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Chronic diseases: Origin and cell mechanisms involved

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ABSTRACT

Chronic diseases are a worldwide health problem directly related to society, lifestyle, and the development of unhealthy habits over time. Cardiovascular disease, cancer, chronic respiratory disease, and diabetes are the main causes of death. Environmental factors, such as air pollutants, poor diet, genetic predisposition, or a combination of these, are related to the development of these diseases. These factors activate cell mechanisms, such as DNA damage, oxidative stress, endoplasmic reticulum stress, autophagy, inflammation, and cell death. Depending on the dose and duration of exposure to causative agents, this cell damage can be acute or chronic. Activating these cell mechanisms can rescue normal cell function and cause permanent damage, unleashing the degeneration of tissues and organs over time. A wide variety of treatments help control chronic diseases; however, they cannot be cured completely. This fact leads to complications, dysfunctions, and disabilities. Herein, we discuss some of the principal mechanisms involved and how cellular stress can lead to these diseases when they persist for a long time.

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Introduction

Chronic diseases (CDs) are progressive disorders with a slow and prolonged course that do not resolve spontaneously and rarely resolve completely. CDs can last for months or years. This fact differentiates them from acute diseases, which may last a few days or weeks. CDs are responsible for 74% of deaths worldwide. Cardiovascular diseases (CVDs), cancer, chronic respiratory diseases (CRDs), and diabetes have the highest mortality rate (1). Other diseases with lower mortality rates are arthritis, Crohn's disease, depression, bipolar disorder, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and dementia (2-7).

The major causes of CD are environmental and lifestyle factors. Good dietary and exercise habits and reducing exposure to environmental factors play an important role in reducing their prevalence. Some authors have linked these diseases with age-related processes. However, in recent years, CDs have occurred in younger individuals, posing a challenge to the health system and the economy (8-11).

Changing environmental factors and habits expose our cells to stress, and our cells possess different mechanisms to cope with this stress. However, depending on the stress level, cells may not overcome this damage. These mechanisms counteract damage-causing factors such as oxidative stress, accumulation of misfolded proteins, and damage to the genome. Interestingly, these processes are conserved over time, allowing species survival and evolutionary development. Herein, we discuss how these mechanisms are related to various degenerative diseases.

This study aimed to complement the current preventive model for CDs. This model includes raising awareness of hereditary factors, limiting exposure to agents that trigger diseases, maintaining good eating habits, and promoting physical activity to achieve a healthy body.

Origin of chronic diseases

The origin of CDs is directly linked to time, that is, at the species and individual levels (12). All factors that interfere with normal cell function induce adaptations, and if cells cannot adapt, they malfunction or even die. The time and intensity with which a stimulus affects cells dictate the adaptation rate of those cells. The environment is continuously changing, affecting cell function at different levels. These changes include slow changes, such as lifestyle changes throughout human history, and fast changes, such as those occurring within a generation. The greatest impact is environmental changes that occur during different periods of our lifetime, from the womb to old age. The greater the speed of change, the greater the impact on

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cell function.

Evolution, aging, and chronic diseases

Human evolution and development have brought many benefits to society. Among these, access to technology and ease of obtaining resources contribute to a better quality of life and greater life expectancy. Nevertheless, the modification of environmental factors is directly related to human lifestyle and has negative health consequences (13,14).

Evolution involves accumulating characteristics gained through mutations that support the survival or extinction of a species in changing environments. These changes are random and influenced by the environment. They occur over time and depend on the habits of the species (15).

Humans were mainly hunters and gatherers during the Stone Age (Lower Paleolithic). However, their life expectancy was between 20 and 40 years, as they lived in a highly unpredictable environment. They constantly avoided predators and sought refuge near their food sources (16). This situation changed when humans acquired agricultural knowledge. This change reduced their exposure to danger in unknown regions, promoting technological development for their survival and improving their quality of life and expectancy. In the early 20th century, acute infectious diseases were prevalent. Nonetheless, thanks to the development of antibiotics and vaccines, life expectancy increased significantly from 46 years in 1950 to 72 years in 2016 (17,18).

This increase in life expectancy may be related to an increase in CDs. Some theories explain the relationship between aging and the diseases associated with this process. One of these theories is the "accumulation of mutations," which indicates that aging decreases the efficiency of eliminating genetic variants related to diseases that manifest in later stages of life, causing the accumulation of these mutations, a process known as senescence (19). Additionally, the "antagonist pleiotropy theory" proposes that these mutations could be favored if they protect against a disease that could manifest in the fertile period or if they increase reproductive possibilities, notwithstanding that they lead to diseases later in life (20).

In addition, the new fast-changing environmental conditions (in the evolutionary timescale), such as dietary and lifestyle changes, limit the adaptive capacity of the population to keep pace with these changes (12). This limitation leads to increased susceptibility to CD development, which could be linked to the onset of CD at younger ages (Figure 1). Therefore, CDs result from a gene maladaptation to the modern environment (21).

The maternal environment influence

The "developmental origin of health and disease" is a recent theory that proposes that exposure to certain stimuli during critical development periods (particularly the embryonic, fetal, and neonatal stages) may increase the triggering of diseases in adulthood (22). This concept was proposed after observing that a lower birth weight was related to a higher prevalence of death due to ischemic heart disease (23). The main stimuli that act as stressors in the early stages of life are poor nutrition, exposure to chemicals or drugs, infections, stress, and hormonal imbalances (24). Additionally, the dysregulation of maternal and fetal circadian rhythms (known as gestational chronodisruption) has been associated with increased susceptibility to noncommunicable diseases in adult life (25). Maternal environmental influences have been associated with a greater risk of acute lymphocytic leukemia (26), type 2 diabetes (27), metabolic syndrome and obesity (28,29), congenital heart disease (CHD) (30), and neurodegenerative diseases such as Alzheimer's disease, among others (31). These influences reflect the complexity of the physiological process needed for correct fetal development and how these factors affect adult health.

Genetic factors

There is evidence of the relationship between genetic factors and how they influence the development of diseases (32); however, genetic influence has a small effect on the relative risk of CDs (33). On the other hand, genetic predisposition can be modified by different factors such as physical activity (34). Various studies have shown the importance of genetic predisposition in developing CDs by carrying out comparative studies between monozygotic or dizygotic twins against unrelated individuals, showing a higher prevalence of type 2 diabetes (35) and CVDs between twins (36,37).

Hereditary factors, such as genetic predisposition, and environmental factors, such as exposure to different toxic molecules mixed in the air, soil, and water, end up as part of our diet and, in turn, play an important role in CD development. Recent studies have shown the importance of genetic predisposition to major depressive disorder in their interaction with environmental pollutants, such as particles (PM2.5) and nitrogen oxides (NOx) (38).

A correlation has been observed between stressors. For example, a study with 23 years of follow-up showed that patients with a previous diagnosis of cancer as a stressing factor, and even with a low genetic predisposition for CVD, have a higher risk of presenting CVDs (39). Other researchers have shown that genetic predisposition in monozygotic twin models is not the dominant factor in CD development since epigenetic factors play an important role (40,41).

Environmental factors

CDs are related to the environment according to the

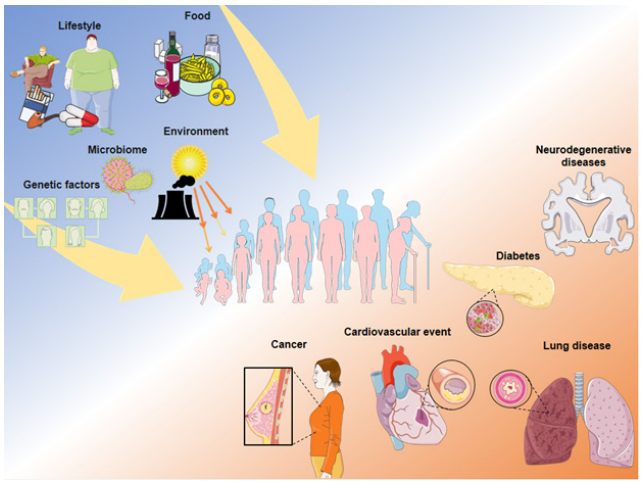

Figure 1. Factors contributing to CD development. Different factors that interact with humans can trigger different CDs, depending on the time and concentration of these factors. This figure was created using modified templates from (Medical Art, https://smart.servier.com/).

analysis of the fractions attributable to leukemia, asthma, neurological diseases, cancer, lung diseases, and CVD (42). Environmental contamination by polluting particles directly affects human health. Soil contamination carries toxic agents such as chemical products, nanoplastics, and heavy metals to humans through crops; in turn, bodies of water are contaminated when soils with toxic agents are washed by rain or artificial sweeping into rivers. Finally, the removal of soil by deforestation or rotating crops leads to air pollution by particles released in the dust (43).

