Human Metabolic Diseases; An Overview

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Abstract

Metabolic diseases are important public health-threatening problems due to the high incidence, disability, and mortality. These diseases are classified as inherited or acquired. Inherited or inborn metabolic disorders are due to a genetic variation or mutation, in the genomic or mitochondrial DNA, that alters metabolic or biochemical pathways. Acquired metabolic diseases are characterized by a genetic predisposition associated with a strong interaction with metabolic and environmental factors and whose prevalence is dangerously increasing as a consequence of the actual unhealthy lifestyles. The dietary habits that include excessive food consumption and bad quality of what is consumed, associated with an absence or reduced physical activity, have led to an increase in the number of people who develop metabolic diseases. Overweight and obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome, are the most prevalent and have a high social and economic cost for the patient, the family, and the health systems. Great efforts have been made to understand the physiopathology of these diseases and to establish effective treatments. There are different treatment alternatives, lifestyle changes, and pharmaceutical and phytotherapeutic treatments, to control or reverse these conditions. Still, an important factor should also be considered, the patient and family members´ education.

Introduction

Metabolism is the process that must be carried out to obtain energy from the proteins, lipids, and carbohydrates contained in the foods we consume. Energy is required for vital processes such as respiration, digestion, and circulation, or can be stored in muscles, liver, or in the form of body fat when the consumption and content of food exceed the energy required for vital functions and physical activity (Lam & Ravussin, 2016; Carpentier et al., 2018).

Metabolic diseases are classified into: inherited and acquired. Inherited diseases or inborn errors of metabolism (IMDs) are monogenic disorders that can be inherited in an autosomal recessive form or, less frequently, in autosomal dominant or X-linked patterns. These mutations can occur in the genomic or the mitochondrial DNA. As a result, it produces alterations in a protein that, depending on the function it performs, can block different metabolic processes. Whether as a receptor-transporter, hormone, enzyme, or as part of a cellular organelle, they cause the inability to adequately process food to transform it into usable energy, so their clinical manifestations depend on the severity of the blockage, the affected pathway, and the age (Barroso & McCarthy, 2019).

Due to their hereditary nature, it is common to identify them as pediatric diseases; glycogenosis type I, galactosemia, fructose intolerance, or phenylketonuria can be detected in newborns (Raimann, 2008; Campistol, 2023), but they can also manifest at other stages of life. During adolescence, they correspond to mitochondrial diseases that generate a deficit in the energy metabolism, as well as lysosomal and peroxisomal disorders (disorders of the metabolism of complex molecules). In adulthood, they appear as neurological diseases, such as homocystinuria, aceruloplasminemia, or metachromic leukodystrophy (Corbetta & Vici, 2023). Despite they are individually rare, the estimated birth prevalence of all IMDs combined is 50.9 per 100,000 live births (LB). Due to the advances in genetics and biochemistry, more knowledge of the pathophysiology, early diagnosis, and treatments are now available, so that there is an increase in survival and a reduction in morbidity.

Acquired metabolic diseases (AMD) are chronic progressive diseases in which there is a genetic predisposition due to family history. Their manifestation depends on the interaction between metabolic and environmental factors. Dietary habits are determinant to this type of disease; the excessive consumption and the quality of the consumed food are the most important factors. Foods with excess saturated fats, trans fats, and cholesterol, simple sugars and refined flours; or with low dietary fiber are the worst combination. Additionally, the lack of physical activity that affects general health, also contributes to the development of metabolic diseases such as overweight, obesity, T2D, hypertension, and dyslipidemia (Botchlett et al., 2017; Hoffman et al., 2021), These metabolic diseases have a high prevalence and are individually considered as a public health problem (Botchlett et al., 2019).

