Metabolism-Related Diseases

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Non-communicable diseases (NCDs), also known as chronic diseases, are not directly transmissible from person to person, but are the combination of genetic, physiological, environmental, and behavioural factors. The main NCDs are diabetes, cardiovascular diseases, cancers, and chronic respiratory diseases. The first three are associated with metabolic changes that increase the risk of suffering them.

NCDs obesity diabetes MAFLD cardiovascular diseases metabolism

1. Introduction

Throughout the 20th and 21st centuries, the incidence of non-communicable diseases (NCDs), also known as chronic diseases, has been increasing worldwide. Changes in dietary and physical activity patterns, along with genetic conditions, are the main factors that modulate the metabolism of individuals, leading to the development of NCDs. The main NCDs are diabetes, cardiovascular diseases, cancers, and chronic respiratory diseases. The first three are associated with metabolic changes that increase the risk of suffering them. These changes are hypertension, overweight/obesity, hyperglycemia, and hyperlipidemia (WHO). The importance of these diseases was highlighted in the report of the World Health Organization (WHO) [1], in which it was reported that over 50% of the 57 million deaths worldwide, in 2016, occurred from diabetes (1.6 million people), cancer (9 million), and cardiovascular diseases (17.9 million) [2], posing a significant global health challenge. As well as genetics, unhealthy habits such as smoking, harmful use of alcohol, physical inactivity, and a calorie-rich diet are determinants for developing metabolism-related diseases; such behavioral factors lead to metabolic disorders such as hypertension, hyperglycemia, hyperlipidemia, and obesity, which comprise the major NCDs risk factors [3]. Furthermore, over the past two decades, the understanding of the association between metabolic disorders and metabolic associated fatty liver disease (MAFLD)—a less commonly discussed NCD—has placed it as an emerging risk factor for diabetes, cancer, and cardiovascular diseases (CVDs) [4].

In view of NCDs' global threat, the WHO has adopted priority targets to reduce NCDs mortality and risk factor prevalence until 2025 [1]. However, the global prevalence of risk factors is still concerning. In 2015, one in four men and one in five women had hypertension, corresponding to 22% of the adults aged 18 years and over [5]. In recent decades, hypertension prevalence in high-income countries has declined; on the other hand, many low- and middle-income countries had stable or increasing levels. The contrast among income groups was slight regarding blood glucose levels in 2014. Most countries had between 7% and 9% of the population with hyperglycemia—except for the Eastern Mediterranean Region, which showed the highest levels (14%) [6]. Globally, the adult obesity prevalence in 2016 was 13% (650 million people); it is almost three times higher than in 1975 [5]. Although adult obesity rates distinguish between low- (7% of the population) and high-income countries (25%), the numbers keep rising in all income groups [2]. The prevalence of childhood obesity has also increased at higher rates in recent decades. From 1975 to 2016, the number of obese children and adolescents worldwide increased approximately eight-fold, reaching 124 million in 2016 [5]. Among obese and diabetic individuals, about 70–80% have MAFLD; this is the leading chronic liver disease worldwide, with a prevalence of 20–30%, affecting 1.8 billion people [7].

Countries' ability to deal with NCDs proved to be even more critical during the coronavirus disease 2019 (COVID-19) pandemic, since the association between NCDs and COVID-19 severity have been reported. Hypertension, ischemic heart disease, type 2 diabetes (T2D), and cancer were among the most prevalent NCDs in Italian COVID-19 victims [8]. This association has also been observed in Spain, China, and the USA [9][10][11]. Additionally, a Chinese study showed that severe patients and non-survivors were overweight or obese, suggesting an association between body mass index (BMI) and COVID-19 severity [12]. In this scenario, given COVID-19's restrictive measures, economic instability, and health crisis, NCDs' prevention and management became even more challenging [13].

Considering the global relevance of NCDs and the constant research progress, this topic review briefly covers the current understanding about NCDs and their related risk factors, summarizing the knowledge about their pathophysiology and highlighting therapeutic strategies. A better understanding of this critical health issue and potential therapeutic approaches can help mitigate NCDs' global impact.

