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Community Medicine

NUTRITIONAL BIOMARKERS: AN OVERVIEW

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ABSTRACT The role of diet as far as risk of majority of chronic diseases in human beings is concerned cannot be underestimated. Measurement error in self reported dietary assessment have obscured strong and consistent associations from observational studies of dietary consum ption in relation to chronic disease risk. Introduction of biomarkers to calibrate the measurement errors in dietary studies is a welcome step to improve estimates of magnitude of contribution of diet in affecting individual disease risk within populations. Advances in omics has generated hope to obtain new biomarkers, besides which are currently available, of various kinds using genomics, epigenomics, lipidomics, metabolomics etc. New biomarkers are needed to support evidence based clinical guidance and effective health programs and policies related to food, nutrition and health.

KEYWORDS : Diet, Epidemiology, Nutritional Biomarkers

Diet in relation to health and disease outcome are known to humankind since ages. But it was only in the 1980s that first large scale epidemiological studies were carried out to establish relationships between diet and diseases. The structured dietary questionnaires like food frequency questionnaire (FFQ) were used as cost effective and suitable method for self administration. But FFQs were criticized in ranking the individuals on the basis of dietary intake while the methodological limitations of FFQ lead to bias in dietary exposure measurement as well as estimated relative risks which in all likelihood obscure diet disease associations. Later on, evidence has shown that repeated open ended qualitative 24 hour dietary recalls (24 HDRs) may outperform the FFQ in assessing accurately the individual nutritional intake. Methods of measuring diet are associated with random and systematic error. The errors arise due to use of food tables, assessment of frequency of food consumption, portion size, daily variation and failure to report usual diet due to changes in habits or misreporting of food amount. In this context, it would be pertinent to mention the key role of randomized control trial (RCT) designs in nutritional epidemiology. Randomized controlled intervention trial have the considerable advantage of avoiding confounding by all pre-randomization factors whether recognized as such or not. These trials provide a context for unbiased outcome ascertainment.

Nutritional studies, in addition to ascertaining the dietary intake of a group of people, also study the association between food intake and the outcome in terms of a certain health problem. It would be apt to add that accurate assessment of dietary exposure is crucial in investigating associations between diet and disease. So the need is for a formative means to know the food and nutrient intake (along with non nutritive food components) contributed by the same with greater validity and accuracy than obtained through the above mentioned self reported measures.

In this context, role of nutritional biomarkers is emerging of paramount importance for future research into association between diet and health as they can provide an objective assessment method for dietary exposure. As defined by Biomarker Definition Working Group (1), a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention.

The study of nutritional biomarker whether it be biochemical, functional or clinical indicies of nutrient intake or of metabolism are making a paradigm shift in our understanding the role of nutrients and food components in the domain of health and disease. Nutritional biomarkers offer the possibility of an objective indicator of compliance with a particular dietary regimen in RCTs investigating the health effects of dietary modifications. Biomarkers are indicated not only to assess the omics of normal nutrition but also the insults that can influence requirements under diseased conditions. The increasing interest in use and development of new biomarkers led the Sackler Institute for Nutrition Science and the New York Academy of Sciences to organize a conference in 2012 entitled Biomarkers in Nutrition - New priorities in Research and Application. It aimed to get scientists and practionners from industry, academia and government organizations to work together on assessing the current state of knowledge about nutritional biomarkers, to identify important challenges and unanswered questions and to catalyze new research to enable a better measuring of food intake, its effects and its association with the state of health and disease.

Role of nutritional biomarkers has evolved from markers of deficiency in a single disease (vitamin A and eyes) to an array of chronic conditions like cardiovascular, respiratory, digestive, immune, nervous system etc. On the basis of temporality, biomarkers can be categorized into short term (reflecting intake over past hours/days), medium term (reflecting intake over weeks/months) and long term biomarkers (intake over months/years). Another classification of biomarkers distinguishes them as 1) recovery 2) concentration 3) replacement & 4) predictive biomarkers.

1. Recovery biomarkers – provide an estimate of absolute intake levels based on metabolic balance between intake and excretion over a fixed period of time. These biomarkers being not subject to personal characteristics are useful to evaluate measurement error structure of assessment instruments. Recovery biomarkers are biological products related to intake e.g., DLW (doubly labeled water) which is utilized to measure the metabolic rate and total energy expenditure; urinary total nitrogen/potassium which are utilized to estimate total protein consumption and potassium intake respectively (2,3). DLW is an important advance in the measurement of energy expenditure since it can be used on free living individuals with virtually no interference with everyday life. The use of 24 hour urine nitrogen depends on the assumption that subjects are in nitrogen balance, there being no accumulation due to growth or repair of lost muscle tissue or loss due to starvation, slimming or injury. As a biomarker of diet, 24 hour urinary potassium has an advantage because a greater variety of foods are good sources of potassium than those containing protein.

