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PATTERNS AND CONSEQUENCES OF OBESITY ON CARDIOVASCULAR CONCERNS PREVALENCE, FLUCTUATIONS, AND HEALTHCARE DILEMMAS.

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Abstract

Background: Obesity has emerged as a pressing global health concern, with escalating prevalence rates.

Objective: To assess the global prevalence, regional disparities, and associated healthcare implications of obesity.

Methods: A comprehensive review of epidemiological data was conducted, focusing on regional patterns and demographic variations.

Results:

- Over 1.6 billion individuals surpass their ideal weight, with over 500 million categorized as obese.
- Surprisingly high obesity rates are observed in historically undernourished regions, including Ibero-American countries, East Middle regions, Oceania, China, Australasia, Vietnam, and the Pacific Islands.
- Africa and Asia exhibit notable obesity prevalences.
- Obesity is implicated in over 300,000 annual deaths and incurs substantial healthcare costs.

Conclusion: Obesity's pervasive presence underscores the urgent need for targeted interventions and policy measures to address its multifaceted challenges.

Introduction

Given the growing sensitivity to this situation, the WHO admitted in 2001 that we are facing a pandemic that agreed to call *"globesity"* in an attempt to draw attention to the global problem and, what is more, problematic in terms of public health, its continued expansion and growth, especially among children and adolescents. This situation could endanger the years of life expectancy gained in the last century. Concern about obesity is not new, and notable efforts have been raised for treatment for centuries. However, until recently, it had not been considered a disease in the sense of identifying it as a specific target of medical therapy. This has meant notable advances in their knowledge and in the development of research, industrial applications, and treatments of different kinds, whether dietetic, oriented towards physical exercise, or searching for valuable medicines. Again, data from the US show annual spending on drugs or surgical techniques for treating obesity is over $4 billion, while the market for OTC weight loss remedies exceeds $50 billion annually. However, conceptually speaking, treating obesity should not pose a severe problem. We have known for many years the way to deal with it: as simple as seeking an adequate energy balance in the sense of income bills. This simplification has led to considering obesity as a personal problem based on the unwillingness of each person to maintain their ideal weight. However, today, this concept is changing dramatically and moving away from the individual the exclusive "guilt"

In the US, the advisory committee of the *2010 Dietary Guidelines for Americans* points to obesity as "the greatest threat to public health" and highlights that "basic dietary recommendations have not changed substantially in the last 30 years..." but adds that "it has become increasingly difficult eat well.." He continues, "As long as the food environment is not changed, it will be challenging for people to follow dietary guidelines or recommendations." In the UK, the *UK Foresight Report* sends a similar message: "obesity is one of the burdens of the modern world, in which high-value or calorie-dense foods are plentiful, and labor-saving (physical)(Zhang, Li et al. 2023) technologies proliferate." In this environment, "excess Weight loss harmful to health becomes frequent concerning the individual choice of diet, the exercise stopped practicing and the so-called lifestyle. Therefore, a complex social and biological network makes us vulnerable to weight gain. This means that the objective must limit the "obesogenic" environment in which we live immersed and to which we are exposed (Kwiatkowska, Olszak et al. 2023).

Obesity, due to its high prevalence and health and social significance, is of interest to researchers and specialists -especially internists, endocrinologists, and cardiologists- as well as to those doctors and researchers who wish to deepen their knowledge. Other factors, such as genetic factors, play a role in this multifactorial disease. The harmful consequences of obesity are due to complex interactions with different conditions and equally complex mechanisms that explain the deterioration of the patient and the appearance of complications becoming increasingly apparent. Known. Along with obesity, diabetes is a true pandemic of the 21st century that carries a particular risk of suffering from cardiovascular diseases or cancer (Zuercher, Harvey et al. 2023).

The DRECE study: Diet and risk of cardiovascular diseases in Spain

Arteriosclerosis and cardiovascular diseases (CVD) constitute, along with cancer, the leading cause of mortality and morbidity in developed countries. CVDs affect the heart or blood vessels (arteries and veins). While technically, the term refers to any pathology that is of interest to the cardiovascular system (MeSH C14), it is usually used to refer to those related to arteriosclerosis. These diseases share similar causes, mechanisms, and treatments. Due to their frequency and severity, the term CVD in the medical literature focuses primarily on coronary or ischemic heart disease and cerebrovascular diseases. According to the World Health Organization (WHO), CVDs cause 17.5 million deaths

yearly, account for half of all deaths in rich countries, and increase in many developing countries. Together, they are the first cause of death in our environment, although they tend to be equal to cancer (Farazi, Jayedi et al. 2023).

