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Review

Nutritional biomarkers and foodomic methodologies for qualitative and quantitative analysis of bioactive ingredients in dietary intervention studies

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ABSTRACT

Traditional dietary assessment methods, such as 24-h recalls, weighted food diaries and food frequency questionnaires (FFQs) are highly subjective and impair the assessment of successfully accomplished dietary interventions. Foodomic technologies offer promising methodologies for gathering scientific evidence from clinical trials with sensitive methods (e.g., GC–MS, LC–MS, CE, NMR) to detect and quantify markers of nutrient exposure or subtle changes in dietary patterns. This review provides a summary of recently developed foodomic methodologies for the detection of suggested biomarkers, including the food specificity for each suggested biomarker and a brief description of the key aspects of 24-h recalls that may affect marker detection and stability, such as mixed nutrients and cooking processes. The primary aim of this review is to contribute to the assessment of the metabolic effects of active ingredients and foods using cutting-edge methods to improve approaches to future nutritional programs tailored for health maintenance and disease prevention.

Contents

1. Introduction

According to Regulation (EC) no. 1924/2006 concerning health claims made about foods, it is essential to prove the veracity of the purported health effect provided by the consumption of a functional food and/or its bioactive components [1] in human models.

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Notably, poor dietary intervention trial design and the inability to associate food consumption bioavailability with health effects are the primary reasons for which the European Food Safety Authority (EFSA) most often rejects health claim applications submitted by food companies.

Although the quality of randomised controlled trials (RCTs) of food components have improved with time, they continue to inadequately describe important details of the methods, and many of them lack important information, particularly regarding the composition of the food intervention. For this reason, the 22-item checklist of the Consolidated Standards of Reporting Trials (CONSORT) statement [2] has been developed to help authors and editors improve their reporting of the RCTs of dietary interventions.

Although there are a variety of methods available to assess diet, including 24-h recalls (24 hR), weighted food diaries and food frequency questionnaires (FFQs) [3], the accuracy of food intake data can be influenced by random and systematic errors [4], in addition to the selective underreporting of energy intake and certain food groups among given population groups [5]. Many reports show differences in their ability to capture the typical diet or the prevalence of a food component during the period covered by the study. In spite of this, these techniques are not without merit because notable validation studies that have been undertaken in a rigorous and thorough manner can be found in the literature [6–8].

In theory, an FFQ should provide a better estimate of typical intake, especially for foods that may be rich sources of a single nutrient (e.g., yams for b-carotene), than techniques that survey single or multiple days of dietary intake, for which consumption might be missed on recording days [9]. Cross-sectional studies typically estimate the intake of nutrients from foods and supplements using daily methods, such as a single or multiple 24 hR, but epidemiological studies have primarily employed variations of an FFQ that has been validated by daily methods or biochemical indicators [10,11]. However, for certain nutrients, dietary intake estimates based on markers of exposure may be preferred, while for others, biological markers may be more problematic than estimates of intake. Exposure to some nutrients can be quantified by both approaches, thereby producing complementary information that is integrated with the so-called triad method. In fact, the triad method has been proposed as a way to validate dietary intake instruments when quantitative intake information from all three methods (FFQ, 24 hR and biological markers) is available. This proposal is based on the concept that although it is not possible to directly measure the true intake (the latent variable), intake can be estimated by means of FFQ and 24 hR indicators and biological markers as manifest variables [12,13]. This link is essential to decide whether the negative outcome of a controlled trial (i.e., lack of functional change in response to supplementation) can be related to the basic hypothesis as a clinical effect or as a lack of subject compliance. Understanding which biomarkers truly reflect nutrient status or health outcome is even more important in epidemiological studies assessing the health effects of dietary components or patterns in populations over long periods. Although several substances found in a wide range of foods may be potential biomarkers of differences in inter-individual absorption, the effects of gender, body mass index, physical activity and amount of fat in the overall diet must also be considered [14–17].

Nutrient profiles from plasma, urine, blood, erythrocytes, platelets and hair samples may be used to search for markers of specific dietary components, but which type of sample is the most appropriate for the detection of a given compound and whether a profile will reflect the recent intake of a given bioactive ingredient must be considered.

This review will discuss this challenge, provide in parallel a description of the cutting-edge technology used to detect nutrient biomarkers and suggest future trends with new approaches to detect and integrate several sources of data to create a binomial true food intake marker. These markers will be discussed here as potential ways to improve compliance in clinical and dietary intervention studies as well as to contribute to efforts to gather scientific evidence through clinical trials.

2. General aspects of nutrient biomarkers

Although there is no consensus about the requirements for useful biomarkers of intake in nutritional studies, there are some criteria that should be satisfied. These are as follows: (a) robustness of quantification and identification by sensitive methods and by the assessment of properly collected and stored samples, (b) changes in concentrations that must be due to changes in the intake of the dietary component of interest, (c) high specificity, and (d) comprehension of the impact of physiological factors and whole diet composition on the kinetics of absorption, metabolism and excretion of the putative biomarker [18].

Biomarkers of dietary intake can be classified into markers based on recovery or on concentration. The former are based on quantification of the balance between intake and excretion of a compound, such as 24-h urinary nitrogen for protein intake. The latter are based on the concentration of a specific compound that can be measured in biological materials, such as blood plasma and urine, among others [19]. In fact, blood, urine, and saliva are the most likely sources of biofluids for human metabolomics. Faecal water offers an opportunity to study gut microflora metabolomics but must be treated cautiously because this biofluid does not indicate the metabolites from the large-bowel microflora that are actually absorbed by the host. The use of other metabolomes (e.g., cerebrospinal fluid, liver, gut, or muscle biopsy specimens) is too invasive and should be avoided, but we can anticipate the use of such tissues with cultured human cells, such as peripheral blood mononuclear cells (PBMCs), for metabolomic studies.

Depending on its use, such a marker should reflect recent intake (reflects compliance in shorter-term studies) or it should reflect intake over a longer period (useful for dietary assessment in epidemiological studies or as a compliance marker in longer-term interventions). Thus, with these considerations, the perfect nutrient exposure biomarker must be independent of memory, it should coincide with the estimated average intake over a period of time, it should avoid errors associated with subjective data [6] and it should provide a powerful tool for estimating the exposure of interest and assessing the risk of trial protocol non-compliance [20].

To select an appropriate biomarker, the investigator should consider the purpose of the study, how it will be evaluated, and the kinetics of a marker with relation to sample acquisition. That is, choose a short-term marker (those that respond to dietary intake within hours) instead of a long-term marker, such as those used in large-scale studies in which markers reflect the average status of the population, or at least the typical long-term status of a population. However, in some cases, such as satiety interventions, it may not be possible to obtain fasting samples. In such cases, investigators should ask the subjects about their recent intake and the types of foods consumed and then use these data in the laboratory or the statistical analysis phase of the study [21].

In addition, foods, such as fruit, vegetables, red wine and coffee, are usually complex mixtures of a large diversity of molecules, nutrients and non-nutrients, present either intentionally or accidentally, all with potential metabolic effects. These, along with the hundreds of thousands of food compounds that do not have metabolic effects but that make food a gastronomic delight, must all be factored into the metabolome. Therefore, the accurate analysis of bioactive ingredients is a topic that demands the development