Food Intake Biomarkers for Increasing the Efficiency of Dietary Pattern Assessment through the Use of Metabolomics: Unforeseen Research Requirements for Addressing Current Gaps

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Current research on nutritional sciences depends upon the precise measurement of food intake. Despite being the most widely used dietary measurement tools, self-reported surveys are not exempt from already recognized limitations (1, 2). Low dietary assessment accuracy contributes to the inconsistency of results already observed in many instances when trying to understand the connections between diet and healthiness or disease risk, thereby weakening their potential translation to clinical and public health applications (1). The drawbacks of conventional instruments have encouraged research on food intake biomarkers (FIBs) as a complementary or alternative measure of dietary intake, being one of the cornerstones of nutritional epidemiology (1). FIBs are those food compounds or food-derived metabolites that allow for recent or average intakes of specific food groups, foods, or food components to be objectively and accurately measured in a biological specimen (3). They are assumed to be a more accurate measurement of dietary exposure than self-reported consumption because they cover the bioavailability of dietary compounds and allow for the drawbacks of composition tables, portion estimation, and subjectivity, among other things, to be handled. However, there are still some gaps that have to be addressed for such biomarkers to reach their full potential for the community. These are related to their specificity, interindividual variation, validation, and quantification. These aspects will be outlined in the following paragraphs.

Metabolomics, which enables the simultaneous measurement in a biological sample of hundreds or even thousands of small molecules, many of which are impacted by dietary exposure, is stirring

up the field of dietary assessment through the discovery and validation of FIBs because it provides a comprehensive snapshot of dietary exposure (1). To date, the use of metabolomics has enabled and is still enabling the identification of a large number of putative novel FIBs (4). Additionally, more recent studies have demonstrated that it is already possible to quantify food intake (g/day) by employing FIBs, as achieved for determining grape or orange juice intake through the determination of urinary tartaric acid and proline betaine, respectively (2, 8).

While, in most cases, the studies have focused on food or food groups, several studies are now emerging, evaluating metabolic profiles associated with dietary patterns, including Mediterranean, Nordic, Western, prudent, and vegetarian dietary patterns, among others (2). The recent interest in moving forward to the assessment of dietary patterns through FIBs relies on the idea of capturing the complex interconnections derived from the different combinations of foods that individuals usually consume following certain patterns and which, at the same time, can act synergistically to improve health and/or prevent chronic diseases (5). Whereas, for foods, in most cases, single metabolites have been used to monitor their intake, this is not the case for dietary patterns. In such studies, researchers tend to provide a global pattern of metabolites associated with individual foods particular to the dietary pattern that is under study (2).

The most common approach in the study of FIBs is a single-biomarker strategy, but because most dietary compounds are widely distributed among different foods, the specificity for most of the already proposed FIBs is seriously limited. In parallel, similar compounds from different food sources, even though they do not have the same structure in the corresponding food sources, can produce common metabolites after their metabolism (1). In the same vein, multimetabolite biomarker panels (MBPs) have emerged as a better estimation of dietary assessment, in terms of both accuracy and precision. This is based on the hypothesis that the metabolites that are building the MBPs are providing complementary information. Additionally, it is easier to obtain a more precise estimation of dietary exposure using a MBP rather than a single biomarker (1). In parallel, another common bias related to specificity is the overselection of potential FIBs that could be derived from a careless interpretation of the underlying biological processes even after applying rigorous statistical corrections for multiple testing (4). Some examples of this involve studies presenting changes in metabolites that, instead of being derived from a dietary component, are related to other parallel endogenous pathways affected by intake. Therefore, these metabolites cannot be used as FIBs (4).

Another important point that should be addressed urgently is a better understanding of the factors affecting the detected levels of the candidate FIBs both within and between individuals. In this frame, it has been hypothesized that food compounds could be better candidates for FIBs rather than compound-derived metabolites, because they are not affected by the factors related to the host and microbiota metabolism (3). On the other hand, microbial metabolites, despite being interesting candidates of habitual dietary patterns as a result of their usual kinetic behavior and also because a significant number of food components are metabolized by microbiota, are those most affected by interindividual variability as a result of the different potential in gut microbiota ecology among individuals. Therefore, FIBs derived from microbiota metabolism should still be used with prudence until a better understanding of the factors affecting their levels is obtained (6).

In parallel, an accurate knowledge related to the kinetics of each FIB will determine the time frame in which it will be able to be used (3). Biomarkers with short half-lives will only be useful for evaluating those dietary components that are very frequently consumed and, for most of them, only when 24 h urine samples are available. Those with longer half-lives will also be useful for those dietary components that are consumed in a more widespread window. Also and in parallel, as used for 24 h recalls, the information provided by more than one biological sample would be a better measurement than using only one sample to capture the day-to-day variation of ingestion and long-term dietary patterns.

Although several FIBs have been proposed, there is still work to do before this knowledge can be translated to clinical practice because only a small number of them have been fully validated (7). One of the main current issues in this field is the specificity of FIBs, along with the lack of established dose–response relationships or the scarce quantitative data available and corresponding thresholds, as well as the sources of interindividual variation that can lead to different measured levels of a FIB following the same levels of intake (1, 2). In parallel, another current weakness of FIBs is that most of the findings have not yet been replicated in independent studies and populations (7). This can be explained by the different profiles of included subjects or divergences in study designs. Those FIBs that reach their full capacity across different populations will be the FIBs whose rapid translation for routine use is more challenging.

Quantification plays a crucial role in translating FIBs to being routinely used in large-scale research studies and clinical practice (7). FIB concentration measures would enable an improved

comprehension of whether the data from FIBs would provide robust measures of dietary pattern assessment because it would allow for comparisons between different study conditions and populations to be made. This type of data would also be important for replicating FIBs in different studies (7). Such data would also allow for the determination of thresholds over which dietary exposure or its absence would be reflected to translate biomarker levels into grams per day of intake (2, 8).

Another gap in the current knowledge is that it has not been tested whether the markers increase with increasing adherence to the dietary pattern (2). A precise FIB should not be detected in the absence of consumption of the food under study, and it should only be quantified in a well-known dose-dependent response following its consumption or in a parallel way for the level of adherence to the dietary pattern being studied (3, 4).

The study design in which the FIB has been described also involves important connotations for understanding its potential use. Randomized controlled trials (RCTs) allow the food intake of participants to be controlled and then the levels of the FIBs measured after the intake of the dietary source of interest (2). Among them, RCTs with a crossover design are the most sensitive for the discovery of FIBs because they allow for intrasubject comparisons (4). On the other hand, observational studies make it possible to see whether the FIBs are robust enough to distinguish the diet, even under free-living conditions, where the overall dietary background is usually highly variable and allows for the magnitude of intersubject variations to be handled (4). However, in this latter case, it is very important to bear in mind that most of these studies are based on dietary exposure being reported through self-reported surveys, which can be prone to misreporting issues and, therefore, can lead to conflicting research findings. This reinforces the importance of using several cohorts to replicate the results (9), always bearing in mind that this does not mean causation, which can only be verified through RCTs (7). To address these difficulties and strengthen causal inferences, recent studies have started to integrate findings from controlled intervention studies and epidemiological cohorts (2).

In summary, huge important strides in the field of FIBs have been made, but there is still an urgent need to solve the current gaps referred to above through high-quality research. Once achieved, the community will be given specific and accurate methods to use for quantifying robust and validated

FIBs reflecting overall dietary patterns. Then, we will be able to transfer this knowledge to clinical practice with a view to reaching their full potential for the community.

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