Nutrition and Health

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Background

There are a variety of ancient texts that describe the benefits and dangers of certain foods, and the relationship between diet and health (Daniel 1: 11-16 Biblica NIV; Totelin, 2015). The absence of essential nutrients, resulting in deficiency diseases, was recognized even before vitamins and minerals were 'discovered' in the eighteenth and nineteenth centuries. Throughout our lives, even before we are born, we are exposed to a complex mixture of food compounds that can have a positive or negative impact on our long-term health. Intricate biochemical processes extract the energy and other useful components that enable us to grow and function, and many compounds that were seemingly unimportant in the past are now accepted as being fundamental for health.

Nutrients

Generally, nutrients are classified as either macro- or micronutrients, based on the amounts we require from the diet (Gibney et al., 2009). Some nutrients can be stored (e.g., glucose as glycogen in the liver, fat-soluble vitamins in fat reserves) while others are required more or less continuously. There are, however, also differences between individuals, meaning some may require specific nutrients more frequently (e.g., iron), and it is challenging to determine whether individuals have adequate levels of most nutrients because levels in the blood offer only a crude measure of cell and organ status (Gibson, 2005).

In recent decades, our need for a broad spectrum of nonnutrients, phytochemicals, has also been recognized (Halliwell and Gutteridge, 2007). These nonnutrients (bioactives) are not essential for life in ways that macro- or micronutrients are, but nonetheless have putative health benefits and, whether acting directly or indirectly, diets rich in these compounds significantly reduce our risk of chronic disease, including cancer and cardiovascular disease. We also require dietary fiber, nondigestible materials, such as cellulose, to support gut function (mechanical) and a healthy microbial population (prebiotics) (Graf et al., 2015).

A lack of nutrients or bioactives, or an excess of these, can cause poor health. Where once poverty led to malnutrition because of a lack of food (energy or specific nutrients), poverty of knowledge and cheap foods high in fat, sugar, and salt are leading to weight gain and obesity as well as specific deficiencies (e.g., vitamin D) (Tulchinsky and Varavikova, 2014).

Macronutrients

There are three macronutrients – carbohydrates, fats, and proteins (Gibney et al., 2009). They provide 'structural materials' (e.g., amino acids, lipids) and energy (joules or kilocalories). When necessary, or as a result of disease, proteins can be broken down to generate energy, but carbohydrates and fats are used preferentially for energy (Lanham-New et al., 2010).

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Carbohydrates

Carbohydrates and fats consist of carbon, hydrogen, and oxygen. Carbohydrates range from simple monosaccharides (e.g., glucose, fructose, galactose) through a range of saccharides, depending on the number of sugars present (e.g., disaccharides such as sucrose or table sugar) to highly complex polysaccharides (starch). Carbohydrates are found mainly in starchy foods (e.g., grain and potatoes), fruits, milk, and yogurt. Other foods such as vegetables, beans, nuts, and seeds also contain carbohydrates, but in smaller amounts.

About half (45–65%) of our daily energy intakes should be sourced from carbohydrates (Gandy, 2014). Cells and tissues use glucose for energy, but glucose is essential for proper functioning of the brain and central nervous system, kidneys, and muscles including the heart. Glucose is stored in muscles and the liver as glycogen for later use, being restored to the blood through glycogenolysis (Lanham-New et al., 2010).

Traditionally, simple carbohydrates were thought to raise blood glucose levels more rapidly than complex carbohydrates. In fact, some simple carbohydrates (e.g., fructose) follow different metabolic pathways (e.g., fructolysis), which result in only partial conversion to glucose, while many complex carbohydrates (e.g., potato starches) – so-called high glycemic index (GI) or high glucose loading (GL) foods – are digested at the same rate as simple carbohydrates (Monro and Shaw, 2008). Glucose stimulates the production of insulin by beta cells in the pancreas, driving uptake by the muscles. Dysfunction in the production of insulin and/or the response of receptors to insulin leads to impaired glucose tolerance and, ultimately, diabetes (Lanham-New et al., 2010).