More than 125,000 deaths and more than 5 million hospital stay due to CVD occur annually in Spain, and these are the leading cause of death and hospitalization in the Spanish population. Many asymptomatic people are at serious risk of presenting a cardiovascular event due to being carriers of two or more risk factors. In more than 60% of cases, these risk factors are not adequately controlled, and improvements in this field remain scarce. More than a third of patients with acute myocardial infarction die before reaching the hospital without receiving adequate treatment. Consequently, coronary incidence and mortality have not improved appreciably in recent decades in Spain. The best way to deal with this situation is to promote the primary prevention of CVD (Collins, Kraus et al. 2023) (Jeong, Wee et al. 2023).

There is a set of risk factors related to CVD. In addition to age, male sex, and family history, high blood pressure, obesity, smoking, diabetes, physical inactivity, and dyslipidemia (high cholesterol, high-density lipoprotein cholesterol) have been identified as such. —HDL— decreased). A primary determinant of CVD risk is the diet's composition. In this sense, the first prospective study that analyzed the relationship between diet and cardiovascular disease in 16 cohorts of men from 7 different countries was published in 1970 by Keys. The study was conducted in Yugoslavia, Italy, Greece, Finland, the Netherlands, the US, and Canada. It showed that the populations of the Mediterranean area and Japan had lower cardiovascular mortality than those of northern European countries and the US. The results of this study revealed the relationship between the intake of saturated fats, cholesterol, and coronary disease (de Frel, Assendelft et al. 2023).

Twenty-five years later, CHD mortality in these cohorts was linearly related to cholesterol levels, with CHD mortality rates increase relative to increasing cholesterol levels. There were, however, significant differences in the absolute rates of CHD mortality for a given cholesterol level, suggesting that. Other factors present in countries with a low risk of CVD -Japan-, such as diet, had to be taken into account with a view to primary prevention. The diet analysis in these populations showed that mortality from coronary disease was directly correlated with the consumption of foods of animal origin. At the same time, the correlation was inverse concerning the consumption of vegetables and alcohol (Perna and Hewlings 2023).

Spain has not been immune to global changes in eating patterns, although significantly to a much lesser extent than in neighboring countries. In 20-25 years, there has been a change from a diet based on the consumption of cereals, legumes, potatoes, fruit, vegetables, olive oil, and, to a lesser extent, milk, and meat products, to a pattern characterized by a lower proportion of hydrocarbon foods (cereals, potatoes, legumes) and an increase in the consumption of meat and dairy products. Although the consumption of fruit and fish has increased, there is a decrease in olive oil (although it is still the majority) and red wine. Despite this, CVD mortality in Spain has decreased in recent years, although when analyzing this trend, we found that the most significant decrease was due to the reduction in cerebrovascular diseases (V: 164.28; M: 139.5 in 1975 vs. V: 45.30; M: 38.91 in 2006 per 100,000 inhabitants/year), while the decrease in mortality from coronary ischemia has been substantially slighter (V: 126.21; M: 60.09 in 1975 versus V: 73.35; M:33.27 in 2006 for every 100,000 inhabitants/year) (Zhang, Li et al. 2023).

This context of possible modification of eating habits, a notable prevalence of cardiovascular risk factors paradoxically linked to low CVD-related mortality rates, in contrast to what is observed in populations from other Western countries of reference, aroused the interest of researchers—Spaniards for scientifically analyzing the situation. So, At the end of the eighties, the DRECE project (Diet and

Risk of Cardiovascular Diseases in Spain) was designed, a set of scientific, clinical, epidemiological, and metabolic studies whose purpose is. Since then, it has been to know the eating habits of the Spanish population, monitor the evolution of cardiovascular risk factors, their relationship with mortality, and the historical and potential behavior of all of them (Qin, Huang et al. 2023).

Prevalence of obesity in DRECE I

The World Health Organization (WHO), through the body mass index (BMI), which is obtained by dividing the weight in kilograms by the square of the height in meters (kg/m^2), defines overweight when the BMI is greater than or equal to 25 kg/m^2, and obesity when the BMI is greater than or equal to 30 kg/m^2. Based on the BMI, the classification of the different degrees of obesity can be seen in Table 1 (Kwiatkowska, Olszak et al. 2023).