Relevant Aspects of the Most Prevalent Acquired Metabolic Diseases

Overweight and Obesity

The World Health Organization (WHO) defines obesity as an "abnormal or excessive fat accumulation that may impair health". The main cause of overweight and obesity is an imbalance between the consumed and expended calories due to a combination of factors like epigenetic and genetic influences, altered eating habits, and, lack of or reduced physical activity. Obesity is an important health problem that affects a high proportion of the adult and child population. Globally, obesity is the fifth cause of death, and according to the World Obesity Atlas (WOF-Obesity-Atlas, 2024), the number of adults with overweight (BMI >25 to 30 kg/m²) will increase from 1.39 billion in 2020 to 1.77 billion in 2035. The number of obese adults (>30 kg/m²) will increase from 0.81 billion in 2020 to 1.53 billion in 2035 (WOF-Obesity-Atlas 2024). To realize the magnitude of this health problem, we must consider the 2022 WHO report: 1 in 8 people in the world were living with obesity. Adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled, 2.5 billion adults (18 years and older) were overweight, and 890 million of these were obese. 43% of adults aged 18 years and over were overweight and 16% were obese. More alarming, 37 million children under 5 years were overweight, and finally, 390 million children and adolescents aged 5 to 19 years were overweight, including 160 million that were living with obesity (WHO, 2024b).

Currently recognized as a multifactorial, recurrent, and chronic disease, obesity significantly compromises the proper functioning of all the body systems (Ruze et al., 2023) and increases the risk of developing other chronic diseases, including cardiovascular diseases, hypercholerolemia, T2D, and metabolic syndrome, among others.

To differentiate between overweight and obesity, a parameter, the body mass index (BMI), a medical screening tool that allows the determination of the difference by establishing a relationship between weight and height,

BMI is calculated by dividing the kilograms of weight by the square of the height in m² (Borga et al., 2018).

$$BMI = \frac{Weight \; in \; kilogram}{(Height \; in \; meter)^2}$$

Body Mass Index Formula

It must be considered that the adipose tissue (body fat) has an important role; it participates as a protector of organs, in the coating and cushioning of joints, in the maintenance and regulation of temperature, and in the reserve of energy, vitamins, and essential nutrients, among others. However, excessive accumulation in the body has harmful effects on health (Carpentier et al., 2018).

Under optimal conditions, the percentage of body fat for men should range between 8.1 and 15.9%, while for women it should range between 15.1 and 20.9%. If these values increase for men between 16.0 and 20.9% and, for women between 21.0 and 25.9%, there is a slight overweight. When these percentages increase between 21.0 and 24.9% in men, and 26.0, and 31.9% in women, the condition is considered overweight. Nevertheless, when they are greater than or equal to 25% in men and 32% in women, the diagnosis must be obesity.

Obesity has been classified according to the BMI and the risk (Table 1) (Cardozo et al., 2016).

Table 1: Obesity types

Type of obesity	Risk	BMI
Type 1	Low risk	30 → 34.9
Type 2	Moderate risk	35 → 39.9
Type 3 or morbid	High risk	40 → 49.9
Type 4 or extreme	Very high risk	>50

It is important to mention that the number and severity of the complications are strictly related to the type of obesity.

Visceral fat storage, sedentary lifestyle, and aging have a close relationship between insulin resistance and obesity. In an obese patient, the organs and tissues with insulin sensitivity (liver, skeletal muscle, and adipose tissue) suffer serious damage at molecular and functional levels (Barazzoni et al., 2018). This occurs because the accumulation of fat generates changes in oxidative stress and redox balance, causing inflammation and alterations in the mitochondria function. The impact on the body includes low production of metabolic energy in the form of ATP (adenosine triphosphate), as well as other cyclic nucleotides (cAMP and cGMP) that generate a decreased insulin response (Czech, 2017; Wu & Ballantyne, 2020; Ahmed et al., 2021). Obesity is also related to cancer progression, including breast and colon cancer, and pancreatic ductal adenocarcinoma (Yang et al., 2022).

