Impact of nutrition on ageing and disease

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Purpose of review

The globe is suffering a tsunami of chronic diseases, affecting especially the elderly and those with a dysfunctioning immune system. The fundamental principles of optimal health and optimal ageing are abstaining from smoking, modest alcohol consumption, regular physical exercise and a diet rich in fish and plants and low in condensed calories, sugar and dairy products.

Recent findings

Dietary supply and production of advanced glycation end products leads to the accumulation of these products in the tissues and is strongly associated with ageing of the vascular endothelium, nervous system, eyes and other vital organs. Telomeres, which are not involved in DNA repair, remain unrepaired and loose with time. A decline in innate and acquired immunity is seen with increasing age and maintenance of low basal immune activity (degree of inflammation) seems important for health and longevity: 'people who are predisposed to weak inflammatory activity may live longer'.

Summary

Supplementation with vitamins has little effect on ageing/prevention of chronic diseases, but antiinflammatory molecules like polyphenols are more effective, especially when combined with reduced intake of calorie-condensed foods. The effect of probiotics on ageing needs further exploration. The effects of caloric restriction, proven effective in other species to control aging and prolong lifespan, have not been fully explored in humans.

Keywords

advanced glycation end products, ageing, chronic diseases, inflammation, lifestyle, telomeres

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Abbreviations

AGE advanced glycation end product
CHD coronary heart disease

1363-1950

Introduction

A discrete but nevertheless gigantic tsunami of chronic diseases is flooding the world, ranging from Alzheimer's disease to polycystic ovary disease, and including prostatic diseases, cancer and hyperplasia. All chronic diseases are interrelated as they contain an element of increased inflammatory response, often to be observed long before the disease is documented clinically [1]. The increase in 'inflammatory tonus' is mainly the result of lifestyle and nutritional habits, making the increase controllable. According to the World Health Organization, 46% of global disease burden and 59% of global mortality are due to chronic diseases [2]. More than 35 million individuals die each year from chronic diseases, and the numbers are increasing steadily. The greatest increases have been seen in cancer, with incidences forecasted to double by the year 2020. Incidences of diabetes are also thought to increase twofold by the year 2050. The global disease burden is expected to be 57% by the year 2020, and this will result in enormous increases in health care expenditure, an expense that societies and governments may find impossible to cope with. The annual health care expenditure in the US was $1.6 trillion in 2002 (about $5440 per person) and is forecasted to double by the year 2011 [3].

Chronological, biological and premature ageing

Ageing is characterized as a 'progressive loss of body functions with decreasing fertility and increasing morbidity and mortality'. Central to ageing is the accumulating damage to cells, which is clearly influenced by genetic and environmental factors. The rate at which cellular damage accumulates is determined by the balance (homeostasis) between damage occurring and the action of defense and repair mechanisms [4••]. Defense and repair systems are highly enzyme dependent. In the absence of the part of the gene(s) necessary for production and function of these particular enzymes, an increased accumulation of cellular damage will occur. Telomeres are not involved in DNA repair mechanisms, which is why telomere injuries tend to remain unrepaired. Telomere length is regarded as a marker of accumulated oxidative stress and 'permanent' low antioxidant capacity and has been suggested as a marker of cumulative damage to the cell and to ageing [5]. It is also associated with an increase in morbidity and mortality [6,7].

Advanced glycation end products in focus

The role of advanced glycation end products (AGEs) in the pathogenesis of unhealthy individuals and