Fiber consists largely of cellulose, which is not digested, but helps maintain gut function by bulking out waste and providing a food source (prebiotics) for gut bacteria (microbiome) (Graf et al., 2015). Low fiber intakes are associated with constipation and increased risk of colon cancer. Diets high in fiber, however, not only reduce symptoms associated with poor gut function, but also help lower cholesterol, and decrease the risk of obesity and cardiovascular disease (CVD) (Mitchell and Shewry, 2015; Valdes et al., 2015). High-fiber foods include fruits, vegetables, and whole grain products.

There are, however, two types of fiber: soluble and insoluble (MedlinePlus, 2014). As suggested by its name, soluble fiber forms a gel with water during digestion, increasing the size of and softening stools, slowing digestion. Formation of this gel reduces the rate of glucose uptake, smoothing out peaks and troughs in glucose and insulin, and helping to reduce the risk of diabetes. In contrast, soluble fiber is found in oat bran, barley, nuts, seeds, beans, lentils, peas, and some fruits and vegetables, and adds bulk to stools, shortening gut transit by stimulating peristalsis, the rhythmic muscular contractions of the intestines.

Fats

Fats (triglycerides) consist of fatty acid monomers, some of which are essential, bound to a glycerol backbone. They are classified as saturated or unsaturated, depending on the detailed structure present, specifically the number of double bonds (Gibney et al., 2009). Although saturated fats from animal sources and, for example, coconut have been a staple food for millennia, unsaturated fats (e.g., vegetable oil) are still considered to be healthier, despite recent evidence suggesting saturated fats might not be as detrimental as previously thought (de Souza et al., 2015). Most saturated fats are solid at room temperature while unsaturated fats are typically liquids (e.g., olive or rapeseed oils).

Trans fats are unsaturated with one or more *trans*-isomer bond; these are rare in nature and typically created during industrial processing, specifically hydrogenation. Unsaturated fats can be classified as monounsaturated (one double-bond) or polyunsaturated (many double-bonds). Depending on the location of the double bonds, unsaturated fatty acids may be classified as omega-3 or omega-6 fatty acids.

Most fatty acids are nonessential, but omega-3 and omega-6 fatty acids can only be obtained from the diet and should be obtained at a ratio of 1:1–1:5. In general, Western diets are deficient in omega-3 and have excess omega-6, which are thought to promote many diseases, including CVD, cancer, and inflammatory and autoimmune diseases (e.g., asthma) (Simopoulos, 2002). Omega-3 and -6 are substrates for prostaglandins, which have a variety of roles in the human body (Lanham-New et al., 2010). Fatty acids, such as conjugated linoleic acid, catalpic acid, eleostearic acid, and punicic acid, in addition to providing energy, are potent immune modulators (Givens, 2015).

Protein

In addition to carbon, hydrogen, and oxygen, proteins contain nitrogen and, in the case of methionine and cysteine, also sulfur. Proteins are structural molecules as well as enzymes. The body cannot store amino acids and requires a continuous source to produce new, and replace damaged, proteins (Gibney et al., 2009). Of the 20 amino acids utilized by humans, 9 are essential (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) and must be sourced from the diet, as the body cannot synthesize them *de novo* (Lanham-New et al., 2010). Complete protein sources contain all the essential amino acids while an incomplete protein source lacks one or more of the essential amino acids. In combination, incomplete sources of protein may provide all the essential amino acids (Gandy, 2014).

Micronutrients

Micronutrients are, generally, minerals and vitamins (Gibney et al., 2009). Dietary minerals are inorganic elements, besides carbon, hydrogen, nitrogen, and oxygen, which are present in most organic molecules. Some minerals are absorbed much more readily as salts (ionic form), and some foods are fortified with minerals to increase uptakes (e.g., iodine in salt, iron in breakfast cereals) (Lanham-New et al., 2010; Gandy, 2014).

