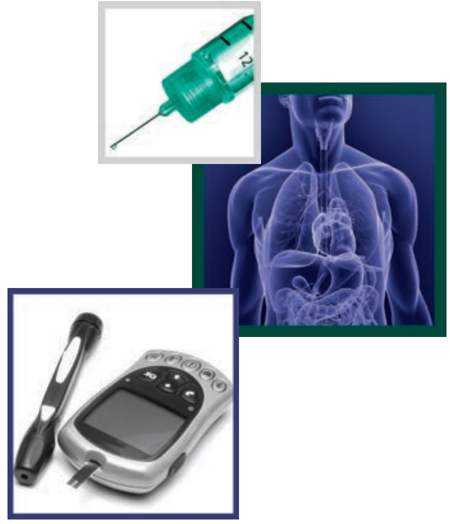
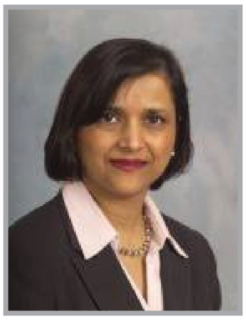
EDITORIAL

Can nutritional biomarkers help to provide the 'missing link' in diet–diabetes associations?





"The availability and use of nutritional biomarkers has opened up possibilities for identifying diet–diabetes associations that have previously not been found, or that have been inconsistent across studies owing to the problem of measurement error using self-report instruments."

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There are two well-known facts regarding diabetes prevention. First, the prevention of diabetes is important, nay urgent, given its increasing burden, with an estimated 366 million individuals worldwide with diabetes in 2011, projected to rise to 552 million by 2030 [1], and it is a leading cause of death [2]. Second, there is evidence from randomized trials that the primary prevention, or at least the delay of onset, of Type 2 diabetes is possible with lifestyle interventions, including diet [3].

What is not well known, however, is which specific dietary factors relate to diabetes risk in what specific ways, and what dietary advice is optimal for populations and individuals for the prevention of diabetes. This is despite the fact that the potential contribution of dietary intake to the prevention of chronic diseases, including diabetes, has been prominently highlighted by many international and national agencies such as WHO [4]. In reality, the scientific literature and the media are full of examples of inconsistent and contradictory reports of associations between dietary factors and the risk of diabetes, or indeed other medical conditions, often leaving the readers confused. Let us consider one example.

It has been reported that eating one or more portions per week of fish versus less than one portion per week was associated with a 25% lower risk of incident Type 2 diabetes among men and women in the EPIC Norfolk study, which included approximately 22,000 participants (odds ratio: 0.75; 95% CI: 0.58–0.96) [5]. In the same year (2009), there were reports from the USA [6] and The Netherlands [7] that fish intake is associated with an increased risk of diabetes, and in the US study an increased risk of diabetes was also associated with greater dietary long-chain fatty acid intake, derived from the food frequency questionnaire [6]. Not surprisingly, the public are confused: should they or should they not eat fish?

The exact reasons for the lack of consensus regarding the associations for fish intake observed between the different studies are unclear, but it has been discussed in a systematic review that they could include geographical or cultural differences, including different cooking methods or levels of contamination of fish, such as by persistent organic pollutants or mercury [8]. What is not known, however, is to what extent these different findings are a result of measurement error introduced by the self-report methods that are currently available to researchers to assess dietary intake. While a validated food frequency questionnaire was

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used in each of the above studies [5–7], the limitations of this instrument are well documented, and include both random and systematic error related to the use of food composition tables and assignment of portion sizes, as well as misreporting variables that might vary by age, sex, level of obesity or social desirability [9]. Statisticians and nutritional epidemiologists have collaborated to develop techniques for measurement error correction [10], but there are limits to the extent to which the problems of measurement imprecision and bias can be dealt with at the analytical stage, thus these do not offer definitive solutions.

Rather than focusing on the continued use of improved food frequency questionnaires or related self-report methodologies [9], it is now increasingly clear that objectively measured nutritional biomarkers offer a way forward for investigating the nutritional etiology of diabetes.