2. Concentration biomarkers- have a correlation with intake but because they are affected by metabolism or characteristics like age, sex, obesity, smoking etc., they can't be used as a measure of absolute intake or for assessing error of self reported intakes in validation studies e.g. serum carotenoids, lipids, vitamins etc.

3. Replacement biomarkers- related to concentration biomarkers but they refer specifically to compounds for which information in food composition databases is not up to the desired levels. e.g. aflatoxins, some phytoestrogens, etc.

4.Predictive biomarkers- are sensitive ,time dependent, have a dose response curve with intake levels and may be affected by personal characteristics but their overall recovery is lower e.g. 24 hour urinary fructose and sucrose.

Different type of biological samples are needed to measure biomarkers. Commonly used are blood, urine and saliva although increasingly more pool is being added in the form of faeces , hair , nails, adipose tissue and other specific tissues. Of all, urine and saliva are the least invasive. In large scale studies, it is advisable to obtain biological samples from a representative subsample instead of all the participants. It would be better to build biobanks and to follow protocols for such purposes. Besides good storage of biological samples , valid lab procedures to analyze biomarkers are essential to allow comparisons so that recommendations regarding appropriate levels be made .

Limitations

For many biomarkers, there are inter-individual factors that could skew biomarkers measures and give false values . These include age, sex, tobacco and alcohol consumption ,physical activity and other lifestyle factors, besides diet, type of biological sample ,obtaining and storage of samples ,the laboratory methodology and inter laboratory variations (4).As the research advances on inter individual variability ,genetic polymorphism in relevant genes are becoming more important . The most commonly studied one is single nucleotide polymorphism (SNPs). The rapid strides in technology has made it easy and fast to incorporate genetic determinations into nutritional epidemiology studies (5).Besides preferences in choice and consumption of food, genetic variation is likely to play a pivotal role in nutrient metabolism ,absorption, biotransformation and excretion of nutrients.

The powerful omics technologies have opened new avenues towards biomarker discovery, identification of signaling molecules associated with cell growth, cell death, cellular metabolism and early detection of cancer. Omic technologies are likely to identify the individuals who will either benefit most or be placed at risk due to dietary change. Among the omic technologies are:-

Genetic biomarkers – it is based on determination of genetics polymorphisms (main SNPs) and can be of intake or of effect/ metabolism or as disease risk. They are important in determining intermediate (plasma, lipids, fasting glucose, oxidative markers etc) as well as incidence of disease (CVS disease, cancer, T2DM, obesity etc). The advances in genetics and its increasing integration into nutrition has led us to Nutritional genomics (6).

Epigenetic biomarkers- they denote a variety of modification to the genome that don't involve changes in the DNA sequence and can results in alteration of gene expression allowing for differential expression of common genetic information.(7) Advantage is that being reversible, it allows a rapid adaptation to the environment.

Transcriptomic biomarkers – provide knowledge of transcriptome, either individually for each specific gene studied or analyzing the expression of various genes simultaneously on different scales. It helps to investigate how exposure to different dietary factors affects the expression of all genes or the specific genes. Limitation is that transcriptome and the epigenome are not the same for all the cells of the organism and that the level of expression varies depending on tissues analyzed, adding a little more difficulty to investigate these biomarkers.

Proteomic , lipidomic and metabolic biomarkers- they are being used to study proteins, lipids and metabolites in nutritional epidemiology. Metabolomics is screening of small molecule metabolites present in samples of biological origins. Characterization of all the metabolites can provide a picture of the metabolism and a molecular finger print (8). Metabolomics can also be used to examine the outcome of nutritional intervention strategies by observing and comparing metabolic marks. Metabolomics has also contributed to detection of environmental chemicals (plagvicides) and different toxins in foods and beverages. Although techniques may be expensive for large scale epidemiological studies, but they hold promise for future to detect the intake of specific foods and other relevant biomarkers of health status.

For biomarker approach to provide a fresh look at nutritional epidemiological association, biomarkers need to be developed for additional nutrients and dietary components. In this regard, a human feeding study of sufficient size could do much to close the so called research gap. Use of biomarkers like DLW, 24 hour urine potassium and sodium have revealed that there could be substantial attenuation of diet effects and loss of statistical power in epidemiological studies .Biomarker studies suggest that improved and more detailed methods of dietary assessment will be necessary if causal associations between diet and disease are to be established in future large scale epidemiological studies. Biomarker studies of practical size and acceptable cost can be conducted within study cohorts to support biomarker calibrated dietary association studies. The possibility of using 24 hour recall approach for physical activity is another exciting proportion for the researchers. Development of longitudinal biomarker along with comprehensive set of nutritional and physical activity biomarker deserve a prominent place in chronic diseases and disease prevention as well as for the research agenda in the years ahead.

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