Environmental stressors include exposure to gases or minerals such as manganese, which is neurotoxic. For example, chronic manganese exposure increases glutamate levels in the brain, causing Parkinson-like brain damage via excitotoxicity (44). It can be ingested through contaminated bodies of water, food, the atmosphere in mines or welding, and as a gasoline additive (45). Some pesticides, such as paraquat and rotenone, are linked to the development of Parkinson's disease. These compounds are used to control pests in agriculture (46), causing the formation of reactive oxygen species (ROS) and dopaminergic neurotoxicity (47,48).

Lifestyle and processed foods

Lifestyle influences the risk of developing chronic disease. Diet is directly associated with multiple forms of CD. Even an excess of certain substances in the diet (i.e., sugar, alcohol, and fat) contributes to the development of cancer, dementia, heart disease, obesity, and diabetes (49). Other factors are tobacco use and low physical activity (50). These factors often interact with cellular machinery at different levels (this will be discussed later), altering the mechanisms involved in gene expression regulation (51).

Ultra-processed foods play an important role in the development of ovarian and brain cancer (52), type 2 diabetes (53), CVDs (54), and CRDs (55). A higher risk of type 2 diabetes mellitus is associated with the consumption of sugar-sweetened beverages, red meat, whole grains, and processed meat (56).

Tobacco and alcohol are known to increase the risk of many types of cancer, such as of the gastrointestinal and respiratory tracts and other tissues, including the oral cavity, pharynx, larynx, esophagus, stomach, colon, bladder, kidney, cervix, pancreas, and leukemia (57,58). In contrast, alcohol is related to rectal, liver, and breast cancer (58). Quitting tobacco reduces the risk of these diseases (59,60) and the appearance of malignant neoplasia (61). Quitting tobacco has also been shown to improve the response to anti-cancer therapy (62).

A sedentary lifestyle or low physical activity is associated with the development of CVDs (heart failure, stroke, and coronary disease) (63) but not with total cancer risk (64). Other reports have shown a correlation between physical activity, obesity, and sedentary behavior in cancer, emphasizing the strong association between higher physical activity levels and a reduced risk of bladder, breast, colon, endometrial, esophageal adenocarcinoma, and gastric cardia cancers (65).

Alterations in the microbiome

The term "microbiome" refers to the compound of viruses, bacteria, and fungi living in the human body (66). It has become clear that these microorganisms and their genetics influence metabolic functions, acting on or against the organism. This influence has a multifactorial dependence that is still under study and is an area of growing interest in proteomics, transcriptomics, and metabolomics (67). Recent studies have shown a link between alterations in the microbiome and the onset of CDs, such as inflammatory bowel disease, atopic asthma, type 2 diabetes, and behavioral disorders (68). As the microbiota has a high frequency of change in its composition, these changes may act as cell stressors (69,70). In addition, the microbiota generates a wide variety of metabolites that regulate immune function and, when altered, may be associated with the generation of oxidative stress, ER stress, and chronic inflammation (71-73).

Chronic diseases and cell stress

Prolonged exposure to and excess environmental components that humans develop impacts cells, altering their homeostasis. Homeostasis allows organisms to maintain their internal conditions to adapt to and survive continuous changes occurring in the external environment (74). An imbalance in homeostasis results in organ and tissue malfunctions. A common example is dehydration, which causes acute symptoms such as thirst and headache; however, prolonged thirst can cause renal damage and even death. These imbalances affect cells, causing acute or chronic cell stress, depending on the time of exposure and concentration of the stressor (75,76).

Cell stress is a response mechanism that generates various processes to repair damage and promote cell survival (77). If it is not possible to recover homeostasis, cell death mechanisms are activated (78).

Damage to genetic material

Stressors can cause cellular changes at different levels. One of the most studied alterations is that of DNA. These alterations can be heritable mutations, depending on whether they occur in germ or somatic cells. These mutations can alter protein expression in cells, causing dysregulation of their processes and cell malfunction. Cancer is most often linked to the accumulation of mutations in somatic cells (42,79).

Stressors, risk factors for CDs, can also induce epigenetic modifications. These modifications allow the regulation of gene expression without altering the DNA sequence. Methylation is an epigenetic mechanism that controls gene expression by adding methyl groups, predominantly at the cytosine of the CpG dinucleotide sequence, through DNA methyltransferase (80). Another epigenetic regulatory mechanism is the acetylation of histones, which are proteins that roll up DNA to maintain its organization and compactness. Histone acetylation regulates gene expression. Depending on the region or different epigenetic factors, it compacts or relaxes DNA configuration, turning these genes on or off and changing cellular functions in response to the environment.

Mitochondrial Stress

In animal cells, mitochondria are the only organelles that contain DNA, in addition to the nucleus, implying that they have their own machinery for RNA and protein synthesis. Evolution has conserved this mechanism to achieve efficient energy production through its four protein complexes involved in the electron transport of the respiratory chain (81). An alteration in the respiratory

chain due to external factors or mutations in the system will cause the overproduction of ROS and a deficiency in the antioxidant enzyme system.

Superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) are antioxidant enzymes. Other components of the antioxidant system that protect cells from oxidative stress include vitamins E and C, glutathione (GSH), and various carotenoids and flavonoids (82). When ROS exceeds the threshold of antioxidants, they cause DNA damage and protein and lipid degradation. Chronic oxidative stress can cause significant alterations in cell and tissue functions (83,84).

Endoplasmic reticulum stress and proteostasis

The endoplasmic reticulum (ER) is the organelle in charge of calcium stores, protein synthesis directed to different organelles, synthesis of secretory proteins, and proteostasis, characterized by controlling protein synthesis, folding, transportation, and degradation (85). However, different physiological and pathological factors can alter ER homeostasis and cause dysfunction in protein synthesis. Examples include increased protein demand, viral infections, nutrient deficiency, hypoxia, inflammatory cytokines, sudden changes in temperature, environmental toxins, and the expression of mutant proteins, leading to the accumulation of misfolded proteins and oxidative stress (86,87).

When the cell is in a state of stress caused by the aforementioned factors, failures in protein synthesis can occur, for example, excess free radicals or mutations in the genome that lead to abnormal protein production (88). Among a cascade of responses, the unfolded protein response (UPR) is activated to counter this damage. This response aims to attenuate the synthesis of general proteins and to overexpress proteins with chaperone functions, which will help relieve the accumulation of misfolded proteins (89). Chaperones guide misfolded proteins to one of their corresponding protein degradation pathways. Depending on their half-life or aggregate formation, they will be degraded by the proteasome pathway or autophagy (90-92) (Figure 2).

Proteasomes are protein complexes present in the cytosol of all eukaryotic cells. It involves the degradation of damaged or unnecessary proteins. Once in the ER, chaperones recognize misfolded proteins that have not been corrected and are labeled with ubiquitin, a 76-amino acid peptide. This label helps retro-translocate the protein to the cytoplasm to direct misfolded proteins to the proteasome for degradation to restore proteostasis (93).

Autophagy

As mentioned above, autophagy is a mechanism responsible for the degradation of long-half-life proteins, and macromolecular complexes are generally degraded by a mechanism called autophagy. There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated. In macroautophagy, one of the factors inducing autophagy is the misfolding of proteins, a process in which substrates are sequestered within double-membrane cytosolic vesicles called autophagosomes (94). In this process, eukaryotic cells recycle macromolecules and organelles. Depending on the context, autophagy can offset stress-induced endoplasmic reticulum expansion, increase cell survival, or commit cells to a non-apoptotic type of death (95). Microautophagy is characterized by the formation of vesicles directly with the invagination of lysosomes. Only lysosomes engulf proteins for degradation (96). In chaperone-mediated autophagy, no vesicles were observed. Soluble proteins cross directly from the cytosol to the lysosome through the membrane with the help of chaperones, such as heat shock cognate protein of 70 kDa (Hsc70) through the KFERQ pentapeptide motif (97,98). Chaperone-mediated autophagy participates in protein homeostasis (proteostasis) by adapting cells to stress. Its deficiency is associated with various pathologies such as cancer, heart disease, neurodegenerative diseases, and immunodeficiency (99). This process may be associated with inflammation-dependent oxidative damage or stress signals in the ER, leading to cell death and feedback inflammation (100-102).