To prevent and control these conditions, it is mandatory to reduce weight, to modify eating habits, to reduce the consumption of foods rich in fats and sugars and soft drinks, to increase the consumption of fruits, vegetables, legumes, and whole grains rich in fiber and very importantly, to perform a complementary exercise routine (Clifton, 2019). This condition is difficult to reverse, and different approaches are needed. There are different pharmacological treatments; the most commonly used are bupropion-naltrexone, liraglutide, orlistat, phentermine-topirate, and semaglutide, but it must be considered that these drugs may not work for everyone and they can induce adverse effects. There are many examples that some of these drugs have been withdrawn from the market due to severe and life-threatening adverse effects. A more recent and promising approach to treat obesity is to include gut microbial reprogramming by fecal microbiota transplantation, and the use of probiotics, prebiotics, or symbiotics. In extreme life-threatening cases, when with all the lifestyle modifications and the pharmaceutical treatments, the weight loss goals have not been achieved, patients, under medical recommendations and supervision, can undergo bariatric surgery, endoscopic sleeve gastroplasty, intragastric balloon, adjustable gastric banding, gastric bypass surgery, and a gastric sleeve or use

hydrogels that help to feel full, or a vagal nerve blockade device that sends electrical pulses to the abdominal vagus nerve that tell the brain the condition full/empty (Fink et al., 2022). These options have surgery risks and can have adverse effects. None of these options is for everybody, and all of them require the additional commitment to modifying lifestyles. A healthcare team is required to comprehensively support weight reduction, including psychological support.

Type 2 Diabetes Mellitus (T2D)

It is a complex and multifactorial metabolic disease, characterized by the abnormal and chronic increase in blood glucose levels (hyperglycemia), caused by the alteration in the secretion and/or resistance to insulin. It is the consequence of underutilization of glucose and an overproduction due to inadequate gluconeogenesis and glycogenolysis. The interaction between environmental and genetic factors determines the onset and evolution of the disease. The main risk factors are associated, with unhealthy eating habits, being overweight, obesity, a sedentary lifestyle, and smoking. The complications associated with this disease comprise two groups: macrovascular and microvascular. Macrovascular complications include peripheral arterial disease, stroke, cardiovascular disease, and diabetic foot syndrome. Microvascular complications are the most important due to their high prevalence and include complications such as nephropathy, neuropathy, and retinopathy (Polanco et al., 2005; Zhou et al., 2020; Revilla, et al., 2024).

Unlike type 1 diabetes (T1D), which requires the constant administration of insulin to control blood glucose levels, T2D does not require insulin, except in cases where glucose levels cannot be controlled with drug treatment and lifestyle changes (proper nutrition and regular exercise). T2D usually appears in adulthood, increasing in frequency with age (Wallia & Molitch, 2014; Nery et al., 2017).

T2D can occur in a low percentage (around 10%) of people who are not overweight, but most cases (90%) are associated with obesity and a family history of genetic and ethnic predisposition, and nutritional factors have a determining role.

Even when circulating insulin levels are normal or higher in response to diet, insulin resistance may occur, due to the muscle, liver, and fat cells cannot use it and metabolize glucose, and therefore, glucose remains in circulation, causing hyperglycemia (Ahmad et al., 2022). Reduced sensitivity to this hormone, which affects some physiological processes (such as cell differentiation and proliferation), produces alterations such as arterial hypertension and a form of dyslipidemia in which very low-density lipoprotein cholesterol (VLDL) increases and can cause atherosclerosis and a decrease in high-density cholesterol (HDL), known as good cholesterol (DeFronzo et al., 2015; Galicia-García et al., 2020).

To realize the magnitude of the problem, we must analyze the report of the International Diabetes Federation (IDF). In 2021, 537 million adults (20-79 years) lived with diabetes (1 in 10), and it is estimated that this number will increase to 643 million in 2030 and to 783 million in 2045. One in two adults (20-79 years old) with diabetes were not diagnosed. (239.7 million, 44.7%) They also reported that 16.9% (21.1 millions) of newborns developed in a hyperglycemic environment, a condition that is a risk factor for developing T2D, obesity, insulin resistance, and other metabolic disorders in adulthood (IDF, Atlas 2021). The danger for those patients that have not been diagnosed is that the untreated disease progresses and patients will develop the micro and macrovasular complications.

Great advances have been made in diagnostic methods and in the establishment of management standards.

