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Identification of Early Molecular Biomarkers of Diet-Related Pathologies for the Development of Health Preventive Nutritional Strategies

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Editorial

Diet-related pathologies constitute the main cause of mortality now a day's [1,2]. Thus, there is an urgent need to establish policies to change dietary habits in order to improve public health. In this sense, the identification of biomarkers to make diet-related metabolic alterations evident before the appearance of any clinical signs could help create proper nutritional strategies to prevent the development of future pathologies. The search of these early biomarkers of disease should be ideally conducted in an easily obtainable biological material collectable at different time points of development of the studied pathology, i.e., blood, urine or saliva as the most common ones. Blood cells, particularly peripheral blood mononuclear cells (PBMC), a subset of blood cells which includes lymphocytes and monocytes, are increasingly being used as a source of clinical and nutritional biomarkers [3]. These cells can be obtained with minimum invasion in humans and they express a wide number of genes of the human genome [4]. Moreover, in addition to their role in immunity, their gene expression reflects metabolic homeostasis adaptations to different stimuli (e.g., diet) which occur in key internal tissues, such as adipose tissue or liver, as well as gene expression patterns characteristic of certain pathologies, including diet-related pathologies (e.g., obesity) [5-7]. Early predictive biomarkers of risk should serve to monitor a progressive deviation of the homeostasis/healthy status due to the intake of unhealthy diets or unhealthy dietary habits, and could range from alteration in the concentration of circulating metabolites to epigenetic modifications, or alterations in the expression of a gene or a pool of genes or proteins in the studied biological material. The fast development of omic technologies in the last decades has allowed a huge increase in the knowledge on the interactions between diet, genes and health, which, in turn, has allowed the progress of nutrigenomics and biomarker research [8]. Moreover, to identify early biomarkers of diet-related diseases, it is crucial to dispose of proper models of pathology predisposition. Animal models offer the opportunity to perform suitable experimental designs to study predisposition to diet-related diseases, which would be impossible or very difficult to perform directly in humans. Using these animal models of predisposition and applying omic technologies, it is possible to detect progressive deviations from the health/control status, in terms of global changes in mRNA or protein expression, epigenetic marks, or metabolite concentrations. These alterations, measured in an easily obtainable biological material, could be used as biomarkers of metabolic risk and could be assayed in humans to test their efficacy. Validation in humans of the usefulness of the potential biomarkers constitutes precisely a key future research challenges. Development of these predictive omic-based biomarkers in humans will facilitate the guidance of future dietetic advice toward individualized health to prevent the development of chronic diseases [9].

One of the main health problems in our society is the dramatic increase in obesity, as this is linked to important medical complications, such as insulin resistance, fatty liver, hypertriglyceridemia/hypercholesterolemia and hypertension [10]. These metabolic risk factors increase the risk of suffering cardiovascular disease, the main cause of dead worldwide which, according to the WHO, has remained the leading cause of death globally in the last 15 years [2]. Obesity and its co morbidities are clearly linked to diet, particularly to the intake of energy dense foods (rich in fats), combined with physical inactivity [11]. To help preserve public health, it is of great relevance to identify early biomarkers of metabolic alterations due to the intake of unbalanced/high-fat diets which could contribute to the prediction of increased risk of suffering obesity and its related medical complications, preventing in this way the development of cardiovascular disease.

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Important advances are being made in this field using different animal models of obesity predisposition and by mainly identifying transcriptomic biomarkers of obesity-related metabolic risk in blood cells [6,7,12-14]. For example, global gene expression analysis using microarray technology has shown that obesity predisposition as a result of gestational under nutrition in rats produces a transcriptomic profile in PBMC which is predictive of a higher risk of obesity [12]. Other studies, using rats fed obesogenic high-fat diets, have shown that PBMC gene expression can reflect the development of an obesogenic profile, as well as of an increased risk of obesity-related complications, even when animals do not yet present overweight or obesity [6,7,13]. Apart from transcriptomic biomarkers, epigenetic biomarkers analyzed in blood is also a rapidly advancing field which has the potential to allow an early diagnosis and intervention [15]. This key type of biomarkers is being developed using human whole blood to predict obesity and related complications, such as insulin resistance [16].

In addition to the above mentioned medical complications (related to the metabolic syndrome), the intake of high-fat diets and obesity is well known to increase cancer risk [17], and efforts are being performed to identify early molecular markers linking nutrition/obesity and cancer [18]. More recently, a connection has also been established with cognitive alterations and, consequently, high fat intake and obesity could have a determinant role in the increasing incidence of neurodegenerative diseases in western societies [19]. Due to the increasing intake of fat-rich foods and to the epidemic proportion of obesity, an important and growing part of the population could be at risk of cognitive disease [20]. In this sense and due to the relative inefficacy of therapies aimed to treat neurological diseases once established, in February 2013 the FDA urged the scientific community to focus on new preventive therapies, which require research and the development of new biomarkers [21]. Because of the almost complete limitation to obtain brain samples, and the urgency to prevent the increase in neurological diseases related to diet, the identification of blood biomarkers of mild cognitive impairment, an early stage of cognitive impairment, constitutes a future challenge of molecular and clinical nutrition research.

In addition to obesity, there is another type of individuals, the "metabolically obese normal-weight (MONW)", who are not obese based on height and weight, but present metabolic features related to obesity and metabolic syndrome (e.g., insulin resistance, visceral adiposity), and a higher risk to develop cardiovascular diseases [22]. This phenotype is related to the intake of unbalanced diets, rich in fats or simple sugars but without an increased energy intake. One of the characteristic features of MONW individuals is fat deposition in liver; this is especially problematic as fatty liver has a central role in the appearance of insulin resistance and metabolic syndrome [23]. It has been estimated that around 20% of the global population present MONW phenotype [24], which constitutes a health problem, as this suggests that an important part of the population could be at higher metabolic risk but will not be easily diagnosed because of the absence of overweight or obesity or even because of the lack of alteration in classical biomarkers of disease. Further characterization of this condition known as norm weight obesity, and identification of predictive biomarkers of MONW individuals and liver fat deposition, also constitutes a new and interesting area of research to develop over the next years. There are already studies using animal models that mimic the MONW phenotype which have shown the usefulness of PBMC as a source of early transcriptomic biomarkers of metabolic alterations, such as insulin resistance, alteration of serum lipid profile and, particularly, increased fat deposition in liver [25].

At this point, we have the knowledge, the technology and a critical mass of researchers working in this field. Thus, the future oncoming years will be highly relevant for the identification, development and, especially, for testing the usefulness of these predictive biomarkers of disease. There is special urgency to identify biomarkers to prevent occurrence of pathologies caused by western society unbalanced dietary patterns since; in fact, these pathologies are the main cause of mortality in our society. Availability and proper development of these early biomarkers of diet-related diseases will be the basis to develop preventive strategies based on clinical nutrition.

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