Physical Inactivity and Chronic Disease

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The objective of this review is to update the state of the art regarding the influence of physical activity on the development of noncommunicable diseases (NCDs) and the physiological mechanisms that may be involved. At present, there is an urgent need to promote physical activity, as 28% of the world's population is physically inactive. Physical inactivity is responsible for 6% of the global disease burden from coronary heart disease, 7% of type 2 diabetes mellitus, 10% of breast cancers, and 10% of colon cancers. Physical inactivity is thought to promote oxidative stress, inflammation, and DNA damage and thus accelerated aging, genome instability, and predisposition to develop NCDs. In addition, physical inactivity can lead to an increase in body fat through an energy imbalance sustained over time, leading to an accumulation of visceral fat, which increases the risk of developing many NCDs, especially cardiovascular and metabolic diseases. The World Health Organization aims to reduce premature mortality from NCDs globally by one-third by 2030. Given the above, physical activity levels should be increased to reach the World Health Organization 2020 recommendations. Nutr Today. 2022;57(5):252–257

Lifestyle

Lifestyle is a concept that refers to the orientation of a person's interests and behaviors. It constitutes the most relevant factor in improving health and reducing the risk of premature mortality.[1] In fact, a healthy lifestyle is an effective strategy to improve health and reduce the incidence of noncommunicable diseases (NCDs). This article discusses the influence of physical inactivity, which is one aspect of a sedentary lifestyle, on chronic degenerative disease and the pathophysiological mechanisms that may be involved.

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Among the behaviors that define a healthy lifestyle, the most clinically relevant is being physically active,[2] and physical inactivity is the major risk factor for developing NCDs.[3] It is important to note that, although the terms sedentary behavior and physical inactivity are used interchangeably, there is a clear difference between them. Sedentary behavior involves spending a large amount of time on low-energy activities in a sitting, reclining, or lying position, spending less than 1.5 metabolic equivalent tasks (METs), whereas physical inactivity is an almost total absence of physical activity.[4] The World Health Organization (WHO) establishes that adults should perform at least 150 minutes of moderate-intensity aerobic exercise (eg, riding a bicycle 30 minutes 5 times a week) or spend at least 600 METs-min per week.[5]

This review was performed looking for articles published in the following data sources: PubMed, Scopus, Web of Science, and CINAHL, from the earliest time point until June 27, 2021. The search terms were as follows: "Lifestyle AND chronic diseases," "Sedentary behavior AND chronic disease," "Diet AND chronic diseases," "Healthy lifestyle."

Epidemiology

The greater use of technology to perform daily tasks that has occurred since the mid-1950s has been identified as one of the causes of the increase in sedentary lifestyle.[6] An increase in the time devoted to sedentary behaviors is associated with adverse cardiometabolic biomarker changes. The effect of sedentary behaviors on these markers is thought to be due to lower energy expenditure that acts independently of demographic and social factors, diet, and body composition.[7]

Today, 28% of the world's population is physically inactive, and women are less active than men. In the case of adolescents, the prevalence of physical inactivity is 80%. These data highlight the urgent need to prioritize actions aimed at promoting physical activity.[8] There is a correlation between physical inactivity and the country's stage of development. The higher the human development index, the higher the prevalence of physical inactivity in the population. Possibly, this is because in countries with higher economic incomes, the possibility of commuting by car is higher, and the share of the tertiary sector of the economy (eg, transport, communication, trade) is much higher than in low-income countries.[7] Between 2001 and 2016, the share of physical inactivity in high-economic-income countries increased from 31.6%

to 36.8%, whereas in the same period, physical inactivity in low-income countries remained at 16%. Currently, high-income countries have the highest levels of physical inactivity (32%), compared with middle- and low-income countries, whose physical inactivity rates are 26% and 16%, respectively.[7,8]

Regarding sedentary behavior, according to 2016 data, more than 60% of people worldwide spend more than 3 hours a day sitting (the global adult average is 4.7 hours sitting per day), with the average being higher in high-income countries.[9]

The lifestyle consequences are palpable: in an epidemiological study conducted in 2014 in Spain with 18 926 adults aged 18 to 74 years, the population that complied with the WHO physical activity recommendations had a 50% lower prevalence of hypercholesterolemia and high blood pressure and a 30% lower prevalence of type 2 diabetes, depression, and anxiety, compared with the population who did not exercise at all.[10] Similar findings are described in other populations.[11]