I DRECE III DRECE IV

study year
2001 2013 2018
sample size
3.243 769 4.200
Middle Ages
38,74 40,99 39,13 %
M**en**
51,26 52,62 53,21 %
W**omen**
48,74 47,38 46,78 Energy and macronutrients
Energy (kcal without alcohol)
2.798 2.744 2.542
C**arbohydrates**
41,0% 40,2% 42,21%
Proteins
16,5% 18,2% 17,55%
total fats
42,5% 41,6% 40,14%
Saturated fats
13,4% 11,9% 12%
monounsaturated fats
19,6% 18,1% 17,7%
polyunsaturated fats
6,7% 7,2% 6,7%

With these premises, the prevalence of overweight and obesity was estimated in 3,161 individuals (1,563 women and 1,500 men) aged #>≥ 20 years. Being overweight affected 37.6% of the population studied and was higher in men (45.9%) than in women (29.7%). In comparison, obesity rates stood globally at 17.4%, taller in women, particularly in the 50-59 age group, coinciding with menopause. By region, it is striking that obesity rates (BMI # > ≥30 kg/m^2) in Andalusia-Extremadura (25.5%) and the Canary Islands (22.2%) are almost double those of Castilla y León (12.04%) and North (10.3%) (Zuercher, Harvey et al. 2023).

Considering the degrees of obesity, the respective global prevalences were as follows:

- Grade I obesity (BMI 30-34.9 kg/m^2): 14,4%.
- Grade II obesity (BMI 35-39.9 kg/m^2): 2,8%.
- Obesity grade III (BMI #> ≥ 40 kg/m^2): 0,9%.

Discussion

The current diet in the European countries of the Mediterranean has undergone an evolution that brings it closer to that of other Western countries, in which CVDs are more frequent. The DRECE study has shown a similar trend in Spain. The results showed an excessive contribution of fats to the total caloric intake at all ages, especially in the child population. The diet's saturated fat and cholesterol consumption is the primary determinant of total cholesterol values. In the study, a positive correlation was observed between the percentage of saturated fat, cholesterol, and ICGS and the figures of TC in the different Spanish regions when measuring LDL-C. The same trend was found, although statistical significance was only reached with cholesterol consumption (Farazi, Jayedi et al. 2023).

On the other hand, we generally observed elevated HDL-C concentrations, which could be interpreted as a counterweight to the atherogenic effects of LDL-C.

Population rate according to countries (%)

The rates of overweight, obesity, and severe obesity are consistent with those presented by the Spanish Obesity Society (SEEDO). In the DORICA study, the prevalence of obesity in the Spanish population aged 25 to 64 is 15.5% (17.5% in women and 13.2% in men) and 0.7% in the case of morbid obesity. This prevalence is based on a group of data that brings together epidemiological studies carried out between 1990 and 2000 in 9 autonomous communities (Andalusia, the Balearic Islands, the Canary Islands, Catalonia, Galicia, Madrid, Murcia, the Basque Country, and the Valencian Community) with homogeneous information gathering protocols. These rates place Spain among the countries with the highest prevalence of obesity in Western Europe, together with the United Kingdom (Collins, Kraus et al. 2023).

With the prevalence of type 2 diabetes, our data are comparable to the Spanish average from other studies, which stands at 6.2% for the age groups 30-65 years. The most striking data, referring to the Canary Islands Community, had already been described previously, reflecting the heterogeneity of the population and that in this community, the incidence and prevalence of diabetes are among the highest in Europe. Thus, in the Guía study (Gran Canaria), the majority of type 2 diabetes was 15.9% and that of prediabetes 25.9%, figures very similar to those obtained in the DRECE study.

In our study, MS rates were 19%, a percentage similar to that of the study in the province of Segovia, which was 17%, far from the 24% registered in the study of the Canary Islands based on the Canary Islands Nutritional Survey (ENCA). Variations between populations are related to the age of the participants and the degree of obesity, as we have also seen in the logistic regression analysis. The Canary Islands was undoubtedly the Spanish region with the highest rates of obesity, MS, and type 2 diabetes, as reflected in all the data from the DRECE I study. Table 10 shows a logistic regression analysis for different parameters evaluated, where MS syndrome is the dependent variable. The MS rate in a population such as the United States, from the NHANES-III study, was 22.7% and showed an increase related to BMI similar to that recorded in our study, namely 4.6, 22.4, and 59.6% for the strata of average weight, overweight and obesity, respectively. Our data and other studies in our country allow us to affirm that the MS rates are similar to those of a country with a high prevalence of obesity, such as the United States (Jeong, Wee et al. 2023).

Obesity, inflammation, and insulin resistance (de Frel, Assendelft et al.)