Nutritional biomarkers can help to unravel diet–disease associations

In a proof-of-principle study, a striking inverse association between plasma vitamin C concentration and the risk of incident diabetes has been demonstrated, while, by contrast, the association with total fruit/vegetable intake measured by the food frequency questionnaire was modest and lacked a 'dose–response' effect [11]. Among nearly 22,000 participants of the EPIC Norfolk study followed-up for 12 years, the risk of diabetes in the top fifth (compared with the bottom fifth) of the plasma vitamin C distribution was 62% lower (95% CI: 48–72% lower), while for a similar comparison of fruit/vegetable intake there was a modest 22% reduction in risk of diabetes (95% CI: 0–40% lower risk). These analyses accounted for other factors, such as age, sex, BMI, potentially healthier lifestyles and socioeconomic status, and vitamin supplement usage among those who may eat greater quantities of fruit/vegetables or have higher vitamin C levels. Since fruit and vegetables are the primary source of dietary vitamin C, the concentration of vitamin C in the blood is considered a good marker of fruit/vegetable intake, and these findings illustrate that we may be able to 'unmask' an association when using an objective biomarker that is more precisely measured, which may remain 'masked' when less precise self-report methods are used.

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Earlier studies found inconsistent associations between dietary vitamin D status assessed by dietary questionnaire and the risk of diabetes, but the measurement of circulating 25-hydroxyvitamin D concentration has led to the illustration of a consistent and convincing inverse association with diabetes [12]. Circulating 25-hydroxyvitamin D levels reflect both an objective measurement of dietary intake as well as accounting for the endogenous synthesis of vitamin D in the skin, which is omitted when only considering dietary intake.

Dietary guidelines have been recommending for a long time the reduction of saturated fat intake to prevent cardiometabolic disease, including diabetes, but a careful evaluation of the evidence has yielded equivocal findings [13]. The availability of techniques to measure fatty acids in the blood, such as the plasma phospholipid fraction or the erythrocyte membrane fraction, have opened up possibilities for more detailed investigation than was possible when we were restricted to dietary questionnaires. It is now emerging that not all saturated fat is the same, but rather that individual saturated fatty acids exert differential effects. For example, odd-numbered saturated fatty acids (C15:0 and C17:0) appear to be inversely associated with incident diabetes [14] and dairy products, the main source of such fatty acids, are also associated with reduced risk of diabetes [15,16]. Furthermore, some of the dairy-derived trans-fatty acids, when measured objectively, also seem to be inversely related to diabetes risk [17]. To return to the point about the inconsistencies in observed associations between fish intake and the risk of diabetes, we can look forward to biomarkers such as objectively measured omega-3 fatty acids shedding further light.

Nutritional biomarkers: challenges & opportunities

While nutritional biomarkers offer many advantages, including greater precision by virtue of not being subject to reporting bias or errors related to self-report and the use of food composition data, some challenges remain. As previously discussed [18,19], biomarkers are not specific to individual foods or often even food groups. Intra- and inter-individual differences in absorption and metabolism may affect the actual or measured concentration, which may depend not only on diet composition, but also on genetic variability; some compounds may undergo extensive metabolism while others may be endogenously synthesized; some biomarkers may not reflect the preferred reference period of intake, limited by a biomarker's short half-life in specimens such as plasma or urine; sample handling and storage might particularly affect some biomarkers; standardized assay methods may not always be available or 'gold-standard' methods may be expensive; and only few nutritional biomarkers are currently available for testing diet–disease associations.

That said, with greater investment into research and crosstalk between analytical chemists and epidemiologists, it will be rewarding to overcome the challenges currently posed by the measurement or interpretation of nutritional biomarkers. Using hypothesis-driven and hypothesis-free discovery approaches with new technologies such as metabolomics, the identification, development and validation of new nutritional biomarkers is already on the horizon [20,21]. The availability of a broad range of nutritional biomarkers will open up possibilities for more robust testing of causality of proposed diet–diabetes associations using genetic Mendelian randomization experiments that overcome issues of confounding and reverse causality that so often plague nutritional epidemiology [22]. Objectively measured nutritional biomarkers will also enable the investigation of the interaction between genes and dietary factors and their effect on the risk of diabetes.

Conclusion

The availability and use of nutritional biomarkers has opened up possibilities for identifying diet–diabetes associations that have previously not been found, or that have been inconsistent across studies owing to the problem of measurement error using self-report instruments. While some challenges have been identified, greater collaboration between epidemiologists, chemists, basic scientists and clinicians will help to improve research questions and methods, and to elucidate issues of interpretation. Further research should focus on the use of objectively measured nutritional biomarkers to gain etiological insights, including addressing questions of causation, which have been difficult to address without objective dietary assessment. Biomarkers should be used in complementary approaches to gain a better understanding, rather than as a replacement for the self-report methods that have been developed and refined over the past decades. With these approaches we should be able to move closer to the goal of better dietary advice for the prevention of diabetes.

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