HEALTH CONSEQUENCES OF A PHYSICALLY INACTIVE AND SEDENTARY LIFESTYLE

Consequences of Being Physically Inactive

The WHO published a report in 2010 naming physical inactivity as the fourth major risk factor for mortality (6% of recorded deaths worldwide).[12] A more recent report estimated that physical inactivity is responsible for 6% of the global disease burden from coronary heart disease, 7% of type 2 diabetes mellitus, 10% of breast cancers, and 10% of colon cancers. By eliminating physical inactivity, the life expectancy of the world's population would increase by 0.68 years[13] (Figure).

The role of physical inactivity as a major risk factor for developing chronic diseases was described in the WHO report published in 2014: mortality was higher among adults with insufficient physical activity compared with those who engaged in at least 150 minutes of moderate aerobic exercise per week.[7]

Lifestyle is thought to be the principal environmental factor responsible for epigenetic factors related to the onset of NCDs,[3] such as the ability to cause DNA methylation, induce histone modifications and microRNA expression, and thus alter genome expression.[14] Physically inactive lifestyles promote oxidative stress, inflammation, and DNA damage and thus are thought to lead to genome instability predisposition to develop NCD and accelerated aging.[15]

The negative clinical consequences of physical inactivity affect several interrelated body systems, such as metabolic, cardiovascular, pulmonary, neurological, musculoskeletal, psychological disorders and some cancers. The metabolic and cardiovascular disorders are the most prevalent because once established, they progress gradually, despite aggressive treatments. Concerning the latter, it has been shown that a physically inactive lifestyle causes loss of metabolic flexibility, that is, inability to adapt substrate oxidation rates in response to changes in fuel availability, and conversely, high levels of physical activity increase this flexibility. It appears that the inability to alternate lipid and carbohydrate oxidation is a relevant feature of chronic disorders such as obesity and type 2 diabetes mellitus.[7]

Physical inactivity is associated with metabolic syndrome, also known as "insulin resistance syndrome," which is defined as "a constellation of interconnected physiological, biochemical, clinical, and metabolic factors" that directly increase the risk of cardiometabolic diseases.[16] Physical inactivity has been linked to all of the risk factors described for metabolic syndrome: dyslipidemia, hypertension, hyperglycemia, visceral fat accumulation, and inflammation.[16]

A physically inactive lifestyle is thought to alter myokine secretion and generate myokine resistance, leading to a

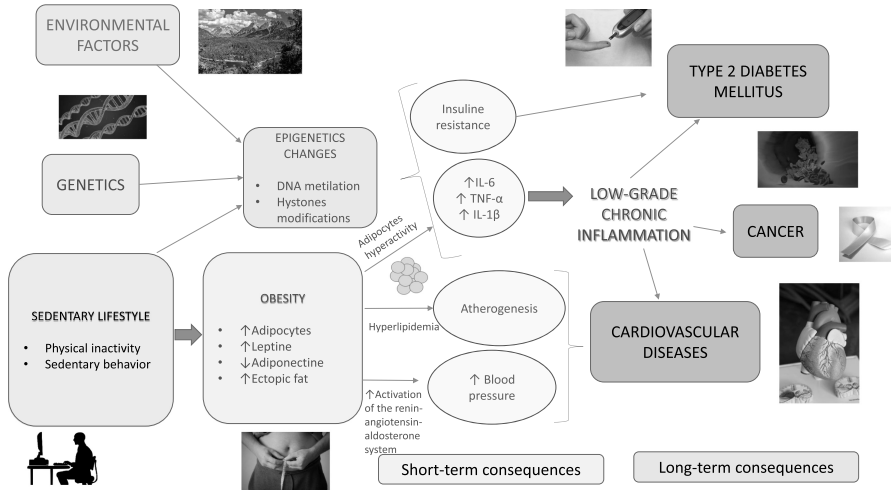

FIGURE. Health impact of an unhealthy lifestyle.