Macrominerals are required in relatively large amounts (RDA greater than 150 mg/day) and have roles in structure (e.g., bone) and function (e.g., electrolyte) and include calcium (e.g., muscle function, digestive health, bone, signaling); chlorine (common electrolyte); magnesium (e.g., ATP processing, bone, peristalsis); phosphorus (e.g., bone, ATP); potassium (common electrolyte, heart and nerve health); sulfur (three essential amino acids); and sodium (common electrolyte). Excessive sodium consumption can deplete calcium and magnesium and is associated with increased risk of hypertension and osteoporosis.

Some elements are only required in trace amounts (RDA < 200 mg day $^{-1}$), usually because they have a role in enzymes, such as cobalt (biosynthesis of vitamin B_{12} co-enzymes); copper (redox enzymes including cytochrome c oxidase); chromium (sugar metabolism); iodine (e.g., biosynthesis of thyroxine); iron (range of enzymes, hemoglobin and other proteins); manganese (processing of oxygen); molybdenum (xanthine oxidase and related oxidases); nickel (urease); selenium (peroxidases); and zinc (enzymes such as dehydrogenase). Deficient or excess intakes of minerals can have serious health consequences (Gibney et al., 2009; Lanham-New et al., 2010; Heaney, 2015).

As with minerals, most vitamins (vital amines) are essential nutrients (e.g., vitamin C). The only exception is vitamin D, which can be synthesized in the skin. Vitamin deficiencies may result in diseases including goiter, scurvy, osteoporosis, certain forms of cancer, and poor psychological health (Heaney, 2015; Johnson, 2015). However, excess of some vitamins are also dangerous to health (e.g., vitamin A) (Gibney et al., 2009; Lanham-New et al., 2010).

Antinutrients

Antinutrients are natural or synthetic compounds that interfere with the absorption of nutrients. Examples include the following:

- Protease inhibitors (e.g., Bowman-Birk trypsin inhibitor in soybeans (Birk, 1985)), which inhibit trypsin, pepsin, and other
 proteases in the gut, preventing digestion and absorption of proteins and amino acids
- Lipase inhibitors (e.g., tetrahydrolipstatin), which interfere with enzymes, such as lipases, which catalyze hydrolysis of some lipids and fats
- Amylase inhibitors in beans, which prevent the action of enzymes that break the glycosidic bonds of starches and other complex carbohydrates, preventing the release of simple sugars and absorption by the body
- Phytic acid in the hulls of nuts, seeds, and grains, which has a strong binding affinity for calcium, magnesium, iron, copper, and zinc, preventing their absorption
- Oxalic acid and oxalates, which are present in many plants, particularly members of the spinach family, bind calcium to prevent its absorption

Many traditional preparation methods (e.g., fermentation) reduce antinutrients, such as phytic acid, increase the nutritional quality of plant foods, and are widely used in societies where cereals and legumes are a significant part of the diet (Reddy and Pierson, 1994). For example, cassava is fermented to reduce levels of both toxins and antinutrients. Glucosinolates (e.g., broccoli, Brussels sprouts, cabbage, and cauliflower), although widely recognized for their putative health benefits, also interfere with the uptake of iodine and flavonoids, and chelate metals (e.g., iron and zinc) thus reducing their absorption (Prakash et al., 2014).

Bioactive Compounds

Bioactive compounds are those food components that have an effect on the body as a whole or specific tissues or cells. They are distinct from nutrients because bioactive compounds are not essential and, currently, there are no recommended daily intake values (Gibney et al., 2009; Lanham-New et al., 2010). However, it is well established that a range of compounds from plant and animal sources has a positive influence on human health (Halliwell and Gutteridge, 2007). These compounds include non-pro-vitamin A carotenoids and polyphenols, phytosterols, fatty acids, and peptides.

The mechanisms of action for the various compounds, especially as related to reduced risk of disease in individuals, are not fully understood. Some act as antioxidants while others stimulate defense mechanisms that enhance the response to oxidative stress, preventing widespread damage or enhancing repair (Halliwell and Gutteridge, 2007). There is insufficient evidence to recommend intakes, efficacy, and safety of these substances, especially as isolate supplements, but it is generally agreed that, consumed as part of a balanced diet, the benefits are significant.