Cell death

Cell death occurs when cellular activity and vital functions cease. Depending on the death-inducing factor, it can be sudden or programmed, triggered by different biochemical pathways that activate death by necrosis or apoptosis. Although many types of cell death have been reported, we focus on these two because they are the most frequent.

The first type of cell death is necrosis, which results in swelling of organelles, rupture of the plasma membrane, and the release of intracellular contents into the extracellular space of the injured tissue. This process is exclusive of aggressive events that cause irreversible cell injury, such as trauma, hypoxia, extreme temperature, radiation, high-energy electrical discharges, poison, and drug toxicity (103,104).

Apoptosis is the second type of cell death. Once the cell survival mechanisms are overwhelmed by factors that

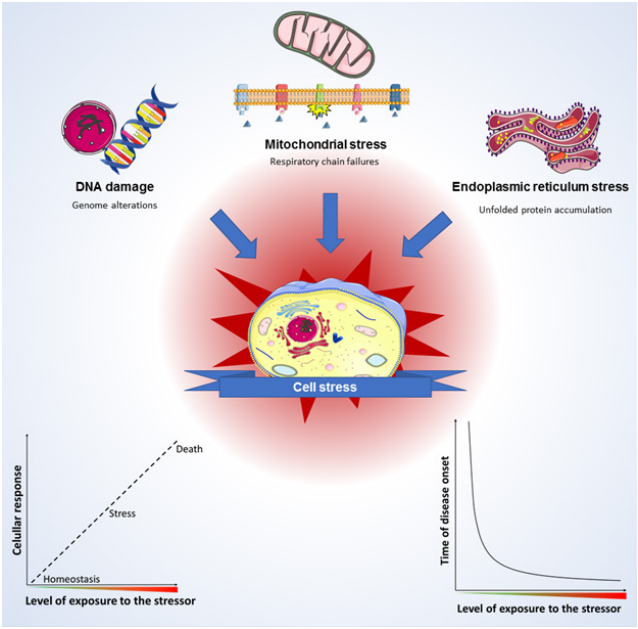

Figure 2. Cellular stress, causes, and consequences. Cellular stress is a response to an imbalance in homeostasis triggered by different factors and their concentrations. Each can be located in a key organelle for cell vitality; therefore, they have regulatory mechanisms to maintain life. If organelle failure exceeds the threshold of survival mechanisms, cell death and/or onset of CDs occur. The figure was created using modified templates from (Servier Medical Art, https://smart.servier.com/).

activate cell stress, apoptosis is activated. It is a molecular process that is dependent on proteins called caspases. Apoptosis is a programmed cell death activated in cells that threaten the organism (105). Apoptosis is a mechanism of great importance in organisms and takes part in different life cycle processes, such as cell turnover in tissues and during embryonic development, for example, when the interdigital membranes of the hands are eliminated. It is also associated with hormone-dependent atrophy and cytotoxic agent-induced cell death. Cell death mechanisms can give rise to inflammation and, thus, inflammatory diseases (106-108).

Chronic inflammation

Metaflammation, a recently studied phenomenon, is a chronic low-grade inflammation throughout the body caused by consuming a high-calorie diet, chronic overeating, and sedentary lifestyles in Western societies (109). Evidence shows that aging and age-related diseases share some basic mechanical aspects that largely converge with inflammation. Inflammation refers to the process that contributes to the pathogenesis of age-related diseases. Several stimuli sustain inflammation from an evolutionary perspective, including pathogens, endogenous cell debris, stray molecules, nutrients, and the gut microbiota (110). Metaflammation is characterized by the same mechanisms that underlie inflammation. Maintenance of proper cell balance is crucial for health and has significant implications for pathological conditions such as diabetes, obesity, CVD, cancer, and degenerative neurological disorders. CDs redundantly accelerate aging and are considered a manifestation of accelerated aging (102,111).

The most prevalent chronic diseases and their relationship with cell stress

CDs share molecular mechanisms of cell stress due to prolonged exposure to different insults. We review the most relevant chronic disorders. In addition, there is information regarding their relationship with cell stress mechanisms.

Cardiovascular disease

CVDs are responsible for 17.9 million deaths annually. Several risk factors are related to CVDs, including genetic factors (intrinsic factors) and personal habits (extrinsic factors). Some lifestyle habits correlated to CVD include excessive consumption of high-calorie diets and a sedentary lifestyle. In addition, they are correlated with the metaflammation. These risk factors can trigger cellular mechanisms leading to metabolic disorders such as atherosclerosis, dyslipidemia, atheromatous plaque formation, and inflammation (112,113). These factors have been associated with chronic stress in endothelial cells of the circulatory system, triggering the response to misfolded proteins that lead to cell death by apoptosis (114), causing hardening and narrowing of the arteries with the formation of atheroma. These areas of the lesion in the innermost layer of an artery are characterized by the accumulation of low-density lipoprotein (LDL) particles that reduce blood flow and distribution of oxygen and nutrients to the tissues (115).

Among CVDs, coronary artery disease (CAD) is the leading cause of death worldwide. CAD causes decreased myocardial blood flow, leading to an excessive increase in ROS and oxidative stress. Consequently, it can lead to cell death, triggering heart failure, angina, or myocardial infarction (116).

Cancer

Cancer, with 9.3 million deaths per year, is the second leading cause of death worldwide, with nine million deaths per year. It is characterized by a loss of cellular growth control, leading to uncontrolled multiplication and dissemination. It is capable of growing on its tissue of origin without invasion (benign tumor) or with invasion into this tissue and dissemination through metastases (malignant tumor) (117).

Although cancer is closely associated with changes at the DNA level, alterations in other organelles, such as the mitochondria and ER, are also related to the induction of this disease. Several agents have been associated with mitochondrial and ER imbalance, such as alcohol abuse and excessive fat intake (118,119), indicating an association between a high rate of cell proliferation and prolonged activation of the UPR, giving rise to different types of cancer (120-122).

Several strategies have been proposed to target the main pathways of cell stress in cancer. For example, acute induction of ER stress with silencing of the GRP78 protein using combined carfilzomib (proteasome inhibitor) and ACY-1215 (human histone deacetylase 6 -selective inhibitor) treatment resulted in a marked accumulation of protein aggregates that induced apoptotic death in a colorectal cancer model (123). Although autophagy and UPR have paradoxical roles in cancer, their correct management could lead to novel therapeutic strategies against this disease (124-126).

Chronic respiratory diseases

CRDs are the third leading cause of death worldwide, with 4.1 million deaths per year. Diseases that affect the airways and other lung structures are caused by dissolved particles in the air, such as tobacco smoke, allergens, domestic wood smoke, chemicals derived from combustion, and respiratory infections.

One of the most common CRDs is chronic obstructive pulmonary disease (COPD) (127). COPD is characterized by chronic airway inflammation, which limits the airflow. It is primarily associated with smoking. However, irritant gases from air pollution play an important role in the development of this disease, generating free radicals (128). These gases include hydrogen chloride, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ammonia (129). Cigarette smoke triggers failures in protein synthesis, and the response mechanisms to misfolded proteins activate an immune response (130). The immune response mainly involves leukocytes and macrophages that release ROS and reactive nitrogen species (RNS). Increased oxidative stress causes cell damage and impairs respiratory function (131,132).

Diabetes

Diabetes causes 2 million deaths annually. It is a group of diseases with an excess of sugar in the blood. Type 2 diabetes, the most frequent type of diabetes, presents with insulin resistance. Insulin is required to move blood glucose into cells (133). Insulin resistance is related to high blood glucose, high body fat, high sodium intake, seden-

tary lifestyle, and genetics in some cases (134).

Insulin resistance is the desensitization of insulin receptors in body cells due to chronic exposure to blood glucose, mainly in hepatocytes, muscle cells, and adipocytes. High blood glucose levels cause oxidative stress, leading to activation of the misfolded protein response, which is related to insulin receptor desensitization (135), which decreases the use of blood glucose for energy.

When there is an increase in blood glucose, pancreatic β-cells maintain glucose homeostasis by secreting insulin (136). As secretory cells, β-cells may have a high metabolic activity; however, they have weaker antioxidant defenses than other cells and tissues, making them more susceptible to free radicals derived from hyperglycemia (137). This susceptibility can cause pancreatic cell death and decrease insulin release. The detailed inflammatory process in metabolic diseases is important for understanding etiopathology. Recently, the role of adipose tissue macrophages was described. In obesity, macrophages residing in the adipose tissue are polarized to a pro-inflammatory M1 phenotype when exposed to free fatty acids, blocking the action of insulin. Therefore, metabolic disorders, such as obesity and dyslipidemia, lead to insulin resistance, resulting in diabetes (138).