There are multiple strategies for the treatment of diabetic patients; due to the close relationship between T2D and overweight and obesity, following a healthy eating plan, incorporating an exercise routine, and avoiding smoking, can be one of the first-line strategies (Sami et al., 2017), but the frequent lack of response or attachment to this treatment requires the administration of pharmacological hypoglycemic drugs or hypoglycemic plant extracts (Revilla et al., 2024). The most used hypoglycemic drugs include sulfonylureas, glinides or metaglinides, biguanides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, and DPP-4 antagonists, all with different mechanisms of action and adverse effects (Revilla et al., 2024), and, again, not all work for everybody.

Hypertension

Hypertension is a chronic disease characterized by an increase in the arterial pressure of systemic circulation. It has been classified into two categories: primary and secondary hypertension. Primary or essential hypertension is present in 85-95% of the patients; the causes can be the interaction of genetic and environmental factors. Secondary hypertension is caused by renal artery stenosis, pheochromocytoma, adrenal adenoma, or single-gene mutations. The most prevalent is essential hypertension, which is diagnosed by a persistent systolic blood pressure of >130 mmHg or >80 mmHg of diastolic pressure (Unger et al., 2020). Pre-hypertension occurs when the measurements are 120-129/80 mmHg and correspond to the initial stage of hypertension. Above these values, hypertension is classified into three levels as shown in Table 2 (Joyner et al., 2016; Flint et al., 2019).

Table 2: Hypertension stages

Stage	Systolic pressure	Diastolic pressure
Stage 1	130 - 139	80 - 89
Stage 2	>140 or higher	90 or higher
Hypertension crisis	>180	>120

According to the WHO, 1.28 billion adults (30-79 years) are hypertensive, and only 42% of the adults that have hypertension are diagnosed and treated, and 46% ignore the presence of this medical condition (WHO, 2023).

The absence of obvious symptoms is the reason for a late diagnosis, so it is considered a "silent disease" or "silent killer". Hypertension represents one of the most important risk factors for strokes, cardiovascular events, heart failure, ischemic heart disease and coronary artery disease, chronic kidney disease, or aneurysms, among other consequences, which seriously endanger people's health and life (Fuchs & Whelton, 2020; Zhou et al., 2021). It is common the simultaneous presence of diabetes and hypertension, a condition that increases the risk for

cardiovascular diseases (Mancia, 2005). Recommendations to prevent the development of hypertension include weight reduction, modifications in eating habits, reducing salt consumption to less than 5 g per day, increasing de potassium consumption, adding fruits and vegetables –rich in vitamins, minerals, and fiber– eliminating or reducing the consumption of trans fats in the diet (butter or margarine), limiting the consumption of foods rich in saturated fats, and reducing the consumption of alcohol and tobacco, in addition to increasing physical activity (WHO, 2023). Besides these first recommendations, which most of the times are not carried out by the patients, there is an alternative, the drug therapy, that consists of the administration of thiazide or thiazidelike diuretic, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a calcium channel blocker (Al-Makki et al., 2022).

Dyslipidemia

This disorder is caused by a high concentration of lipids in the bloodstream, especially triglycerides, and cholesterol, that are absorbed from the intestines and transported via lipoproteins for energy, steroid production, and the formation of bile acid. The main lipids are cholesterol, low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL). Alterations in the levels of these lipids induce dyslipidemia, which is an important risk factor for the development of cerebrovascular diseases and coronary heart disease (Kopin & Lowestein, 2017). Dyslipidemia is classified into two types: primary and secondary. Primary dyslipidemia is inherited as an autosomal dominant, autosomal recessive, or X-linked form; examples of this condition are familial hypercholesterolemia and familial hypertriglyceridemia. Secondary dyslipidemia is the result of lifestyle factors or some medical condition that alters lipid levels, and, depending on the underlying cause, it is reversible. Some of the risk factors for secondary dyslipidemia are: physical inactivity, unhealthy diet, obesity, diabetes, alcohol, and tobacco abuse, and the use of certain drugs like corticosteroids, beta-blockers, and, oral contraceptives (Yanai & Yoshida, 2021).