Diet and Disease

Many compounds have different biological effects within our bodies, and diet and disease are intimately associated (Aruoma, 2015). Apart from the diseases associated with malnutrition or an inadequate supply of a specific compound, leading to deficiency (e.g., scurvy and beriberi), the long-term effects of undernutrition in the developed world are also becoming apparent (Arthur, 2015).

Low birth weight infants experience increased rates of CVD in adulthood, and there is increasing evidence to support an association with obesity and metabolic disorders, such as diabetes (Nightingale et al., 2015). Animal and increasingly human studies suggest that malnourished mothers whether deprived of energy or individual nutrients have offspring that are more susceptible to

chronic disease (Khalil et al., 2015; Armitage et al., 2004). Cancer incidence is significantly higher in subpopulations that consume a greater proportion of animal-derived fats and few if any vegetables, fruits, grains, and cereal (World Cancer Research Fund/American Institute for Cancer Research, 2007). Nutritional disorders in Europe are typical of affluent societies, but age-related chronic diseases occur less frequently and later in life in the populations of Mediterranean countries (Spain, Southern France, Greece, and Italy) than those in Northern Europe (UK and Germany). Thus, given sufficient food, it is important to maintain a balance in which the right amounts of each food component are absorbed and available for use.

Understanding how our bodies respond to what we eat and make the most of what is available is central to unraveling the relationship between food and disease and health. Common to all nutritionally related diseases may be inappropriate changes in gene expression. Studies of diet–gene interactions have been underway for a number of years and have produced many interesting results. Until relatively recently, however, researchers have been limited in their investigations; one or at most a handful of genes, maybe one or two biochemical pathways, and single or simple groups of nutrients rather than whole foods. Nutrigenetics and a nutrigenomics have provided background information and new tools that enable researchers to take a much more global and realistic perspective (Aruoma, 2015; Garg et al., 2014).

Malnutrition

Malnutrition arises from eating a diet that is insufficient in or has excess calories, protein, carbohydrates, vitamins, or minerals. Not enough nutrients leads to undernutrition but the term malnutrition is often, wrongly, used in place of undernutrition. Undernutrition during pregnancy or infancy can result in permanent problems with physical and mental development. Starvation, extreme undernour-ishment, is associated with reduced stature, thin arms and legs (lack of muscle bulk), low energy levels, and swollen legs and abdomen, but symptoms of malnutrition can be as apparently minor as increased frequency of infections and tiredness. Symptoms related to micronutrient deficiencies depend on the substance that is lacking. One of the commonest micronutrient deficiencies globally is iron.

In 2010, there were c.925 million undernourished people in the world, an increase of c.80 million people since 1990 but 2.5% fewer as a proportion of the world population (World Food Programme, 2015; Friedrich, 2015; Arthur et al., 2015). Another billion people are estimated to have micronutrient deficiencies. In 2013, protein–energy malnutrition was estimated to have resulted in 469 000 deaths. Other nutritional deficiencies, which include iodine and iron deficiencies, resulted in a further 84 000 deaths. About a third of deaths in children are believed to be due to undernutrition, but 165 million children have stunted growth – and opportunities – as a result of malnutrition.

In developing countries, overnutrition is beginning to be as much of a problem as it is in many developed countries. Overnutrition is a form of malnutrition, often in combination with a sedentary lifestyle, that increase an individual's risk of (mechanical) disability and disease (e.g., cancer and CVD), reducing quality of life, productivity, and life expectancy. Factors contributing to malnutrition of all types include poverty, socioeconomic status, agricultural productivity (e.g., availability of land, adverse weather, farming skills, lack of technology or resources), and food security (e.g., global warming, conflict, etc. that lead to disruption in global food and resource supply, disease (e.g., colony collapse disorder, wheat stem rust)) (Friedrich, 2015; Arthur et al., 2015).