Interestingly, Latinos suffer from diabetes more than other populations (139). Although genetic factors are not the direct cause of this disease, they are associated with a predisposition in this population.

Some neurodegenerative and mental diseases

Neurodegenerative diseases are characterized by progressive neuronal loss. Depending on the metabolic disorder or the presence of toxic agents, they cause motor, cognitive, and emotional alterations or a combination of these (140). Several studies have shown an association between ER stress and various neurodegenerative diseases. For instance, amyotrophic lateral sclerosis and Guam dementia, a type of Parkinsonism, are present in the natives of Guam on the Mariana Islands. Several compounds have been found in flour extracted from plants of the *Cycas* genus. When consumed, they stimulate the accumulation of α-synuclein protein in neurons, forming hydrophobic aggregates known as Lewy bodies, characteristic inclusion bodies in these diseases (141,142).

Other diseases manifest protein aggregation that leads to cell stress, such as Alzheimer´s disease, Huntington´s disease, and neural prion diseases (143). In addition, patients with schizophrenia show failure in protein degradation and antioxidant systems (144,145).

Exercise reduces the risk of chronic disease

As seen in this review, CDs have different mechanisms in common and thus greatly impact long-term human health. However, they are preventable and treatable. Different studies have shown that modifying environmental factors, lifestyle, diet, and exercise, to mention a few, improves the quality of life of patients with CDs and decreases the risk of onset. Exercise and healthy diets have in common the activation of anti-inflammatory and antioxidant mechanisms, which restore proteostasis (146-149).

Exercise improves CDs, such as coronary disease and heart failure [149], and reduces the mortality of older adults (150). In addition, physical activity decreases the risk of bladder, breast, colon, endometrial, esophageal, renal, and gastric adenocarcinoma (151). Type 2 diabetes mellitus studies have shown that aerobic exercise has an anti-inflammatory effect on the TNF-α/NF-κB pathway [145], decreasing ER stress, increasing autophagy, and reducing insulin resistance (147,152). Physical exercise also benefits chronic mental illnesses such as dementia, attenuates neuropsychiatric symptoms, and helps maintain mental capacities (153). These results were reinforced by Xia et al. They demonstrated that exercise reduces β-amyloid protein (Aβ) plaques and negatively regulates the UPR in an Alzheimer's model in mice (154).

Several studies have reported that exercise mitigates ER stress and thus cell death, counteracting CDs, such as CVD, and neurodegenerative diseases, such as Alzheimer's disease and neurological deterioration (155-160). Although it may seem paradoxical, the activation of inflammation, UPR, and oxidative stress responses during exercise benefits health by improving over time the expression of proteins that regulate endoplasmic reticulum stress, proteostasis, and oxidative stress, inducing adaptation responses (161,162). To better understand cellular stress responses and their relationship with age, researchers have demonstrated that the UPR is more active after exercise in young people aged 27 ± 5 years than in those older than 75 ± 5 years, suggesting that an age-related decline in the activation of the protective UPR after exercise could be associated with the deterioration of skeletal muscle over time (163).

Diet can also improve health through different mechanisms

Various studies have shown that a variety of foods prevent CDs. This is the case for nut and legume consumption for treatment of type 2 diabetes mellitus and CRDs (56,164). In addition, moderate consumption of lean red meat instead of high-fat red meat, replacing red and processed meat with fish, eggs, dairy products, and poultry, and a diet that includes white grains, high-fiber foods, and fruits and vegetables lowers the risk of cancer, CVDs, and CRDs (164-168).

Healthy foods (169-175) also provide exogenous antioxidants and anti-inflammatory effects that improve cell homeostasis, including vitamins A, C, E, K, beta-carotene, ubiquinone (176), polyphenols, such as phenolic acids (ferulic acid, caffeic acid, p-coumaric acid, gallic acid, chlorogenic acid, and rosmarinic acid) (177), and flavonoids (anthocyanidins, flavones, isoflavones, flavonols, flavanones, flavanols, and flavanonols) (178).

Vitamins C, E, and K protect against lipid peroxidation by neutralizing ROS, showing positive effects against cancer, CVDs, neurodegenerative diseases, and diabetes (170,179-181). In turn, vitamin K inhibits the activation of 12-lipoxygenase (12-LOX) (181). In contrast, vitamin A and beta-carotenoids stabilize peroxyl radicals after their combination and neutralize thiyl radicals, which have positive effects against CVD (182). The donation of hydrogen atoms is the main method for the elimination of free radicals in phenolic acids; however, other methods, such as the reactivity of the phenol fraction, which replaces the hydroxyl in the aromatic ring, affect free radical structure stabilization, causing their extinction, and exhibit neuroprotective, anti-carcinogenic, and anti-diabetic activities, among others (177). Ubiquinone (Q10) and flavonoids suppress the generation of ROS (178,183) and improve

CVDs, obstructive pulmonary disease, diabetes, and neurodegenerative diseases (178,184).

Among the anti-inflammatory role of components in healthy foods, vitamin K and Q10 induce the inhibition of the pro-inflammatory NF-κB pathway (181,183) while flavoinoids induce the inhibition of the NF-κB, MAPK, and STAT pathways (178).

Probiotic and prebiotic supplementation also improves general health, reducing the risk of cancer (185), CVDs (186), CRDs (187), and type 2 diabetes (188).

Conclusions

Undoubtedly, quality of life has improved over time. However, our current lifestyle and its interaction with environmental factors and genetic load have negatively affected society. These interactions trigger oxidative stress, genetic material damage, and mitochondrial and ER stress. Excessive exposure to these phenomena leads to the development of CDs. The emergence of CDs leads to increased morbidity and mortality in humans.

CDs alter immune function and increase the risk of death from infectious diseases, such as cytomegalovirus, tuberculosis, herpes zoster, and pneumococcal pneumonia, particularly in the current context of COVID-19.

The CD treatment model aims to reduce mortality through prevention and to avoid complications. We expect that a better understanding of the cell mechanisms shared by these diseases will contribute to their prevention and the generation of novel therapeutic strategies.

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Authors' Contribution

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References

1. World Health Organization. Non communicable diseases. [Internet]. 2023 [cited 2023 Feb 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
2. Feuerstein JD, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. *Mayo Clin Proc* 2017; 92:1088-103.
3. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res* 2018; 6:15.
4. Leboyer M, Kupfer DJ. Bipolar disorder: new perspectives in health care and prevention. *J Clin Psychiatry* 2010; 71:1689-95.
5. Meshkat S, Salimi A, Joshaghanian A, Sedighi S, Sedighi S, Aghamollaii V. Chronic neurological diseases and COVID-19: Associations and considerations. *Transl Neurosci* 2020; 11:294-301.
6. Snowden MB, Steinman LE, Bryant LL, Cherrier MM, Greenlund KJ, Leith KH, et al. Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence? *Int J Geriatr Psychiatry* 2017; 32:357-71.
7. Wistedt B. Schizophrenia, a chronic disease. *Acta Psychiatr Scand Suppl* 1981; 291:9-19.
8. Rappaport SM, Smith MT. Environment and Disease Risks. *Science* 2010; 330:460-1.
9. Reynolds R, Dennis S, Hasan I, Slewa J, Chen W, Tian D, et al. A systematic review of chronic disease management interventions in primary care. *BMC Fam Pract* 2018; 19.
10. Steyn K, Damasceno A. Lifestyle and Related Risk Factors for Chronic Diseases. In: Jamison DT, Feachem RG, Makgoba MW, Bos ER, Baingana FK, Hofman KJ, et al., eds. Disease and Mortality in Sub-Saharan Africa 2nd ed. Washington (DC): World Bank; 2006. p. 247-64.
11. Rojas-Rueda D, Morales-Zamora E, Alsufyani WA, Herbst CH, AlBalawi SM, Alsukait R, et al. Environmental Risk Factors and Health: An Umbrella Review of Meta-Analyses. *Int J Environ Res Public Health* 2021; 18:704.
12. Griffiths PE, Bourrat P. Integrating evolutionary, developmental and physiological mismatch. *Evol Med Public Health* 2023; 11:277-86.
13. Garralda-Del-Villar M, Carlos-Chillerón S, Diaz-Gutierrez J, Ruiz-Canela M, Gea A, Martínez-González MA, et al. Healthy Lifestyle and Incidence of Metabolic Syndrome in the SUN Cohort. *Nutrients* 2018; 11.
14. National Research Council, Institute of Medicine, Steven H. Woolf, Laudan Aron. U.S. Health in International Perspective: Shorter Lives, Poorer Health. Panel on Understanding Cross-National Health Differences Among High-Income Countries, Steven H. Woolf and Laudan Aron, Eds. Committee on Population, Division of Behavioral and Social Sciences and Education, and Board on Population Health and Public Health Practice, Institute of Medicine. [Internet]. U.S. Health in International Perspective: Shorter Lives, Poorer Health. Washington, DC.: National Academies Press, pp. 192-205.; 2013. 192-205 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154491/
15. Loewe L, Hill WG. The population genetics of mutations: good, bad and indifferent. *Philos Trans R Soc Lond, B, Biol Sci* 2010; 365:1153-67.
16. Trinkaus E. Late Pleistocene adult mortality patterns and modern human establishment. *PNAS* 2011; 108:1267-71.
17. Aminov RI. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. *Front Microbiol* 2010; 1.
18. World Health Organization. Mortality and global health estimates.