particularly those with chronic diseases is receiving increasing attention. Of the 3562 papers available on PubMed, no less than 321 were published during the first 6 months of 2005. Almost 100 years have passed since the Frenchman Maillard investigated the browning and toughening that occurs when foods are heated up (cooking, frying, baking, barbequing), a discovery that has been given the name Maillard reaction. High temperature and the presence of sugar and fat increase the reaction during which glycated proteins/AGEs are formed both *ex vivo* and *in vivo*. Once formed, the AGE reaction is not reversible and the products will gradually accumulate in the body [8••]. Reacting with sugars and fats, the proteins turn brown and fluorescent, lose elasticity and crosslink to form insoluble masses, which generate free radicals. Accumulation of AGEs, strongly associated with ageing and chronic diseases, occurs particularly in the vascular endothelium, the nervous system, the eyes and collagen, and most vital organs. This deleterious form of posttranslational modification of macromolecules has been linked in particular to diseases such as Alzheimer's disease, cataract and other degenerative ophthalmic diseases, diabetes, dialysis related amyloidosis, multiple sclerosis, Parkinson's disease, vascular dementia and several other chronic diseases, and to physiological ageing. Accumulation of AGEs in tissues is suggested to play a pivotal role in progression of disease and development of associated macro and microvascular complications. Such accumulation was recently suggested to also be involved in the loss of bone density (and muscular mass) associated with ageing [9••]. In fact, free radicals form in glycated proteins at nearly five times the rate they form in nonglycated proteins [10].

A Third World epidemic

The fastest increase in chronic diseases is now being seen in the Third World. Cardiovascular diseases are more common both in India and in China than in all economically developed countries in the world added together [2]. These diseases were almost nonexistent until fairly recently and still are in traditional cultures, such as those found in certain rural areas of Crete and Japan [11,12]. Furthermore, the differences between different populations are huge – in the case of cancer up to 100-fold [13]. See a recent excellent review for more details [14••].

These diseases seem to have been exported from the Western world together with our cultural, political and religious values, and with our enormous surplus of cheap agricultural products – grains, especially wheat, and dairy products, especially butter. Little consideration has been given to the fact that a large proportion of individuals in these parts of the world are intolerant to molecules such as gluten or lactose. Furthermore, the detrimental effect of such a policy on local production of health-promoting fresh fruits and vegetables has not been fully considered.

Critical illnesses

Critical illnesses, which include medical emergencies such as coronary heart disease (CHD), stroke and acute pancreatitis and intervention-associated conditions induced by surgical and advanced medical treatments, particularly various organ and stem cell transplantations, are increasing in the footprints of chronic diseases. Critical illness particularly targets those with reduced innate immune functions – the aged and chronically ill. Only in the US does severe sepsis affect 751 000 persons annually [15,16], which results in 29% deaths (215 000 patients/year) [16]. The incidence of critical illness is also rising and has done so for some time (about 1.5% per year). The dominating cause of mortality is sepsis, which thus far has remained resistant to most preventive and treatment efforts. Currently in the US sepsis is the tenth most common cause of death.

Historical perspective

The increase in chronic diseases seems to stem from the industrial revolution, that is the mid-1850s. Circumstantial evidence supports an association between chronic disease and change in lifestyle: less physical activity, increased stress and particularly the transition from natural unprocessed foods to processed and often calorie-condensed foods. The last 150 years have been characterized by a significant reduction in intake of plant fibres, plant antioxidants and polyunsaturated fatty acids (PUFAs), especially n-3 PUFAs, and in a doubling of the intake of saturated fats (from approximately 20% to over 40% of daily energy intake) and a more than 100-fold increase in high glycaemic index foods – sugary and starchy products. The annual consumption of sugar, for example, has increased from about 1 lb/person/year in 1850 to about 100 lb/person/year in the year 2000.

Impact of healthy lifestyle

An abundant literature suggests that four different factors have additive effects on quality and quantity of life:

(1) control of physical and mental stress;
(2) limited exposure to chemicals and toxins, especially smoking and alcohol;
(3) physical exercise;
(4) proper nutrition.

Although most studies in the past have focused on CHD and type 2 diabetes, increasing evidence suggests that a healthy lifestyle affects all chronic diseases. A recent study [17••] investigated the effects of a healthy lifestyle over a 12-year period in 2339 apparently healthy men and women aged 70–90 from 11 different European countries. During the period, 935 died – 371 from cardiovascular events, 233 from cancer, 145 from other diseases, and 186 from unknown causes. The hazard ratio for adherence to a Mediterranean-type diet (higher intake