Chronic Diseases

Life-stage, lifestyle, and genetics affect our risk of developing chronic diseases. As we age, our bodies are less effective at avoiding disease. The resulting breakdown in structure and function leads to an increased risk of chronic disease including cancer, CVD, type II diabetes, cataract and macula degeneration, arthritis, etc. Poor diet can accelerate this process while 80% of case-controlled studies support the hypothesis that a diet rich in fruits and vegetables, or more specifically bioactive compounds, can reduce the risks (Halliwell and Gutteridge, 2007).

Diet has a role in the maintenance of health and development of disease. Understanding this relationship has proven very difficult, and what is obvious is that the benefits of some dietary choices are not the same for everyone. Maintaining an appropriate weight for height, moderating consumption of alcohol, not smoking, and taking regular exercise determine whether the majority of the population is at high or low risk of developing chronic disease (Johnson, 2015). However, individual genetic differences in response to diet have been evident for years, e.g., cholesterol and saturated fat intake (Goldstein and Brown, 2015), salt intake, and hypertension (Baldo et al., 2015; WHO, 2015). Some genetic diseases have no association with diet (e.g., sickle cell disease) while others may create specific dietary needs (e.g., cystic fibrosis, phenylketonuria) or may be exacerbated by some foods (e.g., lactose intolerance, celiac and food allergy). Others carry a high risk of developing disease (e.g., BRCA1/2 and breast cancer), which may or may not be affected by diet or other lifestyle choices.

Nutrigenetics examines single gene/single food compound interaction. One of the best-described examples is the relationship between folate and the gene for MTHFR – 5,10-methylenetetrahydrofolate reductase. Nutrigenomics, on the other hand, aims to examine the response of individuals and populations to food/food components using postgenomics technologies ('omics'). The huge advantage in this approach is that the studies can examine people (i.e., populations, subpopulations – based on genes or disease – and individuals), food, life-stage, and lifestyle. For example, to understand the role of vitamin E in the prevention of CVD, nutrigenomics enables researchers to examine lipid and lipoprotein genotypes; glucose metabolism (i.e., the insulinglucagon regulatory mechanism); triglyceride regulation (which retinoids and, therefore, some carotenoids, may act on); and fatty acid metabolism simultaneously. The various techniques, however, also reveal genes, proteins, and metabolites, which might not have predicted as relevant (Aruoma, 2015).

There are, however, fewer than 100 genes – compared with c.25 000 in the human genome – with polymorphisms that appear to confer a significant disadvantage that may be overcome through dietary modification, and our understanding of whole genome—food relationships is still limited. In addition, there are a number of wider issues to consider, not least the ethical, legal, and societal aspects of the research. Genotypes that confer a substantial disadvantage are not usually preserved in a population and those that do, although unrelated to diet, have been shown to offer some other benefit. The fact that the most common polymorphism for MTHFR is present in 15–20% of the European population should at least raise the question why it and the others have persisted so successfully if they only bestow a disadvantage or whether the disadvantage arises only because of modern dietary behaviors. Secondly, we do not know how or which of these genes interact with one another or the consequences of modifying the response of a few on the majority, and the impact on our immediate or long-term health.

Allergy and Intolerance

The public perception is that food allergy is a common condition, affecting up to one in three of the population (i.e., up to 20 million in the UK). Allergy in general is increasing and with it also food allergy. The numbers of foods causing an allergic reaction and the frequency of severe reactions (anaphylaxis) are also increasing, but only around 1–2% of adults are food allergic although rates are higher among children (c.5–8% of under 16) (University of Portsmouth, 2013).

Food allergy is an immune response to a protein or portion of a protein found in food. The allergic reaction can occur at a point of contact (e.g., the lips or tongue) as well as throughout the body (systemic). Symptoms differ greatly between individuals and might present differently in the same person, depending on the route and duration of exposure.