[Internet]. 2020 [cited 2020 Nov 3]. Available from: https://www.who.int/data/maternal-newborn-child-adolescent/monitor
19. Medawar PB. The Uniqueness of the Individual. In London: Routledge; 1957. p. 133-75.
20. Williams GC. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution* 1957; 11:398-411.
21. Hong Y-C. The Age of Chronic and Late Chronic Diseases. *The Changing Era of Diseases* 2019:35-68.
22. Arima Y, Fukuoka H. Developmental origins of health and disease theory in cardiology. *J Cardiol* 2020; 76:14-7.
23. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; 2:577-80.
24. Mandy M, Nyirenda M. Developmental Origins of Health and Disease: the relevance to developing nations. *Int Health* 2018; 10:66-70.
25. Méndez N, Corvalan F, Halabi D, Ehrenfeld P, Maldonado R, Vergara K, et al. From gestational chronodisruption to noncommunicable diseases: Pathophysiological mechanisms of programming of adult diseases, and the potential therapeutic role of melatonin. *Journal of Pineal Research* 2023; 75:e12908.
26. Wang Y, Gao P, Liang G, Zhang N, Wang C, Wang Y, et al. Maternal prenatal exposure to environmental factors and risk of childhood acute lymphocytic leukemia: A hospital-based case-control study in China. *Cancer Epidemiol* 2019; 58:146-52.
27. Dabelea D, Crume T. Maternal Environment and the Transgenerational Cycle of Obesity and Diabetes. *Diabetes* 2011; 60:1849-55.
28. Sharma S, Bhonde R. Dilemma of Epigenetic Changes Causing or Reducing Metabolic Disorders in Offsprings of Obese Mothers. *Horm Metab Res* 2023; 55:665-76.
29. Donato J. Programming of metabolism by adipokines during development. *Nat Rev Endocrinol* 2023; 19:385-97.
30. Wu L, Li N, Liu Y. Association Between Maternal Factors and Risk of Congenital Heart Disease in Offspring: A Systematic Review and Meta-Analysis. *Matern Child Health J* 2023; 27:29-48.
31. Lahiri DK, Maloney B, Zawia NH. The LEARn model: an epigenetic explanation for idiopathic neurobiological disease. *Mol Psychiatry* 2009; 14:992-1003.
32. Sohail M, Palma-Martínez MJ, Chong AY, Quinto-Cortés CD, Barberena-Jonas C, Medina-Muñoz SG, et al. Mexican Biobank advances population and medical genomics of diverse ancestries. *Nature* 2023; 622:775-83.
33. Schork NJ, Murray SS, Frazer KA, Topol EJ. Common vs. rare allele hypotheses for complex diseases. *Curr Opin Genet Dev* 2009; 19:212-9.
34. Kujala UM. Physical activity, genes, and lifetime predisposition to chronic disease. *Eur Rev Aging Phys Act* 2011; 8:31-6.
35. Poulsen P, Grunnet LG, Pilgaard K, Storgaard H, Alibegovic A, Sonne MP, et al. Increased Risk of Type 2 Diabetes in Elderly Twins. *Diabetes* 2009; 58:1350-5.
36. Smith MC, Baker JR, Gleaves E, Singh A, Kazimuddin M, Smith MC, et al. Twinning: Coronary Artery Disease in Monozygotic Twins. *Cureus* 2021; 13.
37. Ballin M, Nordström A, Nordström P. Cardiovascular Disease and All-Cause Mortality in Male Twins With Discordant Cardiorespiratory Fitness: A Nationwide Cohort Study. *American Journal of Epidemiology* 2020; 189:1114-23.
38. Li D, Xie J, Wang L, Sun Y, Hu Y, Tian Y. Genetic susceptibility and lifestyle modify the association of long-term air pollution exposure on major depressive disorder: a prospective study in UK Biobank. *BMC Medicine* 2023; 21:67.
39. Yang H, Zeng Y, Chen W, Sun Y, Hu Y, Ying Z, et al. The role of genetic predisposition in cardiovascular risk after cancer diagnosis: a matched cohort study of the UK Biobank. *Br J Cancer* 2022; 127:1650-9.
40. Erdogan OS, Tuncer SB, Kilic S, Odemis DA, Turkcan GK, Celik B, et al. Genome-wide methylation profiles in monozygotic twins with discordance for ovarian carcinoma. *Oncology Letters* 2020; 20:1-1.
41. Roos L, Spector TD, Bell CG. Using epigenomic studies in monozygotic twins to improve our understanding of cancer. *Epigenomics* 2014; 6:299-309.
42. Rappaport SM. Genetic Factors Are Not the Major Causes of Chronic Diseases. *PLoS One* 2016; 11.
43. Münzel T, Hahad O, Daiber A, Landrigan PJ. Soil and water pollution and human health: what should cardiologists worry about? *Cardiovasc Res* 2022; 119:440-9.
44. Qi Z, Yang X, Sang Y, Liu Y, Li J, Xu B, et al. Fluoxetine and Riluzole Mitigates Manganese-Induced Disruption of Glutamate Transporters and Excitotoxicity via Ephrin-A3/GLAST-GLT-1/Glu Signaling Pathway in Striatum of Mice. *Neurotox Res* 2020; 38:508-23.
45. Peres TV, Schettinger MRC, Chen P, Carvalho F, Avila DS, Bowman AB, et al. "Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies." *BMC Pharmacology and Toxicology* 2016; 17:57.
46. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, Paraquat, and Parkinson's Disease. *Environ Health Perspect* 2011; 119:866-72.
47. Le W, Sayana P, Jankovic J. Animal Models of Parkinson's Disease: A Gateway to Therapeutics? *Neurotherapeutics* 2014; 11:92-110.
48. Testa CM, Sherer TB, Greenamyre JT. Rotenone induces oxidative stress and dopaminergic neuron damage in organotypic substantia nigra cultures. *Molecular Brain Research* 2005; 134:109-18.
49. Fuhrman J. The Hidden Dangers of Fast and Processed Food. *Am J Lifestyle Med* 2018; 12:375-81.
50. Ng R, Sutradhar R, Yao Z, Wodchis WP, Rosella LC. Smoking, drinking, diet and physical activity—modifiable lifestyle risk factors and their associations with age to first chronic disease. *Int J Epidemiol* 2020; 49:113-30.
51. Lu C, Thompson CB. Metabolic regulation of epigenetics. *Cell Metab* 2012; 16:9-17.
52. Chang K, Gunter MJ, Rauber F, Levy RB, Huybrechts I, Kliemann N, et al. Ultra-processed food consumption, cancer risk and cancer mortality: a large-scale prospective analysis within the UK Biobank. *eClinicalMedicine* 2023; 56:101840.
53. Duan M-J, Vinke PC, Navis G, Corpeleijn E, Dekker LH. Ultra-processed food and incident type 2 diabetes: studying the underlying consumption patterns to unravel the health effects of this heterogeneous food category in the prospective Lifelines cohort. *BMC Med* 2022; 20:7.
54. Zhong G-C, Gu H-T, Peng Y, Wang K, Wu Y-Q-L, Hu T-Y, et al. Association of ultra-processed food consumption with cardiovascular mortality in the US population: long-term results from a large prospective multicenter study. *Int J Behav Nutr Phys Act* 2021; 18:21.
55. He Q, Sun M, Zhao H, Sun N, Han Q, Feng Z, et al. Ultra-processed food consumption, mediating biomarkers, and risk of chronic obstructive pulmonary disease: a prospective cohort study in the UK Biobank. *Food Funct* 2023; 14:8785-96.
56. Schwingshackl L, Hoffmann G, Lampousi A-M, Knüppel S, Iqbal K, Schwedhelm C, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* 2017; 32:363-75.
57. Choi J-W, Hua TNM. Impact of Lifestyle Behaviors on Cancer Risk and Prevention. *J Lifestyle Med* 2021; 11:1-7.