of fruits, vegetables and fish, olive oil, lower intake of sugar, starch, dairy products) was 0.77 (confidence interval (CI) 0.68–0.88), for moderate use of alcohol it was 0.65 (CI 0.67–0-91), and for nonsmoking it was 0.65 (CI 0.57–0.75). The combination of four low-risk factors lowered the all-cause mortality rate to 0.35 (CI 0.28–0.44). The prolongation of life by healthy lifestyle in a cohort of very old people is most interesting and suggests that application of a similar lifestyle on younger people will almost certainly show even greater benefits. In an excellent commentary to this European study, Rimm and Stampfer [18•] point out that their studies in the US demonstrated an 83% reduction in the rate of CHD [19], a 91% reduction in diabetes in women [20], and a 71% reduction in colon cancer in men [21] adhering to a similar lifestyle. Comparable observations were made in a recent Greek study involving 22 043 adults [22]: adherence to a Mediterranean-type diet was reported to reduce adjusted hazard ratio for total mortality to 0.75 (CI 0.64–0.87), death in CHD to 0.67 (CI 0.47–0.94) and death due to cancer to 0.76 (CI 0.59–0.98).

Consumption of advanced glycation end products aggravates disease

Only recently has more attention been given to the fact that AGEs are delivered to the body and absorbed through the food we eat: foods rich in both protein and fat, and cooked at high heat, tend to be the richest dietary sources of AGEs, whereas low-fat, plant fibre rich foods tend to be relatively low in AGEs. Reduced dietary supply of vitamins C, B6, B12 and high AGE consumption triggers inflammation [23•] and binding of AGEs to the receptor for advanced glycation end products (RAGE), and induces significant activation of the transcription factor nuclear factor κB (NF-κB) and subsequent expression of NF-κB-regulated cytokines [24••].

A large content of AGEs is observed in numerous heat-produced foods such as brewed coffee, custard, pretzel sticks, and especially in pasteurized dairy products [25••,26•]. Plant food is, however, no exception: roasted nuts and fried or boiled tofu show relatively high levels of AGEs, while low-fat plant-derived foods – boiled or baked beans – are typically low in AGEs. Supplementation of taurine seems to minimize endogenous AGE production [27•]. Dietary AGE restriction has been reported to support the suppression of several immune defects, reduce insulin resistance and diabetic complications – both genetic and diet-induced – and in patients with persistent diabetes [28••]. Carnosine, an endogenous and carnivorous diet-supplied, histidine-containing dipeptide [29••,30•], and various plant-derived antioxidants – flavonoids [31•,32•] and curcuminoids [33•] – are also reported to reduce the accumulation of AGEs in tissues.

Ageing and immune functions

Most researchers agree that there is a decline in both innate and adaptive immunity with advancing age. They disagree, however, whether this is due to normal ageing or just induced by lifestyle. The capacity of the innate immune system to respond properly to mental and physical stress, including influenza and pneumococcal vaccination, is increasingly impaired. The cytotoxicity of natural killer cells and natural killer T cells and the production of IFN-γ are observed to decrease with age [34•]. Significant alterations in functions of human macrophages and neutrophils [35•,36•] – superoxide anion production, chemotaxis, apoptosis and signal transduction – have also been reported. A low capacity of standardized lipopolysaccharide challenge to produce various pro and antiinflammatory cytokines has also been observed in the elderly and frail, and suggested to be predictive of outcome [37••]. Elderly people with a discrete permanently increased level of inflammation and elevated basal levels of IL-6 and C-reactive protein are known to be at risk of increased morbidity and mortality. Maintenance of low basal immune activity (degree of inflammation) seems to be very important for health and longevity: 'immunity may be an ally early in life, but turns out to be an enemy as we age' [38•] and 'people who are predisposed to weak inflammatory activity may live longer' [39].

Supplementation with vitamins most often is ineffective

Numerous attempts in recent years have been carried out to use various vitamins, alone or in combination, to prevent or reduce the impact of chronic diseases, but they have usually failed and sometimes even produced adverse effects. More than 5000 people aged 70 years or older who had suffered a fracture were randomly assigned to 800 IU daily of oral vitamin D3, 1000 mg calcium, oral vitamin D3 (800 IU per day) combined with calcium (1000 mg per day), or placebo and followed for periods up to 62 months. A total of 698 (13%) of 5292 participants developed a new low-trauma fracture, 183 (26%) of which were of the hip, but no difference was observed between the treatment group and the placebo group [40•]. In a similar study in 3314 women aged 70 and over and with one or more risk factors for hip fracture, daily supplementation with 1000 mg calcium and 800 IU cholecalciferol was provided and the outcome compared with controls. The rate of fractures after a median follow-up of 25 months was lower than expected in both groups, and no difference was observed in outcome between the groups [41•]. A recent Cochrane metaanalysis reviewing 18 randomized trials involving 1306 participants found nutritional supplementation in the aftercare of hip fractures had at best only a weak effect [42•]. The experience is similar when other chronic diseases are considered.

