Anthropogenic Pressure and Lifestyle are the Underlying Cause of Pandemic Chronic Diseases

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Dramatic changes in the environment in recent decades have resulted in low-nutrient food and excessive intake of heavy metals and toxins through air, drinking water, and dietary habits. Non-communicable diseases (NCD), which are responsible for almost 70% of global deaths, are mainly caused by modifiable risk factors. These include behavioral and metabolic risk factors such as unhealthy diet, tobacco smoke and alcohol. Epigenetic factors have high attributable risks of 80% for most NCDs. Xenobiotics such as persistent organic pollutants, food additives and occupational toxicants, together with nutritional deficiencies, contribute to the development of chronic diseases.

Precision medicine integrates the individual variability in genes, environment, and lifestyle of each person for the prevention and treatment of disease. Metabolomics, the quantitative and comprehensive evaluation of metabolites, has emerged as a novel and powerful tool in precision medicine. Analysis of metabolites gives precise data on nutritional deficiencies, metabolic imbalances, environmental toxins, and microbiome conditions and uncovers underlying genetic predispositions that can be modified through diet, lifestyle, supplements or medications. Critical signs of systemic dysfunction at the molecular level can be revealed years before clinical symptoms appear. Thus, through the assessment of the overall health status, early detection of diseases and intervention to restore these deficiencies is feasible. Lifestyle interventions to improve longevity and metabolic balance are being discussed.

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Резкие изменения окружающей среды в последние десятилетия привели к недостатку питательных веществ в пище и чрезмерному потреблению тяжелых металлов и токсинов через воздух, питьевую воду, за счет пищевых привычек. Неинфекционные заболевания (НИЗ), которые являются причиной почти 70 % смертей в мире, в основном вызваны модифицируемыми факторами риска. К ним относятся поведенческие и метаболические факторы риска, такие как неправильное питание, курение табака и алкоголь. Эпигенетическим факторам приписываются 80 % рисков для большинства НИЗ. Ксенобиотики, такие как стойкие органические загрязнители, пищевые добавки и производственные токсикианты, наряду с дефицитом питательных веществ, способствуют развитию хронических заболеваний. Точная медицина объединяет индивидуальную изменчивость в генах, особенности окружающей среды и образа жизни каждого человека для профилактики и лечения заболеваний. Метаболомика, количественная и всесторонняя оценка метаболитов, стала новым и мощным инструментом в точной медицине. Анализ метаболитов дает точные данные о дефиците питательных веществ, метаболическом дисбалансе, токсиках окружающей среды, состоянии микробиома и раскрывает основные генетические предрасположенности, которые можно изменить с помощью диеты, образа жизни, добавок или лекарств. Критические признаки системной дисфункции...
на молекулярном уровне могут быть выявлены за годы до возникновения клинических симптомов. Таким образом, посредством оценки общего состояния здоровья возможно раннее выявление заболеваний и вмешательство для устранения этих недостатков. В статье обсуждаются мероприятия по улучшению образа жизни для увеличения долголетия и улучшения метаболического баланса.

Ключевые слова: метаболомика, диета, ксенобиотики, хронические заболевания.

Introduction

Humans have developed mechanisms to combat continuous exposure to harmful agents, which have multiplied during evolution and economic industrialization (Golokhvast et al., 2015; Veskoukis et al., 2012). However, rapid cultural changes have overcome the possibility of genetic adaptation, leading to an increase in chronic diseases (Eaton et al., 1988). It has been suggested that chronic diseases are the human body’s attempt to adapt to harmful lifestyle behaviors (Ruiz-núñez et al., 2013). According to the World Health Organization (Fig. 1), 80% of diseases, such as cancer, heart disease, and autoimmune diseases, are due to lifestyle and diet (WHO, 2019).

The role of toxicants

Living in a highly toxic environment including occupational, environmental, biotoxic, and lifestyle concomitant factors, has significantly burdened defense mechanisms (Gangemi et al., 2016). The toxic burden is aggravated by constant exposure to pesticides, heavy metals, food additives, and endocrine disruptors (Docea et al., 2018; Hernandez and Tsatsakis, 2017; Tsatsakis et al., 2016).