Triglycerides are the most common lipid responsible for dyslipidemia, produced as part of the liver metabolism and the consumed foods. The ideal blood concentration should be less than 150 mg/dl. Any value above this level determines the presence of hypertriglyceridemia, a level that represents a risk factor for cardiovascular diseases (Berberich & Hegele, 2022).

According to triglyceride levels, they are classified as mild-moderate (150 to 885 mg/dl), severe or serious (more than 885 mg/dl), and very serious (more than 1770 mg/dl). In some cases, high triglyceride levels are associated with genetic or primary causes, which prevent the formation of proteins responsible for processing this type of lipid. Among the causes of hypertriglyceridemia, secondary to diseases or medications, in addition to genetic predisposition, is the excessive food consumption that contributes to developing overweight and obesity problems, diabetes mellitus, and alcohol consumption, which favor this condition, and can cause diseases such as acute pancreatitis or coronary heart disease. A proper diet, physical exercise, and alcohol abstinence help to keep triglyceride levels within normal limits. If lifestyle changes fail to control triglyceride levels, pharmacological treatment should be used (Nordestgaard & Varbo, 2014; Budoff, 2016; Wiesner & Watson, 2017).

In the case of cholesterol, it is a type of fat that comes naturally from the liver and the consumed food. In cells, it appears as a structural component of membranes. In addition, it participates in the synthesis of steroid hormones (testosterone, progesterone, cortisol, and estradiol), bile acids, and vitamin D. There are two main types of cholesterol. Low-density lipoprotein (LDL), called "bad cholesterol". It comes from foods rich in saturated fats, which tend to accumulate in the lining of blood vessels, preventing proper blood flow. High-density lipoproteins (HDL) or "good cholesterol", promote–the elimination of LDL from the bloodstream and is considered a "heart protector" (Wang et al., 2013; Jeong et al., 2018).

Hypercholesterolemia, is a hereditary disorder generally associated with LDL alterations. It represents one of the main cardiovascular risk factors, due to the implications that arise from the reduction of blood flow. Likewise, together with fatty acids, macrophages, and triglycerides, they can form plaques in the blood vessels called *atheromas*. The most harmful are the smallest ones, since due to the action of the bloodstream they can break off and form a thrombus with fatal consequences. To maintain adequate levels of LDL, a significant reduction in the consumption of industrialized, processed, or precooked foods, rich in sugars, saturated and trans fats is needed. On the other hand, increasing the consumption of foods rich in omega-3 and dietary fiber (present in fruits and vegetables), regularly performing aerobic exercise, and abstaining from tobacco use are recommended (Cabezas-Zábala et al., 2016; Arvanitis & Lowenstein, 2023).

Dyslipidemia can induce inflammation, oxidative stress, cardiovascular diseases, and other metabolic alterations, so it is important to perform an early diagnosis and treatment. Management of dyslipidemia requires lifestyle changes that include dietary modifications. Increasing physical activity, besides reducing lipid concentrations, lowers blood pressure, increases insulin sensitivity, and reduces weight and cardiovascular risk. Reduction of smoking and alcohol consumption is also required. Frequent complications of dyslipidemia, which is associated with obesity, diabetes, and metabolic syndrome, are the high levels of total triglycerides and a reduction in HDL and apolipoprotein B (ApoB) transporters and a discrete increase of LDL-c, that which are responsible for atherogenic dyslipidemia that increases the risk of cardiovascular diseases (Pascual et al., 2022).

Besides these lifestyle modifications, pharmaceutical treatment is frequently required, and the administration of statins, fibrates, ezetimibe, bile acid sequestrants, niacin, and Omega-3 fatty acids may help to control the lipid levels (Pappan et al., 2024).

Metabolic Syndrome (MetS)

Metabolic syndrome (MetS) consists of a group of metabolic alterations that include insulin resistance, impaired glucose metabolism, atherogenic dyslipidemia, central obesity, hypertension, and genetic and acquired conditions. It occurs when there is an association between obesity, T2D, hypertension, and dyslipidemia. It is a highly dangerous, chronic, and progressive disease that causes multisystem failure. Obesity with high central abdominal fat accumulation and diabetes mellitus (specifically insulin resistance) are determinants in the progression of this disease (Fernández-Travieso, 2016; Gluvic et al., 2017).

