodological factors may influence analytical and functional markers to assess carotenoid bioavailability although the different subclasses of carotenoids may not be equally affected.

Contents

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1. Introduction

Carotenoids are fat-soluble pigments of plant origin that humans cannot synthesize although they can partially modify them. From a nutritional and physiological viewpoint, interest in carotenoids has been focused on the provitamin A activity of some of them but carotenoids also display other biological functions that may confer beneficial effects against chronic diseases.

Prior to exerting their bioactivity, however, these compounds must be bioavailable. Bioavailability can be defined as the proportion of a dietary nutrient (or its metabolites) that is ultimately available for utilization or storage by target tissues after digestion, absorption and distribution (Ball, 1998). Nevertheless, because of the practical and ethical difficulties when measuring bioactivity and because of nutritional status also determine the amount of a nutrient that the body may use, store or excrete, the term "bioavailability" is usually referred to as the fraction of a given compound or its metabolites that reaches the systemic circulation without considering bioactivity (Carbonell-Capella, Buniowska, Barba, Esteve, & Frígola, 2014; Holst & Williamson, 2008).

In vitro models based on human physiology have been developed as simple and reproducible tools to study digestive processes (i.e. stability, micellization, intestinal transport) and to predict the bioavailability of different food components (i.e. carotenoids). Overall, reasonable correlations between in vitro bioaccessibility, in vivo observations and results from human bioavailability trials have been reported. Broadly, for lutein, β-carotene, lycopene and β-cryptoxanthin both qualitative and (semi)quantitative correlations have been found suggesting that in vitro bioaccessibility can be indicative of the amount available for uptake in the (in vivo) gastrointestinal tract (Bohn et al., 2015; Granado-Lorencio, Olmedilla-Alonso, Herrero-Barbudo, Pérez-Sacristán, & Blanco-Navarro, 2007b; Granado-Lorencio et al., 2007a; Maiani et al., 2009; Reboul et al., 2007). Caco-2 cells have been also used as surrogate for enterocytes and human absorption, including chylomicron secretion (Failla & Chitchumroonchokchai, 2005). Nevertheless, different Caco-2 cell lines may generate distinct metabolite profiles and these cells take up a wide range of carotenoids, even those not detected in human serum (i.e. neoxanthin, xanthophyll esters) (During, Hussain, Morel, & Harrison, 2002; Failla & Chitchumroonchokchai, 2005; Sugawara et al., 2001), a fact that compromise its comparability with in vivo (human) situations.

In general, the behaviour of carotenoids under in vitro gastrointestinal conditions does not fully explain the changes observed in vivo (Bohn et al., 2015). In vitro models may provide relevant information regarding food factors influencing bioavailability but they cannot totally simulate in vivo human situations, especially those concerning biological variability, timing of intervention, postprandial metabolism and distribution, and biological effects upon regular intake (Granado-Lorencio, Donoso-Navarro, Sanchez-Siles, Blanco-Navarro, & Pérez-Sacristán, 2011). Overall, carotenoid bioavailability in animals and humans have been approached using different methods including balance studies, dose-effect relationships and isotope-labeled compounds plus compartment modeling (Ball, 1998; Bohn, 2008; Failla & Chitchumroonchokchai, 2005). However, regardless of the method used, absorption, status, distribution and storage in humans are assessed with the use of biochemical markers.

Within this context, the present article aims to review several methodological, host-related and modulating factors relevant on assessing and interpreting carotenoid bioavailability. We briefly describe approaches and variables affecting the assessment of the bioavailability of carotenoids in humans, including the type of markers, analytical issues, the time of exposure, qualitative and quantitative issues of the response as well as modulating and confounding factors affecting the interpretation of data. Overall, the paper provides an overview from a nutritional biochemistry perspective regarding the use of markers to assess carotenoid bioavailability.

2. Biomarkers

A key issue in the design of human nutritional studies is the choice of the right markers which, in turn, depends on the objective of the study. Overall, for essential nutrients, nutritional status (as a surrogate of bioavailability) can be approached by clinical, dietetic, anthropometric and biochemical markers. Nevertheless, for carotenoids, and especially for non-provitamin A carotenoids, most of these approaches are not applicable since nutritional status cannot be properly defined and inadequate intake does not result in biochemical or clinical signs of deficiency.

As for other micronutrients and phytochemicals, biomarkers for carotenoid bioavailability can be broadly divided into direct, biochemical or "analytical" markers and indirect, physiological or "functional" indicators. Usually, analytical markers refer to biochemical indicators of intake and/or status (exposure) of a given nutrient or food component. In turn, functional markers evaluate the effect or a biological activity associated with a nutrient or its absence.

2.1. Biomarkers of exposure

Traditionally, the assessment of carotenoid exposure in humans has been performed by dietary or biochemical methods, both of which have advantages and limitations. In general terms, markers of exposure evaluate biological accessibility although a critical issue is to assess to what extent the marker reflects actual dietary exposure (Ellwood et al., 2014). Overall, concentrations of carotenoids in serum and tissues are considered more reliable than dietary methods since they provide a more accurate measurement of the amounts available to tissues (Maiani et al., 2009; Raiten, Namasté, Brabin, Combs, L'Abbe, Wasantwisut, & Darnton-Hill, 2011; Scalbert et al., 2014; Tanumihardjo et al., 2016; Van den Berg et al., 2000). However, serum carotenoids may be influenced by the bioavailability and in vivo metabolic changes and thus, they do not represent a true measurement of dietary exposure. Even so, blood concentrations of biomarkers provide direct relationships between nutrient input, status and availability for tissue metabolic requirements (Thurnham & Northrop-Clewes, 2016).