Food allergy develops in two stages: sensitization occurs when the immune system encounters an unrecognized molecule (almost always a protein). At this stage, individuals have indication they are potentially allergic. An allergic reaction is triggered only when the individual eats the same food or is exposed to the allergen (protein) in a different food.

Clinical experience suggests that food allergies are limited to a relative small group of foods including cow's milk, egg, soy, peanut, tree nuts, cereals, crustaceans and fish, and seeds (Nwaru et al., 2014). One theory suggests that the modern obsession with cleanliness explains why allergies are becoming more important. The reduced incidence of previously common infections and increased use of antibiotics may have shifted the immune system toward sensitization. In truth, however, although we know how people become allergic, the why remains elusive.

At present there is no cure for food allergy. The only treatment is avoidance of the problem food(s), but even this can be problematic meaning food allergy can have a detrimental impact beyond simply what can and cannot be eaten.

Food Intolerance

Not all reactions to food are an allergy; it can be food intolerance (e.g., lactose intolerance) or symptoms of a disease (e.g., celiac). Food intolerance, unlike food allergy, can have a number of different causes. It is also much more common than food allergy. The onset of symptoms is usually slower and persists for several hours or longer. Intolerance to several foods or groups of foods is not uncommon, making identification of the cause much more challenging (Turnbull et al., 2015). Those with food intolerance(s) can sometimes tolerate small amounts of the food that induces symptoms, but too much or too frequent consumption leads to symptoms, which can also vary significantly between individuals or depending on the route of exposure. Symptoms include fatigue, gastrointestinal disturbance (e.g., diarrhea, vomiting, bloating, irritable bowel, etc.), and skin-related symptoms (e.g., urticaria, eczema, etc.). Causes of intolerance can be genetic (e.g., enzyme defects/deficiency, lactose intolerance and gluten intolerance (celiac disease)), which means substance in the food cannot be digested correctly, pharmacological (e.g., caffeine intolerance), or toxicity (e.g., histamine). However, apart from celiac disease and lactose intolerance, there are no reliable or validated tests to identify food intolerance.

Conclusions

Until a few decades ago, virtually all known health effects of foods were related to their content of essential nutrients. Clinical descriptions of most diet-related illnesses mirrored the symptoms of nutrient deficiencies, and the key public health concern was ensuring that everyone consumed enough food. It is only in the past 50 years that epidemiological observations and nutritional intervention studies have begun to associate noncommunicable diseases with intakes of dietary constituents including fat, fiber, and bioactive substances (e.g., phenolic compounds).

Taking advantage of the emergence of 'omic technologies and digital informatics, researchers have been able to generate and interrogate increasingly large sets of data and, for the first time, understand the impact of changes in diet and lifestyle choices on the health of populations. In parallel, concerns have shifted from eating enough to avoiding excess and, finally, to eating well. Defining what to 'eat well' has, however, turned out to be far more complex than defining minimum needs for essential nutrients.

Firstly, there is no single paradigm to study these relationships, given the wide variety of biological mechanisms and long exposure involved; indeed there is no satisfactory definition of health except as the absence of disease. Secondly, many of the experimental models in humans used to define needs for essential nutrients, and an array of nonnutrient bioactive compounds with putative health effects, are not applicable in the study of long-term effects of diet in free-living populations. It is clear that experiments with isolated dietary compounds do not reflect adequately the effects of the complex mixture of foods we consume daily, let alone the relationships between these foods and our genetic and phenotypic makeup or vice versa.

While the discovery of essential nutrients and their role in health was the domain of a few specialties speaking a common language (primarily biochemists and physiologists), the study of the long-term effects of whole diets in humans must by necessity involve epidemiologists, social and behavioral scientists, food scientists, clinicians, dietitians and nutritionists, policy experts, etc., making the development of consensus far more difficult. Thus, it is hardly surprising that we have not achieved agreement on how to 'eat well.' Nevertheless, although the increasing numbers of questions seem impossibly complicated, modern nutrition sciences are ideally placed to determine what we should be eating.

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