58. Rumgay H, Shield K, Charvat H, Ferrari P, Sornpaisarn B, Obot I, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *The Lancet Oncology* 2021; 22:1071-80.
59. Choi S, Chang J, Kim K, Park SM, Lee K. Effect of Smoking Cessation and Reduction on the Risk of Cancer in Korean Men: A Population Based Study. *Cancer Res Treat* 2018; 50:1114-20.
60. Su Z, Jia X-H, Zhao F-H, Zhou Q-H, Fan Y-G, Qiao Y-L. Effect of Time Since Smoking Cessation on Lung Cancer Incidence: An Occupational Cohort With 27 Follow-Up Years. *Front Oncol* 2022; 12:817045.
61. Luo SJ, Choi E, Aredo JV, Wilkens LR, Tammemägi MC, Le Marchand L, et al. Smoking Cessation After Lung Cancer Diagnosis and the Risk of Second Primary Lung Cancer: The Multiethnic Cohort Study. *JNCI Cancer Spectr* 2021; 5:pkab076.
62. Chellappan S. Smoking Cessation after Cancer Diagnosis and Enhanced Therapy Response: Mechanisms and Significance. *Curr Oncol* 2022; 29:9956-69.
63. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary Behavior, Exercise, and Cardiovascular Health. *Circulation Research* 2019; 124:799-815.
64. Kubota Y, Evenson KR, MacLehose RF, Roetker NS, Joshu CE, Folsom AR. Physical Activity and Lifetime Risk of Cardiovascular Disease and Cancer. *Med Sci Sports Exerc* 2017; 49:1599-605.
65. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. *Mol Oncol* 2021; 15:790-800.
66. Lederberg J, Mccray AT. `Ome Sweet `Omics--A Genealogical Treasury of Words. *The Scientist* 2001; 15:8-8.
67. Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol* 2015; 31:69-75.
68. Durack J, Lynch SV. The gut microbiome: Relationships with disease and opportunities for therapy. *J Exp Med* 2019; 216:20-40.
69. Riccio P, Rossano R. The human gut microbiota is neither an organ nor a commensal. *FEBS Letters* 2020; 594:3262-71.
70. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* 2019; 7:14.
71. Kunst C, Schmid S, Michalski M, Tümen D, Buttenschön J, Müller M, et al. The Influence of Gut Microbiota on Oxidative Stress and the Immune System. *Biomedicines* 2023; 11:1388.
72. Hou K, Wu Z-X, Chen X-Y, Wang J-Q, Zhang D, Xiao C, et al. Microbiota in health and diseases. *Sig Transduct Target Ther* 2022; 7:1-28.
73. Ke X, You K, Pichaud M, Haiser HJ, Graham DB, Vlamakis H, et al. Gut bacterial metabolites modulate endoplasmic reticulum stress. *Genome Biol* 2021; 22:292.
74. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. *Front Physiol* 2020; 11.
75. Doremus-Fitzwater TL, Paniccia JE, Gano A, Vore A, Deak T. Differential effects of acute versus chronic stress on ethanol sensitivity: evidence for interactions on both behavioral and neuroimmune outcomes. *Brain Behav Immun* 2018; 70:141-56.
76. Pickering AM, Vojtovich L, Tower J, Davies KJA. Oxidative Stress Adaptation with Acute, Chronic and Repeated Stress. *Free Radic Biol Med* 2013; 55:109-18.
77. Barouki R. Cellular stress. *FEBS Letters* 2007; 581:3581-3581.
78. Fulda S, Gorman AM, Hori O, Samali A. Cellular Stress Responses: Cell Survival and Cell Death [Internet]. Vol. 2010, International Journal of Cell Biology. Hindawi; 2010 [cited 2020 Sep 22]. p. e214074. Available from: https://www.hindawi.com/journals/ijcb/2010/214074/
79. Vijg J, Dong X. Pathogenic mechanisms of somatic mutation and genome mosaicism in aging. *Cell* 2020; 182:12-23.
80. Jang HS, Shin WJ, Lee JE, Do JT. CpG and Non-CpG Methylation in Epigenetic Gene Regulation and Brain Function. *Genes (Basel)* 2017; 8.
81. Osellame LD, Blacker TS, Duchen MR. Cellular and molecular mechanisms of mitochondrial function. *Best Pract Res Clin Endocrinol Metab* 2012; 26:711-23.
82. Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2017; 1863:1066-77.
83. Guo C, Sun L, Chen X, Zhang D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen Res* 2013; 8:2003-14.
84. Zamudio-Cuevas Y, Martínez-Flores K, Martínez-Nava GA, Clavijo-Cornejo D, Fernández-Torres J, Sánchez-Sánchez R. Rheumatoid Arthritis and Oxidative Stress. *Cellular and Molecular Biology* 2022; 68:174-84.
85. Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell Mol Life Sci* 2016; 73:79-94.
86. Oslowski CM, Urano F. Measuring ER stress and the unfolded protein response using mammalian tissue culture system. *Meth Enzymol* 2011; 490:71-92.
87. Yuzefovych LV, Musiyenko SI, Wilson GL, Rachek LI. Mitochondrial DNA Damage and Dysfunction, and Oxidative Stress Are Associated with Endoplasmic Reticulum Stress, Protein Degradation and Apoptosis in High Fat Diet-Induced Insulin Resistance Mice. *PLOS ONE* 2013; 8:e54059.
88. Hamdan N, Kritsiligkou P, Grant CM. ER stress causes widespread protein aggregation and prion formation. *J Cell Biol* 2017; 216:2295-304.
89. Reid DW, Chen Q, Tay AS-L, Shenolikar S, Nicchitta CV. The Unfolded Protein Response Triggers Selective mRNA Release From the Endoplasmic Reticulum. *Cell* 2014; 158:1362-74.
90. Ding W-X, Ni H-M, Gao W, Yoshimori T, Stolz DB, Ron D, et al. Linking of Autophagy to Ubiquitin-Proteasome System Is Important for the Regulation of Endoplasmic Reticulum Stress and Cell Viability. *Am J Pathol* 2007; 171:513-24.
91. Fujita E, Kouroku Y, Isoai A, Kumagai H, Misutani A, Matsuda C, et al. Two endoplasmic reticulum-associated degradation (ERAD) systems for the novel variant of the mutant dysferlin: ubiquitin/proteasome ERAD(I) and autophagy/lysosome ERAD(II). *Hum Mol Genet* 2007; 16:618-29.
92. Li X, Zhu F, Jiang J, Sun C, Zhong Q, Shen M, et al. Simultaneous inhibition of the ubiquitin-proteasome system and autophagy enhances apoptosis induced by ER stress aggravators in human pancreatic cancer cells. *Autophagy* 2016; 12:1521-37.
93. Vembar SS, Brodsky JL. One step at a time: endoplasmic reticulum-associated degradation. *Nat Rev Mol Cell Biol* 2008; 9:944-57.
94. Feng Y, He D, Yao Z, Klionsky DJ. The machinery of macroautophagy. *Cell Research* 2014; 24:24-41.
95. Høyer-Hansen M, Jäättelä M. Connecting endoplasmic reticulum stress to autophagy by unfolded protein response and calcium. *Cell Death Differ* 2007; 14:1576-82.
96. Parzych KR, Klionsky DJ. An Overview of Autophagy: Morphology, Mechanism, and Regulation. *Antioxid Redox Signal* 2014; 20:460-73.
97. Kaushik S, Massey AC, Cuervo AM. Lysosome membrane lipid microdomains: novel regulators of chaperone-mediated autophagy. *EMBO J* 2006; 25:3921-33.
98. Massey AC, Zhang C, Cuervo AM. Chaperone-Mediated Autoph-