Low-fat/high-plant diet most promising

It is promising that polyphenols, abundant in many plant and vegetables, exhibit much stronger effects, and several studies confirm their efficacy in the prevention of degenerative diseases [43•,44••]. An 18-year follow-up study [45••] found that elderly men consuming a combination of at least five servings of fruits and vegetables per day and 12% energy or less from saturated fat were 31% less likely to die of any cause ($P < 0.05$), and 76% less likely to die from CHD ($P < 0.001$) relative to those consuming less than five servings of fruit and vegetables per day and over 12% energy from saturated fat. These findings clearly demonstrate that the combination of both behaviours is more protective than either alone and also suggest that their beneficial effects are mediated by different mechanisms.

A role for pre/pro/synbiotics?

In a recent controlled study [46•], 60 individuals who were at least 70 years old received daily supplementation over 4 months in addition to their regular diet. The supplement consisted of a synbiotic mixture of 109 cfu *Lactobacillus paracasei* and 6 g of fructo-oligosaccharides (FOS) combined with vitamins (E, B12, folic acid) and nutrients. After the study period, all participants underwent vaccination against influenza and pneumococcus. Various immunity-related parameters – lymphokine production by mononuclear cells (PBMCs), lymphocyte subpopulations and natural killer cells – were measured at the start of the study, before and after vaccination. Natural killer cell activity increased significantly ($P < 0.001$) in the supplemented group compared with the nonsupplemented group. IL-2 production by PBMCs and the proportion of T cells with natural killer activity decreased significantly in the control group but remained unchanged in the supplemented group. No difference between the groups in lipopolysaccharide-stimulated PBMC production of IL-1 and TNF-α was observed, nor were any differences in IFN-γ production noted following influenza vaccination. After vaccination, phytohaemagglutinin-stimulated IL-2 production decreased after vaccination in the controls but remained unchanged in the supplemented group. During a 12-month follow-up period after the supplementation, the supplemented individuals reported significantly less infections ($P = 0.02$). In another study seven patients were totally tube fed by percutaneous endoscopic gastrostomy and received a synbiotic mixture of 107 cfu *Bifidobacterium longum* plus 2.5 g FOS over 12 days [47•]. Although the density of *B. longum* in the stools increased by one log, no significant differences could be observed in episodes of fever, episodes of diarrhoea, use of antibiotics, or any effects on nutritional status [body mass index (BMI)].

Conclusion

The effects of caloric restriction, which has proven so successful in controlling ageing and prolonging lifespan in other species including primates, have not been fully explored in humans. There is increasing support, however, that in addition to abstaining from smoking, regular physical exercise and modest intake of alcohol, a diet low in inflammation-inducing molecules, saturated and trans fatty acids, dairy products and sugars and high in anti-inflammatory molecules, ω-3 fatty acids, plant fibres, vitamins and antioxidants, particularly polyphenols, is effective in supporting optimal ageing and reducing the incidence of chronic diseases. A recent study [48••] has suggested that of all the 'healthy nutrients', consumption of legumes appears to be the most effective, showing a 7–8% reduction in mortality hazard ratio for every 20 g increase in daily intake.

The importance of a healthy lifestyle, like the need for reducing emissions of ozone-depleting substances, has not been fully appreciated even in Western societies. Still, future life on this planet is very dependent on our willingness to deal with these issues. Thus far, the need for a healthy lifestyle has only been accepted by a small fraction of society, mostly individuals with a higher educational background. A recent survey from the United States reported that 76% adhere to nonsmoking, 40% to weight control, but only 23% to healthy eating (five fruits and vegetables per day) and 22% to regular physical activity [49•]. Most worrying of all, only a small minority of 3% adhere to all four principles.

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