Environmental pollutants such as dioxins, which are in the group of persistent organic pollutants, are considered highly dangerous to health (Iatrou et al., 2019; Vassilopoulou et al., 2017). Dioxins are toxic to many organs and have long half-lives (7 to 11 years), and humans, who are at the top of the food chain, are exposed to these pollutants through the food they consume.
chain, receive high concentrations of dioxins (WHO, 2016; Iatrou et al., 2019). For example, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) has been classified as a “known human carcinogen” by the WHO’s International Agency for Research on Cancer (IARC). In addition, several studies have associated levels of polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) in adipose tissue with cancer (Xu et al., 2016). Apart from cancer, dioxins have also been linked to cardiovascular disease, mood changes and cognitive function even 10 years after the initial exposure (Kodavanti, 2005). PCB exposure resulted in high levels of HDL-cholesterol and triglycerides in the blood, even in the absence of signs of intoxication (Lee et al., 2011). Other related conditions include thyroid disease, diabetes, stress, and fatigue (Gaum et al., 2019). Di-(2-ethylhexyl) phthalate (DEHP), a compound used in plastic, didecyldimethylammonium chloride (DDAC) and ethylene glycol (EG) have been shown to trigger inflammatory responses in animal models (Guo et al., 2012; Kwon et al., 2016). DNA methylation, the on and off switch mechanism of genes, is an additional mechanism in which environmental pollutants, smoking, and alcohol consumption have been shown to affect the inflammatory response (Baccarelli et al., 2009; Bigazzi, 1997).

In a systematic review of 103 articles on autoimmunity and chemical exposures, the authors concluded that multiple sclerosis, systemic sclerosis and primary systemic vasculitis were associated with organic solvents and that people carrying autoimmunity genetic variants need to avoid organic solvents (Barragan-Martinez et al., 2012). Reactive organic compounds cause toxicant-induced immunity through multiple mechanisms, and two of the most common are as follows: 1. They cause sudden cellular apoptosis, which exposes cell material to the antigen presenting cells; and 2. They bind to human tissue, covalently forming neoantigens, thus inducing an inflammatory response. For example, halogenated compounds found in nail polish have been reported to bind to mitochondrial proteins, inducing antimicrobial antibodies and primary biliary cirrhosis (PBC) (Vojdani, 2014).

Modern living is characterized by intense stress, lack of water and consumption of processed foods that have lost their nutritional value and are high in calories, chemical additives, sugar, and fats, which deteriorate health (Bosma-den Boer et al., 2012; Vakonaki et al., 2017). Monosodium glutamate (MSG), a food enhancer widely used in Chinese food and found in many processed foods, has been linked to several chronic diseases, especially after long periods of consumption (Zanfirescu et al., 2019). Salt has been directly linked to hypertension and cardiovascular mortality (Karpanen and Mervaala, 2006). In a salt-reduction program, which started during the 1970s and was supported by industries and government, the Finnish tried to reduce salt intake and achieved a 75% mortality reduction and a lifespan extension of 6-7 years. Unprocessed sea salt, which contains over 80 essential minerals and elements, is indispensable for the normal function of the thyroid, adrenal glands and the nervous system, and for natural detoxification. Industrially processed food items have significantly altered ratios of sodium, potassium, calcium, and magnesium, which exert the hypertensive effect of salt. A determinant factor of the success of the salt reduction program in Finland was the consumption of sodium-reduced, potassium- and magnesium-enriched healthier salt alternatives, highlighting the pivotal role of nutrient intake at the correct ratios (Karpanen et al., 1984; Geleijnse et al., 1994).
Diet and dietary patterns associated with chronic diseases

What would be an ideal and healthy diet? The Mediterranean diet, the vegetarian diet, the “paleo” diet, fasting, intermittent fasting, the low glycemic index diet, the protein diet and the diet high in “good” fat and low in carbohydrates all are diets that have been successful for some people. However, this one-size-fits-all diet model has not been successful in combating chronic diseases, stressing the need for more precision medicine approaches (Clish, 2015; Zeisel et al., 2008).

A generally accepted concept is that eating fruits and vegetables is a healthy eating habit. However, studies have shown that before changing their traditional diet in the 1960s, Eskimos followed a diet consisting mainly of foods of animal origin – reindeer, seals, fish, whale fat – without fruits and vegetables, and they had a low risk of heart disease (Dyerberg et al., 1975; Dinicolantonio and Keefe, 2018; Fumagalli et al., 2015; Wagh et al., 2012; Biss et al., 1971; Mann et al., 1964). However, such an effect does not mean that rice or feta are unhealthy foods.