Over the past ten years, adipose tissue (AT) has been firmly recognized as an active endocrine organ with a central regulatory role. In body homeostasis, through an enormous interplay of humoral signals and active interference between adipocytes and most of their organs. In this sense, TA is a crucial source of many "signals," such as cytokines, chemokines (called "adipokines" or "adipocytokines"), growth factors, and complement proteins, which are synthesized and expressed on the surface of the

cell. Fat cell. In addition, many other "signals" from immunocompetent cells (e.g., macrophages) are released locally and into the general circulation within the TA (de Frel, Assendelft et al. 2023).
A functional classification of adipokines encompasses hormones (e.g., leptin, adiponectin, angiotensin), proinflammatory cytokines (e.g., tumor necrosis factor [TNF], interleukins [IL-10, IL-6], binding protein 4 [RBP4]), monocyte chemotactic protein 1 (MCP-1), growth factors (e.g., vascular endothelial growth factor [VEGF]), molecules with different functions (e.g., aquaporin 7, caveolins, visfatin) and proteins of the cell matrix and the complement system, among many others. Whichever method is used to classify adipokines, their number steadily increases, indicating that secretome Specific "real" characterizes ED. According to this, the idea of the TA as an endocrine organ is of fundamental importance in studying the links between Ob and T2DM. The primary hypothesis is that altered secretions of adipokines by the expanded adipocyte in Ob have an important influence on insulin sensitivity. And it is just as crucial that low-grade inflammation ('parainflammation') is a typical feature of 'obese ED,' creating conditions that lead to increased circulating fatty acid concentrations and thus causing lipid overload. In non-TA tissues (e.g., obesity, lipoatrophy, lipodystrophy, catabolic states), a lipotoxic effect and an IR state (Perna and Hewlings 2023).
The connection between Ob and inflammation is a relatively recent groundbreaking conceptual advance, showing that the inflammatory marker TNF-α is (unequivocally and consistently) expressed in the BP of Ob/Ob mice. Experimental and clinical data confirm these observations, supporting that a key pathophysiological hallmark of PD in Ob in animals and humans is "a low-intensity chronic inflammatory state. Among the many comments that have led to this conclusion, the following deserve special mention (Zhang, Li et al. 2023):

Massive macrophage infiltration of the AT in animal models of Ob and obese humans has been consistently demonstrated. Such macrophage infiltration in animal models of obesity (Ob/Ob mice) does not exist in similar lean animals. Furthermore, in obese animals, generalized microcirculatory changes (such as increased vascular permeability and massive adhesion of leukocytes and platelets to the endothelium) and significant tissue hypoxia (more accentuated in the abdominal fat compartment) are typical characteristics of their "inflamed" BP. Inflammation originating in "obese BP" can be somewhat "exported" to other tissues and organs, thus becoming a systemic process. There is often an increased number of circulating mononuclear cells, lymphocytes, and specific inflammatory biomarkers (e.g., TNF-a and IL-6) in obese humans (more in visceral fat) (Qin, Huang et al. 2023).
Typically, hyperplasia and hypertrophy of adipocytes cause the "expansion" of the TA mass in the Ob, but also angiogenesis is an essential part of the adipogenesis of the "obese." This expansion of the TA ultimately creates a "space conflict" that makes it difficult for the TA microcirculation to supply adequate oxygen to meet the demands of "obese adipocytes" and other cellular components of the TA (immunocompetent cells), thus creating an environment " "local hypoxic" that favors the expression of hypoxia-inducible factors (HIF, hy*poxia-inducible factors*). The HIF-1 gene activates the elevated production of VEGF, a highly stimulating factor of angiogenesis and preadipocyte proliferation. All these events strongly favor angiogenesis and stimulate the recruitment of immunocompetent cells (macrophages, microcytes) in the TA. All these complex changes could also be due to an increase in the local flow (TA) of FFA, which would close a pathophysiological circle that would further enhance the proinflammatory state in "obese TA." (Kwiatkowska, Olszak et al. 2023).

Consequences of inflammation associated with obesity

A wealth of scientific evidence from animal and human models has shown that one of the most consistent "responses" to Ob-associated inflammation is the development of IR in "*target organs*» essential to insulin, liver, skeletal muscle, vascular endothelium, and also within the fat tissue itself. Therefore, adipocytes, immunocompetent cells (monocytes, macrophages), and vascular endothelium in the RA create a local virtual environment that favors the development of IR. According to Schenk

et al., the pathophysiological sequence of events from the original "local" inflammation of the AT to a systemic state could be as follows: Excess nutrients stimulate "spreading," and an increase in the number of fat cells to accommodate the energy overload in the form of triglycerides leads to relatively reduced local microcirculatory flow and local hypoxia. Under hypoxic conditions, the expression of several inflammatory genes (e.g., TNF-a, IL-6) promotes further worsening of the inflammatory process (Potrykus, Czaja-Stolc et al. 2023).