proinflammatory state that favors sarcopenia and visceral fat accumulation, which may promote insulin resistance, atherosclerosis, and tumor growth, and thus favors the development of cardiovascular diseases, type 2 diabetes, cancer, dementia, and depression.[17] As for the association between physical inactivity and cardiovascular diseases, it may be due partly to a decrease in melatonin production,[18] which contributes to poor sleep quality and early fatigue.[19] Fatigue and sleep disturbance increase the sympathetic response, which could elevate resting heart rate and blood pressure, thus contributing to the development of cardiovascular diseases.[20] In addition, oxidative stress produced by physical inactivity might be a prominent mediator of endothelial dysfunction, which is particularly harmful to cardiovascular health, as it imposes high loads on the left ventricle, which can lead to heart failure.[14]

Consequences of Excess of Sedentary Behavior

Every hour of sedentary behavior per day impacts our health because compared with subjects who sit for 6 hours a day, those who sit for 8 hours have a 14% higher cardiovascular risk, and those who sit for 10 hours a day, 29% higher.[21] According to other analyses, each additional hour spent sitting or lying down per day while awake increases the risk of being overweight by 13%, having high levels of visceral fat by 26%, developing metabolic syndrome by 39%, and developing type 2 diabetes mellitus by 22%.[11,22]

An excess of sedentary activities (eg, sitting, watching TV, activities spending <1.5 METs) is a risk factor that acts independently of an individual's physical activity levels (METs-min per week), so that an excess of sedentary behavior could diminish the beneficial effects of the physical activity.[23,24] Therefore, in addition to complying with WHO 2020 exercise recommendations,[5] people must reduce their sedentary time.[11] This interaction between sedentary time and physical activity levels is highlighted in many studies. Blood glucose and insulin levels rise more during prolonged periods of sitting compared with people who take breaks within a sitting period by walking a little.[25] In addition, prolonged periods of sitting suppress lipoprotein lipase activity in skeletal muscle, with a negative impact on lipid profile.[26] These short breaks within periods of sedentary behavior seem to increase the expression of anti-inflammatory and antioxidant mechanisms. These data indicate that the large metabolic alterations observed with sedentary behavior result from metabolic alterations at the muscle level.[25] In a recent meta-analysis of prospective cohort studies, Ekelund et al[27] reported a dose-response association between sitting time and TV time with cardiovascular and cancer mortality among the participants with lower levels of physical activity. Spending more than 8 hours' sitting per day was considered a relevant cardiovascular risk factor.[27]

In addition, sedentary lifestyles have a negative impact on maximal oxygen uptake (VO_{2max}), which is a strong protector against the development of numerous chronic pathologies.[22]

Possible Consequences of Physical Inactivity on Body Composition

According to numerous observational studies, the change in lifestyle that has taken place in many countries over the last 50 years has led to reduced levels of physical activity and increased sitting hours due to the predominance of computer-based work, coinciding with increased obesity prevalence.[28] Notably, obesity is a major risk factor for NCDs, associated with a decrease in life expectancy of 5 to 20 years, depending on the severity of the condition and comorbid disorders.[29] A sedentary lifestyle coupled with a poor diet can lead to an increase in body fat through an energy imbalance sustained over time, with an excess of calories consumed and a deficit of calories expended.[30]

Adipose tissue accounts for approximately 20% of the total body weight in a healthy human being and contributes to the regulation of body homeostasis, but if altered over a prolonged period, it can lead to harmful diseases and lifestyle disorders. The adipose tissue, in addition to being a source of energy, also plays an important role in the regulation of lipid and glycemic metabolism.[31] Adipocytes are not an inert energy storage depot but are metabolically active, and therefore fat tissue gain has a relevant metabolic impact, especially visceral fat.[32]

Visceral, or ectopic, fat tissue corresponds to the storage of triglycerides around vital organs, outside the adipose tissue, such as in the liver, heart, and pancreas, interfering with the normal function of the organs and increasing the risk of many NCDs,[33] especially cardiovascular and metabolic diseases.[34]

In fact, visceral fat secretes inflammatory cytokines, the most relevant being C-reactive protein, interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and IL-1b. Excess TNF-α may be a cause of insulin resistance,[35] whereas elevated IL-6 production by adipose cells has been linked to an increased risk of developing cardiometabolic diseases,[22,36] partly because it stimulates C-reactive protein liver synthesis. Higher C-reactive protein concentration has been positively associated with body mass index and triglyceride levels.[37] All of these events together are referred to as a chronic low-grade inflammatory state, which contributes to the development of numerous NCDs.[38]