2. Obesity

Obesity, a multifactorial and preventable disease, is characterized by an excessive accumulation of body fat [14], that is essentially an outcome of a long-term imbalance between energy consumpitions and expenditure. The complexity of this pathogenesis relies on its multiple causes, such as environmental, sociocultural, physiological, genetic, epigenetic, and various other factors that act together to contribute to the origin, as well as the persistence, of this condition.

Obesity management demands a multidisciplinary approach with individualized programs. Current interventions are mainly based on controlling food intake and energy expenditure with changes in dietary and physical activity. However, in some cases, behavioral changes alone are not enough, so pharmacotherapeutic or surgical interventions can also be part of the treatment [15].

Currently, there is no single optimal medication to treat the whole spectrum of obesity. The effectiveness of a particular medication is proven with the loss of at least 5% of total weight occurring after three months of treatment. Other efficiency criteria are the improvement in current comorbidities, prevention of new associated diseases, and maintenance of weight loss [16][17][18]. Still, weight loss must be realistic and aim for long-term adherence. In most cases, 5%–10% of total weight loss in six months is achievable and sustainable over the long term.

Topiramate is a gamma-aminobutyric acid (GABA) receptor modulator initially approved for seizures and migraine treatment. Topiramate administration in epilepsy treatment promoted significant weight loss, persuading the interest in this drug for obesity treatment [19]. The mechanism of action of Topiramate on weight loss is not yet totally understood; however, it is known as an appetite suppressant and satiety enhancer, acting as a neurostabilizer and enhancing thermogenesis [20].

Semaglutide is a novel GLP-1 agonist with an extended half-life that allows subcutaneous administration once a week. This peptide also has increased affinity for GLP-1 receptor and demonstrates superior efficacy in weight loss when compared to liraglutide [21][22]. Oral GLP-1 agonists are being tested as alternatives to injectable agents. In addition to the semaglutide in oral form [23], TTP-054 and ZYOGI have demonstrated promising results in effective weight loss with minimal side effects [24].

Cannabinoid receptor type 1 (CB1) neutral antagonists stimulate anorexigenic signaling, leading to weight loss by reducing food intake [25]. AM-6545 is a novel peripheral CB1 antagonist that has limited penetration in CNS and has demonstrated promising effects on weight loss, without the central side effects of the formerly commercialized CB1 antagonist rimonabant.

AM-6545 presented high affinity and selectivity for the CB1 receptor, with dose-dependent reduction in food intake and food-reinforced behavior [26][27].

3. Diabetes Mellitus

Diabetes mellitus is characterized by chronic hyperglycemia that impairs food metabolism. Under normal metabolic conditions, food ingestion triggers insulin secretion by pancreatic β-cells, which induces glucose uptake in peripheral tissues and suppresses endogenous glucose production. Insulin acts directly on skeletal muscle, liver, and adipocytes via specific signaling pathways to induce various processes involved in glucose homeostasis [28]. In muscle, insulin improves glucose utilization by increasing the glucose transporter, GLUT4, and storage, promoting glycogen synthesis [29]. In the liver, the hormone activates glycogen synthesis and regulates lipogenic and gluconeogenic gene expression programs [30]. In adipocytes, it stimulates glucose uptake and lipogenesis, while decreasing lipolysis [31]. All of these integrated processes work simultaneously to keep blood glucose levels constant. To maintain the homeostasis, the blood glucose level must be sustained within a small interval despite the oscillations in supply and demand that occur in fasting/feeding cycles. Failures in insulin signaling block glucose uptake, leading to a prolonged hyperglycemic state [28].

Diabetes is a metabolic disease related to β-cell failure, which can be auto-immune due to β-cell destruction or a progressive impairment of β-cells function that leads to insufficient insulin secretion. If insulin secretion is insufficient to regulate glucose uptake in peripheral tissues, β-cells need to increase the amount of secreted insulin in order to lower plasma glucose, a process called IR. The stress caused by constant overproduction of insulin can lead to β-cell failure followed by cell death [32].