agy in Aging and Disease. In: Current Topics in Developmental Biology Academic Press; 2006. p. 205-35.
99. Levine B, Kroemer G. Autophagy in the Pathogenesis of Disease. *Cell* 2008; 132:27-42.
100. Dai J, Zhang X, Li L, Chen H, Chai Y. Autophagy Inhibition Contributes to ROS-Producing NLRP3-Dependent Inflammasome Activation and Cytokine Secretion in High Glucose-Induced Macrophages. *CPB* 2017; 43:247-56.
101. Qian M, Fang X, Wang X. Autophagy and inflammation. *Clin Transl Med* 2017; 6:24.
102. Zhang K. Integration of ER stress, oxidative stress and the inflammatory response in health and disease. *Int J Clin Exp Med* 2010; 3:33-40.
103. Ruffolo PR. The Pathogenesis of Necrosis I. Correlated Light and Electron Microscopic Observations of the Myocardial Necrosis Induced by the Intravenous Injection of Papain. *Am J Pathol* 1964; 45:741-56.
104. Walker NI, Harmon BV, Gobé GC, Kerr JF. Patterns of cell death. *Methods Achiev Exp Pathol* 1988; 13:18-54.
105. Guo M, Lu B, Gan J, Wang S, Jiang X, Li H. Apoptosis detection: a purpose-dependent approach selection. *Cell Cycle* ; 20:1033-40.
106. Elmore S. Apoptosis: A Review of Programmed Cell Death. *Toxicol Pathol* 2007; 35:495-516.
107. Fotedar R, Diederich L, Fotedar A. Apoptosis and the cell cycle. *Prog Cell Cycle Res* 1996; 2:147-63.
108. Rock KL, Kono H. The inflammatory response to cell death. *Annu Rev Pathol* 2008; 3:99-126.
109. Christ A, Lauterbach M, Latz E. Western Diet and the Immune System: An Inflammatory Connection. *Immunity* 2019; 51:794-811.
110. Franceschi C, Garagnani P, Morsiani C, Conte M, Santoro A, Grignolio A, et al. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. *Front Med (Lausanne)* 2018; 5.
111. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000; 908:244-54.
112. Morales-Villegas E. Dyslipidemia, Hypertension and Diabetes Metaflammation. A Unique Mechanism for 3 Risk Factors. *Curr Hypertens Rev* 2013; 9:278-96.
113. Yang X, Li Y, Li Y, Ren X, Zhang X, Hu D, et al. Oxidative Stress-Mediated Atherosclerosis: Mechanisms and Therapies. *Front Physiol* 2017; 8.
114. Hong J, Kim K, Park E, Lee J, Markofski MM, Marrelli SP, et al. Exercise ameliorates endoplasmic reticulum stress-mediated vascular dysfunction in mesenteric arteries in atherosclerosis. *Sci Rep* 2018; 8:7938.
115. Choy PC, Siow YL, Mymin D, O K. Lipids and atherosclerosis. *Biochemistry and Cell Biology = Biochimie Et Biologie Cellulaire* 2004; 82:212-24.
116. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol* 2019; 234:16812-23.
117. Patel A. Benign vs Malignant Tumors. *JAMA Oncology* 2020; 6:1488.
118. O'Malley J, Kumar R, Inigo J, Yadava N, Chandra D. Mitochondrial Stress Response and Cancer. *Trends Cancer* 2020; 6:688-701.
119. Yadav RK, Chae S-W, Kim H-R, Chae HJ. Endoplasmic Reticulum Stress and Cancer. *J Cancer Prev* 2014; 19:75-88.
120. Andruska N, Zheng X, Yang X, Helferich WG, Shapiro DJ. Anticipatory Estrogen Activation of the Unfolded Protein Response is Linked to Cell Proliferation and Poor Survival in Estrogen Receptor α Positive Breast Cancer. *Oncogene* 2015; 34:3760-9.
121. Li C, Xu J, Li F, Chaudhary SC, Weng Z, Wen J, et al. Unfolded Protein Response Signaling and MAP Kinase Pathways Underlie Pathogenesis of Arsenic-Induced Cutaneous Inflammation. *Cancer Prev Res* 2011; 4:2101-9.
122. Sheng X, Arnoldussen YJ, Storm M, Tesikova M, Nenseth HZ, Zhao S, et al. Divergent androgen regulation of unfolded protein response pathways drives prostate cancer. *EMBO Mol Med* 2015; 7:788-801.
123. Forsythe N, Refaat A, Javadi A, Khawaja H, Weir J-A, Emam H, et al. The Unfolded Protein Response: A Novel Therapeutic Target for Poor Prognostic BRAF Mutant Colorectal Cancer. *Mol Cancer Ther* 2018; 17:1280-90.
124. Bustos SO, Antunes F, Rangel MC, Chammas R. Emerging Autophagy Functions Shape the Tumor Microenvironment and Play a Role in Cancer Progression - Implications for Cancer Therapy. *Front Oncol* 2020; 10:606436.
125. Martínez-Puente DH, Garza-Morales R, Pérez-Trujillo JJ, García-García A, Villanueva-Olivo A, Rodríguez-Rocha H, et al. Targeting E7 antigen to the endoplasmic reticulum degradation pathway promotes a potent therapeutic antitumor effect. *J Drug Target* 2021:1-9.
126. Ojha R, Amaravadi RK. Targeting the unfolded protein response in cancer. *Pharmacol Res* 2017; 120:258-66.
127. World Health Organization. Chronic obstructive pulmonary disease (COPD) [Internet]. 2023 [cited 2023 Feb 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
128. Szalontai K, Gémes N, Furák J, Varga T, Neuperger P, Balog JÁ, et al. Chronic Obstructive Pulmonary Disease: Epidemiology, Biomarkers, and Paving the Way to Lung Cancer. *J Clin Med* 2021; 10:2889.
129. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. *Front Public Health* 2020; 8:14.
130. Kelsen SG. The Unfolded Protein Response in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2016; 13:S138-45.
131. Jiang X-Q, Mei X-D, Feng D. Air pollution and chronic airway diseases: what should people know and do? *J Thorac Dis* 2016; 8:E31-40.
132. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. *The European Respiratory Journal* 2006; 28:219-42.
133. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* 2020; 21:6275.
134. Weickert MO. Nutritional Modulation of Insulin Resistance. *Scientifica (Cairo)* 2012; 2012:424780.
135. Tang X, Shen H, Chen J, Wang X, Zhang Y, Chen L, et al. Activating transcription factor 6 protects insulin receptor from ER stress-stimulated desensitization via p42/44 ERK pathway. *Acta Pharmacologica Sinica* 2011; 32:1138.
136. Burgos-Morón E, Abad-Jiménez Z, Martínez de Marañón A, Iannantuoni F, Escribano-López I, López-Domènech S, et al. Relationship between Oxidative Stress, ER Stress, and Inflammation in Type 2 Diabetes: The Battle Continues. *J Clin Med* 2019; 8.
137. Wang J, Wang H. Oxidative Stress in Pancreatic Beta Cell Regeneration. *Oxid Med Cell Longev* 2017; 2017:1930261.
138. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; 542:177-85.
139. Mercader JM, Florez JC. The Genetic Basis of Type 2 Diabetes in Hispanics and Latin Americans: Challenges and Opportunities. *Front Public Health* 2017; 5.
140. Dugger BN, Dickson DW. Pathology of Neurodegenerative Diseases. *Cold Spring Harb Perspect Biol* 2017; 9.