The inflammatory effects of adipose tissue are thought to be partly because a positive energy balance prolonged over time by an inadequate lifestyle generates an initial inflammation as a physiological adaptation.[39] This inflammatory environment promotes angiogenesis to prevent tissue hypoxia of adipose tissue, induces insulin resistance to protect adipocytes from lipid overaccumulation, and promotes adipose tissue expansion, preventing ectopic lipid deposition in

other tissues.[40,41] Adipocytes expand in size (hypertrophy) and number (hyperplasia) to accommodate the need for increased lipid storage and the anabolic force of hyperinsulinemia. Thus, although insulin resistance favors the development of cardiometabolic diseases, it initially develops as an adaptive physiological response to obesity, which resists the anabolic pressure of insulin aimed at reducing excessive nutrient storage.[39,42] Adipocytes eventually reach a threshold where they cannot withstand further anabolic pressure due to restrictions in cell and tissue expansion, which causes them stress and a change in cytokine secretion, increasing inflammation.[42] Furthermore, increased fat mass is associated with a general increase in the number of macrophages, in particular proinflammatory M1 macrophages, which are characterized by a high production of IL-6 and TNF-α, are a hallmark of adipose tissue inflammation, and are associated with the development of insulin resistance.[43] On the other hand, visceral adipose tissue has approximately twice the levels of proinflammatory macrophages as subcutaneous white adipose tissue,[44] highlighting the clinical relevance of visceral fat accumulation, which generates a hyperinsulinemic environment initiating, promoting, and regulating several types of cancer.[45] Indeed, excess body fat is associated with an increased risk of at least 13 different types of cancers,[46] especially those affecting digestive organs in men and women and hormone-sensitive organs in women.[33] Production of adiponectin, an apoptosis-inducing adipokine, is reduced in response to increased production of proinflammatory cytokines, contributing to a state of "hypoadiponectinemia" and increased tumorigenesis.[45]

Finally, the release of inflammatory cytokines leads to increased free radicals, thereby increasing oxidative stress.[47] Some of the underlying causes are hyperglycemia, as it causes damage to arterial walls by facilitating low-density lipoprotein oxidation,[48] and dyslipidemia, as it is associated with the infiltration of oxidized low-density lipoprotein, causing an inflammatory response in the arterial walls.[36]

To remove adipose tissue, bariatric surgery is an effective solution for people with body mass index of greater than 35 kg/m^2 and has been associated with a higher insulin sensitivity as long as the weight loss is maintained.[49] In people less obese, effective removal of excess abdominal fat through lifestyle interventions has been associated with decreased triglycerides and fasting blood glucose levels.[50] These beneficial effects on metabolic syndrome parameters are more notable if they come from visceral fat reduction than if due to subcutaneous fat reduction,[50] so visceral fat removal is a priority. To remove a clinically significant amount of visceral fat, people should lose 1 kg of total body fat,[51] reduce their body weight by 5%,[52] or reduce their waist circumference by 3 cm.[53] In addition, a higher proportion of lean mass reduces the risk of metabolic syndrome,[54] so increasing muscle mass should also be a goal when trying to prevent cardiometabolic diseases. However, lifestyle interventions should be performed before becoming overweight, because adipose tissue appears to retain its inflammatory state for some time.[55] In fact, having been overweight at some stage of life, regardless of subsequent weight loss, increases all-cause mortality.[56]

WHO 2030 Target for NCDs

In 2030, sedentary behavior will increase by 1.5 hours per day, and energy expenditure will decrease by 19% to 27% from 2005 levels.[57] Lack of physical activity is associated with 5 million premature deaths each year, whereas its regular practice is associated with a lower risk of developing NCDs, in particular, cardiometabolic diseases.[58]

The WHO aims to reduce premature mortality from NCDs globally by one-third by 2030,[59] as they are the leading cause of disease worldwide and account for 7 out of every 10 deaths.

The countries that would benefit most from the implementation of physical activity promotion policies are high-income countries, which have the lowest levels of physical activity at present.[8,58]

Given the above, physical activity levels should be increased to reach the WHO 2020 recommendations.[5] A key message should be "perform an activity like cycling for 30 minutes at a moderate-intensity (70%-80% heart rate max),[60] 5 times a week"

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