Insulin has been widely used in patients with diabetes. Therapy is based on the patient's weight and typical doses range from 0.4 to 1.0 units/kg/day, depending on the glycemia (always self-monitored), meal size, and tissue glucose demand. There are several types of insulin, which are categorized from fast-acting to long-acting, from insulin analogues to human insulins, primarily based on how it works and how quickly it acts [33]. Long-acting insulin analogues are thought to result in fewer hypoglycemic episodes and are given 1–3 times a day according to the patient's pharmacokinetic properties to control glucose levels between meals and fasting. Postprandial insulin treatments comprise fast-acting analogues or regular short-acting insulin, which are given before each meal and each time a correction of high blood glucose is required, occurring mainly 3 times a day [34].

In addition to insulin, glycemic control can also be achieved by administering other antidiabetic medications that reverse the effects of damaged insulin signaling. There are different classes of antidiabetic treatments and their choice varies according to several factors, such as the nature of diabetes, age, and the progression of the disease.

4. Cardiovascular Diseases (CVDs)

CVDs are still the main cause of mortality and morbidity worldwide [35], which is increasing globally [36], along with cardiovascular risk factors, such as obesity [37], type 2 diabetes [38] and metabolic syndrome (MetS) [39]. The underlying cause of almost all CVDs is commonly preclinical atherosclerosis [35]. Although CVDs studies have been traditionally focused on the clinical aspects of the disease, numerous studies have shifted their focus on the metabolic basis of such conditions [36].

These MetS-associated cardiovascular risk factors, especially obesity, IR, and atherogenic dyslipidemia, lead to a myriad of vascular and cardiac diseases [40], including coronary atherosclerosis and calcification [41], cardiac dysfunction, myocardial

infarction, and heart failure [42]. However, it is not completely understood how these risk factors contribute to the development of such a spectrum of cardiovascular conditions.

Evidence associates obesity and IR with an increased risk of CVDs [43]. Thus, obesity is especially related to two cardiovascular conditions: heart failure (also known as obesity cardiomyopathy) and cardiac atherosclerosis [44]. The major physical consequence of obesity is developing atherosclerotic CVDs, which increases the risk through risk factors brought by obesity, such as hypercholesterolemia, hypertension, hyperglycemia, atherogenic dyslipidemia, IR, proinflammatory state, and prothrombotic state [45]. However, obesity leads to alterations in the hemodynamic phenotype such as increased left ventricular mass [46]. In addition to that, although not fully understood, underlying molecular mechanisms, such as myocardial Ca 2+ handling, are also deregulated, which is caused by changes in the expression of SERCA2A and ryanodine receptors, responsible for calcium transportation and, ultimately, leading to myocellular dysfunction in obesity and MetS [47].

Several studies have explored miRNA-based treatment in CVDs, such as myocardial infarction, cardiac fibrosis, and atherosclerosis. Upregulation of miR-146a in a myocardial ischemia/reperfusion injury in mice showed a 55% reduction in myocardial infarct size and an improvement in cardiac function after myocardial infarction [48]. Likewise, overexpression of miR-99a in C57/BL6 mice subjected to myocardial infarction attenuated cardiac remodeling by preventing cardiomyocyte apoptosis and promoting autophagy, cardiac function gain and increasing survival ratio [49]. Conversely, downregulation of miR-433 in mice ameliorates cardiac fibrosis and ventricular dysfunction after myocardial infarction [50]. Similarly, the administration of miRNA mimetics is also explored for CVDs treatment, which act on mRNA degradation and translation inhibition [51]. Thereby, systemic administration of a miR-100 mimic in an LDLR-deficient atherosclerotic mouse model decreased 55% of the plaque area, attenuating atherosclerosis [52]. In addition, intracardiac administration of miR-199a-3p and miR-590-3p mimetics immediately after myocardial infarction in mice led to cardiac repair, reducing infarct size and preserving cardiac function [53].

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