141. Kurland LT. Amyotrophic lateral sclerosis and parkinson's disease complex on Guam linked to an environmental neurotoxin. *Trends in Neurosciences* 1988; 11:51-4.
142. Soto-Rojas LO, Martínez-Dávila IA, Luna-Herrera C, Gutierrez-Castillo ME, Lopez-Salas FE, Gatica-Garcia B, et al. Unilateral intranigral administration of β-sitosterol β-D-glucoside triggers pathological α-synuclein spreading and bilateral nigrostriatal dopaminergic neurodegeneration in the rat. *Acta Neuropathol Commun* 2020; 8.
143. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. *Nature Reviews Neuroscience* 2003; 4:49-60.
144. Bošković M, Vovk T, Kores Plesničar B, Grabnar I. Oxidative Stress in Schizophrenia. *Curr Neuropharmacol* 2011; 9:301-12.
145. Merenlender-Wagner A, Malishkevich A, Shemer Z, Udawela M, Gibbons A, Scarr E, et al. Autophagy has a key role in the pathophysiology of schizophrenia. *Mol Psychiatry* 2015; 20:126-32.
146. Li N, Shi H, Guo Q, Gan Y, Zhang Y, Jia J, et al. Aerobic Exercise Prevents Chronic Inflammation and Insulin Resistance in Skeletal Muscle of High-Fat Diet Mice. *Nutrients* 2022; 14:3730.
147. Cheng F, Dun Y, Cheng J, Ripley-Gonzalez JW, Jiang W, You B, et al. Exercise activates autophagy and regulates endoplasmic reticulum stress in muscle of high-fat diet mice to alleviate insulin resistance. *Biochemical and Biophysical Research Communications* 2022; 601:45-51.
148. Griffiths K, Aggarwal BB, Singh RB, Buttar HS, Wilson D, De Meester F. Food Antioxidants and Their Anti-Inflammatory Properties: A Potential Role in Cardiovascular Diseases and Cancer Prevention. *Diseases* 2016; 4:28.
149. Jiang S, Liu H, Li C. Dietary Regulation of Oxidative Stress in Chronic Metabolic Diseases. *Foods* 2021; 10:1854.
150. Länsitie M, Kangas M, Jokelainen J, Venojärvi M, Timonen M, Keinänen-Kiukaanniemi S, et al. Cardiovascular disease risk and all-cause mortality associated with accelerometer-measured physical activity and sedentary time – a prospective population-based study in older adults. *BMC Geriatrics* 2022; 22:729.
151. McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc* 2019; 51:1252-61.
152. Viollet B, Lantier L, Devin-Leclerc J, Hébrard S, Amouyal C, Mounier R, et al. Targeting the AMPK pathway for the treatment of Type 2 diabetes. *Front Biosci (Landmark Ed)* 2009; 14:3380-400.
153. Sampaio A, Marques-Aleixo I, Seabra A, Mota J, Carvalho J. Physical exercise for individuals with dementia: potential benefits perceived by formal caregivers. *BMC Geriatrics* 2021; 21:6.
154. Xia J, Li B, Yin L, Zhao N, Yan Q, Xu B. Treadmill exercise decreases β-amyloid burden in APP/PS1 transgenic mice involving regulation of the unfolded protein response. *Neuroscience Letters* 2019; 703:125-31.
155. Hong J, Kim K, Kim J-H, Park Y. The Role of Endoplasmic Reticulum Stress in Cardiovascular Disease and Exercise. *Int J Vasc Med* 2017; 2017:2049217.
156. Kang E-B, Kwon I-S, Koo J-H, Kim E-J, Kim C-H, Lee J, et al. Treadmill exercise represses neuronal cell death and inflammation during Aβ-induced ER stress by regulating unfolded protein response in aged presenilin 2 mutant mice. *Apoptosis* 2013; 18:1332-47.
157. Meijering RAM, Henning RH, Brundel BJJM. Reviving the protein quality control system: Therapeutic target for cardiac disease in the elderly. *Trends in Cardiovascular Medicine* 2015; 25:243-7.
158. Kang J-S. Exercise copes with prolonged stress-induced impairment of spatial memory performance by endoplasmic reticulum stress. *J Exerc Nutrition Biochem* 2015; 19:191-7.
159. de Sousa Fernandes MS, Badicu G, Santos GCJ, Filgueira TO, Henrique RDS, de Souza RF, et al. Physical Exercise Decreases Endoplasmic Reticulum Stress in Central and Peripheral Tissues of Rodents: A Systematic Review. *Eur J Investig Health Psychol Educ* 2023; 13:1082-96.
160. Hong J, Park E, Lee J, Lee Y, Rooney BV, Park Y. Exercise training mitigates ER stress and UCP2 deficiency-associated coronary vascular dysfunction in atherosclerosis. *Sci Rep* 2021; 11:15449.
161. Powers SK, Deminice R, Ozdemir M, Yoshihara T, Bomkamp MP, Hyatt H. Exercise-induced oxidative stress: Friend or foe? *J Sport Health Sci* 2020; 9:415-25.
162. Estébanez B, de Paz JA, Cuevas MJ, González-Gallego J. Endoplasmic Reticulum Unfolded Protein Response, Aging and Exercise: An Update. *Frontiers in Physiology* 2018; 9.
163. Hart CR, Ryan ZC, Pfaffenbach KT, Dasari S, Parvizi M, Lalia AZ, et al. Attenuated activation of the unfolded protein response following exercise in skeletal muscle of older adults. *Aging (Albany NY)* 2019; 11:7587-604.
164. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of Diet in Chronic Obstructive Pulmonary Disease Prevention and Treatment. *Nutrients* 2019; 11:1357.
165. Eat wholegrains, vegetables, fruit and beans [Internet]. WCRF International. [cited 2023 Oct 18]. Available from: https://www.wcrf.org/diet-activity-and-cancer/cancer-prevention-recommendations/eat-wholegrains-vegetables-fruit-and-beans/
166. Ubago-Guisado E, Rodríguez-Barranco M, Ching-López A, Petrova D, Molina-Montes E, Amiano P, et al. Evidence Update on the Relationship between Diet and the Most Common Cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: A Systematic Review. *Nutrients* 2021; 13:3582.
167. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* 2017; 46:1029-56.
168. Bazzano LA, Serdula MK, Liu S. Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Curr Atheroscler Rep* 2003; 5:492-9.
169. Gilbert C. What is vitamin A and why do we need it? *Community Eye Health* 2013; 26:65.
170. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in Disease Prevention and Cure: An Overview. *Indian J Clin Biochem* 2013; 28:314-28.
171. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The Role of Vitamin E in Human Health and Some Diseases. *Sultan Qaboos Univ Med J* 2014; 14:e157-65.
172. Booth SL. Vitamin K: food composition and dietary intakes. *Food Nutr Res* 2012; 56:10.3402/fnr.v56i0.5505.
173. Marcelino G, Machate DJ, Freitas K de C, Hiane PA, Maldonade IR, Pott A, et al. β-Carotene: Preventive Role for Type 2 Diabetes Mellitus and Obesity: A Review. *Molecules* 2020; 25:5803.
174. Saini R. Coenzyme Q10: The essential nutrient. *J Pharm Bioallied Sci* 2011; 3:466-7.
175. Cory H, Passarelli S, Szeto J, Tamez M, Mattei J. The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. *Front Nutr* 2018; 5:87.
176. Simioni C, Zauli G, Martelli AM, Vitale M, Sacchetti G, Gonelli A, et al. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. *Oncotarget* 2018; 9:17181-98.
177. Kumar N, Goel N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnol Rep (Amst)* 2019; 24:e00370.

178. Ginwala R, Bhavsar R, Chigbu DGI, Jain P, Khan ZK. Potential Role of Flavonoids in Treating Chronic Inflammatory Diseases with a Special Focus on the Anti-Inflammatory Activity of Apigenin. *Antioxidants (Basel)* 2019; 8:35.
179. Blaner WS, Shmarakov IO, Traber MG. Vitamin A and Vitamin E: Will the Real Antioxidant Please Stand Up? *Annu Rev Nutr* 2021; 41:105-31.
180. Vervoort LMT, Ronden JE, Thijssen HHW. The potent antioxidant activity of the vitamin K cycle in microsomal lipid peroxidation. *Biochemical Pharmacology* 1997; 54:871-6.
181. Simes DC, Viegas CSB, Araújo N, Marreiros C. Vitamin K as a Diet Supplement with Impact in Human Health: Current Evidence in Age-Related Diseases. *Nutrients* 2020; 12:138.
182. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radical Biology and Medicine* 1999; 26:746-61.
183. AL-Johani NS, Al-Zharani M, Aljarba NH, Alhoshani NM, Alkeraishan N, Alkahtani S. Antioxidant and Anti-Inflammatory Activities of Coenzyme-Q10 and Piperine against Cyclophosphamide-Induced Cytotoxicity in HuH-7 Cells. *Biomed Res Int* 2022; 2022:8495159.
184. Gutierrez-Mariscal FM, Arenas-de Larriva AP, Limia-Perez L, Romero-Cabrera JL, Yubero-Serrano EM, López-Miranda J. Coenzyme Q10 Supplementation for the Reduction of Oxidative Stress: Clinical Implications in the Treatment of Chronic Diseases. *International Journal of Molecular Sciences* 2020; 21:7870.
185. Śliżewska K, Markowiak-Kopeć P, Śliżewska W. The Role of Probiotics in Cancer Prevention. *Cancers (Basel)* 2020; 13:20.
186. Wu H, Chiou J. Potential Benefits of Probiotics and Prebiotics for Coronary Heart Disease and Stroke. *Nutrients* 2021; 13:2878.
187. Du T, Lei A, Zhang N, Zhu C. The Beneficial Role of Probiotic Lactobacillus in Respiratory Diseases. *Front Immunol* 2022; 13:908010.
188. Marques AM, Sarandy MM, Novaes RD, Gonçalves RV, Freitas MB. Preclinical relevance of probiotics in type 2 diabetes: A systematic review. *Int J Exp Pathol* 2020; 101:68-79.