In this complex syndrome, there is a coexistence of risk factors such as abdominal obesity, atherogenic dyslipidemia, hypertension, a prothrombotic and proinflammatory state, insulin resistance (IR), and higher glucose levels, factors associated with an increased risk of

developing chronic conditions, such as T2D and cardiovascular diseases (CVD). The characteristic inflammatory states and meta-inflammation induce the increase in the serum concentration of pro-inflammatory cytokines, that originate from the chronically inflamed adipose tissue and are associated with oxidative stress. The increase of ROS (reactive oxygen species) affects the antioxidant systems, leading to oxidative stress. In addition, hyperglycemia increases oxidative stress and the production of advanced glycosylation end products (AGEs), which are related to cellular and molecular dysfunction.

To diagnose a patient with metabolic syndrome, the coexistence of three or more of the following metabolic abnormalities is required: 1) Waist circumference greater than 100 cm in men and 87.5 cm in women. 2) Serum triglyceride level ≥ 150 mg/dL in both sexes. 3) HDL cholesterol <40 mg/dL for men and HDL <50 mg/dL for women. 4) Fasting blood glucose level (glycemic index) ≥100 mg/dL, both sexes. 5) Blood pressure >130/80 mmHg, both sexes (Saklayen, 2018).

For patients who have the syndrome, the risks of suffering serious illnesses tend to increase significantly. To name some, the risk of suffering from T2D increases fivefold, cardiovascular diseases twofold, and myocardial infarctions and stroke fourfold (Kaur, 2014). In advanced cases, sarcoplasmic reticulum stress, chronic inflammation, and prothrombosis may occur. The prognoses range from serious, and in some cases death may occur (Fragoso-Ramos, 2022). Likewise, there is an association of metabolic syndrome with accelerated atherosclerosis, early onset of T2D, and premature atherosclerotic cardiovascular diseases (Neeland et al., 2024). Additionally, sleep health and hygiene must be considered because sleep apnea or sleep deprivation can induce the development of MetS.

Although visceral fat appears to be the main triggering factor, there is also a genetic predisposition. Likewise, lifestyle and nutritional habits influence the pathogenesis. In addition to a balanced diet, the systematic practice of exercise results in preventive measures that can reduce the number of people affected (Kim & Yi, 2018; Swarp et al., 2024).

According to the WHO, the global prevalence of metabolic syndrome in 2020 was 2.8% for children and 4.8% for adolescents. Around 25.8 million children and 35.5 million adolescents were living with metabolic syndrome (Noubiap et al., 2022).

The treatment of MetS requires the identification and treatment of the risk factors and considers the lifestyle modifications and pharmaceutical management. Drug therapy is recommended for dyslipidemia, hypertension, and insulin resistance or T2D, components of the MetS, and must consider the associated co-morbid conditions in addition to the risk factors. Some plants extracts have proven to be a possibility, but further research is needed, especially in life-threatening conditions.

Conclusions

Metabolic diseases are a group of disorders that have been escalating in terms of prevalence and morbidity. The lifestyles adopted in recent decades have driven the increase in the number of people who suffer from them. Although there are genetic factors that increase susceptibility, the truth is that today more than ever, maintaining a healthy and balanced diet is crucial to prevent the development of all the mentioned metabolic diseases. An excessive diet, deficient in nutrients, rich in fats and carbohydrates, and little or no physical activity, is the perfect formula for developing these diseases. Strengthening prevention and control requires reinforcing efforts from research centers, through the generation and transfer of knowledge and the commitment of health institutions to promptly address these health problems. The approach to prevent, control, and treat these diseases must be with a multidisciplinary medical team, starting with the primary care physician, and must consider frequent screening, especially if the patients have risk factors that include age. Together these strategies will contribute to provide patients with a better quality of life and save lives. It is not only a matter of costs for the health systems; it is a matter of quality of life and life for millions of people all around the world. An important additional factor should be considered: the patient and family members´ education. Being informed is the first step to prevent these diseases.

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