In recent years, for example, atopic dermatitis has been a common childhood disease, affecting 26.5% of children aged 12-23 months in Korea (Yu et al., 2012). These children consume, among other things, rice 4-5 times per day, as rice is a primary food in Korea and accompanies all meals. Preliminary results from the metabolomic analysis performed in these children showed that reducing rice consumption to 2 times a day not only did not worsen their health but also improved atopic dermatitis progression (Tsoukalas, 2018a). However, if we recommended that an American or a Mediterranean resident eat rice twice a day, we would considerably increase their risk of developing diabetes and obesity (Sun et al., 2010).

The above picture is further complicated considering that age, sex, and levels of physical activity and stress shape different nutritional needs and deficiencies.

Metabolomics: the science behind the phenotype

Metabolomics can identify with precision what foods are best metabolized by an individual at a given time and what deficiencies or nutritional needs he/she has (Fig. 2) (Tsoukalas et al., 2017; Tsoukalas et al., 2019; Zeisel et al., 2008). Metabolomics is the science that measures the small molecules that shape human metabolism. Metabolism refers to all the chemical reactions that keep us alive and includes the absorption...
of food, the production of energy, and the construction of cells that form the skin, the muscles, and the organs, as well as substances such as hormones, that regulate body functions (Guijas et al., 2018).

All possible combinations of lifestyle, nutrition, body deficiencies, and pharmaceutical interventions are potentially infinite. Metabolomics measures what is happening within the body and indicates the exact combination of interventions that will bring the best therapeutic effect if we can substantially intervene and improve health (Trivedi et al., 2017; Papamichael et al., 2019). Additionally, it provides accurate data for the treatment and prevention of chronic and autoimmune inflammatory diseases such as diabetes, hypertension, thyroid disease, lupus erythematosus, rheumatoid arthritis, psoriasis, Hashimoto’s, Crohn’s disease, atopic dermatitis, allergies, asthma, and others (Kang et al., 2015; Huang et al., 2014; Sirotti et al., 2017; Papamichael et al., 2019).

**Response to xenobiotics and drugs**

Drug treatment can have positive results in a percentage of the population, neutral to some and negative to others (Kantae et al., 2017). Metabolomics can assess the ability of the individual to metabolize a drug. Thus, it provides information that leads to the adaptation of treatment according to the patient’s needs, aiming for the best response and the minimum adverse effects (Golomb and Evans, 2008; Mesnage et al., 2018). For example, the use of medication that reduces cholesterol levels has an absolute indication in people who have had a heart attack. Often, however, this class of drugs causes muscle aches, fatigue, increased blood sugar levels and depression (Golomb and Evans, 2008).

The above side effects arise mainly because they block the production of a major substance of the coenzyme Q10 (Kantae et al., 2017; Golomb and Evans, 2008). Some patients are more sensitive to this compound and some

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**Fig. 2. Metabolomics can A. assess the metabolism of hormones, carbohydrates, lipids, proteins, nucleic acids, and xenobiotics. B. provide information on the status of mitochondrial function, vitamin and mineral levels, intestinal microflora and inflammation**
are less affected. Metabolomics can provide information on the effect of the drug on the patient, allowing the physician to modify the treatment and improve the patient’s response and health progress.

Towards health and longevity

Health is not merely the absence of disease, but it requires the proper function of all the cells and systems to their full potential (Jadad and O’Grady, 2008). Metabolic imbalance and aging are common denominators in aging-related diseases (Tsoukalas et al., 2018; Ames, 2006; Epel et al., 2004). Metabolomic Medicine Health Clinic and Toxplus, a University of Crete spinoff company, investigate the impacts of lifestyle on chronic diseases with the application of metabolomics (Tsoukalas et al., 2019; Tsoukalas et al., 2017; Papamichael et al., 2019) and highly advanced tools in telomere biology (Tsatsakis et al., 2019). Ongoing human studies indicate that nutritional supplementation is positively associated with longer telomeres (Tsoukalas et al., 2019a; Fragkiadaki et al., 2017) and improved neuroprotective mechanisms against ischemic episodes (Faggi et al., 2019). Individuals with asthma or atopic dermatitis have been shown to have altered metabolic pathways (Papamichael et al., 2019; Tsoukalas, 2018a), and ongoing clinical studies will define the metabolic fingerprints of rheumatoid arthritis, Hashimoto’s thyroiditis, psoriasis, Crohn’s disease, and ulcerative colitis to identify predictive biomarkers (Tsoukalas, 2018b).

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