These hypoxic effects secondary to nutrient overload trigger stress in the ER and the RPSP, whose accentuated repercussions on the onset and progress of low-grade inflammation have already been referred to. At the same time, the "hypoperfusion" of TA, through activation of the HIF-1 gene, affects the proinflammatory JNK/IKK pathways. Again, as indicated, these hypoxia-induced changes are much more intense in the abdominal than in the subcutaneous fat compartment (Duangjai, Phanthurat et al. 2023).

Origin and progress of low-grade inflammation in obesity

Low-grade (chronic) inflammation associated with Ob is a common feature of many metabolic complications (usually T2DM). In obese subjects and obese rodents, accumulation of bone marrow-derived macrophages is highly correlated with body weight, BMI, and total body fat. Macrophage accumulation and inflammation in ED are dynamic processes controlled by multiple mechanisms. Investigating the role of macrophages in the biology of ED and the mechanisms involved in their recruitment and activation in Ob will provide valuable insights for obtaining new therapeutic approaches for IR-related diseases (Dybvik, Svendsen et al. 2023).

In this context, several recent investigations have explored the crosstalk between proinflammatory and anti-inflammatory molecules within the specialized population of proinflammatory tissue macrophages. Some have focused on specific G protein-coupled receptors (GPCRs). *G* *protein-coupled receptors*) which are important signaling molecules involved in different aspects of cell functions. For example, the anti-inflammatory effect of GPR120 has been demonstrated under the stimulation of omega-3 fatty acids (AGOh-3), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), which promote insulin sensitization and improve IR in Ob. Other studies have focused on the mechanisms underlying Ob-mediated vascular disorders. They have revealed that adipocytes and TA secrete abundant inflammatory proteins that mediate atherogenesis and, most significantly, a decrease in the potent cardioprotective adipokine ('anti-RI') *adiponectin*. These findings may help explain the close correlation between the vascular pathological consequences of MetS and increased visceral Ob. Furthermore, most of the recent results of anti-Ob and anti-inflammatory therapeutic interventions corroborate this causal relationship (McIntosh and Gutterman 2023).

The origin and progress of inflammation in ED are complex and not fully understood. Some data indicate that the inflammation that occurs during the "expandability" process of fat cells is initiated by the influence of a group of extracellular signals, including cytokines, an excessive flow of nutrients (lipids, glucose), or the intracellular "mediators" driven by the ER stress response and excessive ROS production due to mitochondrial dysfunction. Other, less well-characterized effects related to alterations in the intestinal microflora or even to specific microorganisms that "infect" the BP (e.g., viruses, parasites) are being studied (Perler, Friedman et al. 2023).

Other experiments *in vitro* indicate the "toxic proinflammatory" effects of high glucose concentrations on monocytes and endothelial cells, while studies*live*have shown activation of the nuclear factor pathwayKB (NF-KB) and increased production of ROS as well as concordant elevated concentrations of "inflammatory" biomarkers (IL-6, TNF-a) in subjects with T2DM after an oral glucose test. On the other hand, very well-reproducible and intense postprandial inflammatory responses have been found in healthy, obese, and T2DM subjects after the consumption of meals rich in saturated fats, which

were characterized by elevated circulating concentrations of IL-1, IL-6, IL- 18, biomarkers of oxidative stress, ceramides and activation of the NF-pathwayKB. Relevant recent data are from animal models in which parenteral administration of a lipopolysaccharide toxin (*Escherichia coli*) reproducibly causes an inflammatory state promoted by a fatty diet with high circulating concentrations of proinflammatory cytokines, IR, and NF-activation. KB. This situation is due precisely to the interaction of saturated fats with specific receptors of the type *toll* (TLR, usually TLR-4) on immune cells, clearly indicating a vital role for these receptors in the mechanism diet-induced Ob can promote vascular inflammation and IR (Bork, Lundbye-Christensen et al. 2023).
Thus, signal crosstalk between fat cells and immunocompetent cells (macrophages) is crucial in initiating and progressing inflammation in Ob. Some of the macrophages are "normal" residents of the AT, but others (as noted above) are recruited, mainly in the bone marrow, probably to serve as "scavengers" of dead macrophages and other "toxic lipid debris" to try to attenuate or resolve the inflammatory process (Lu, Chen et al. 2023).

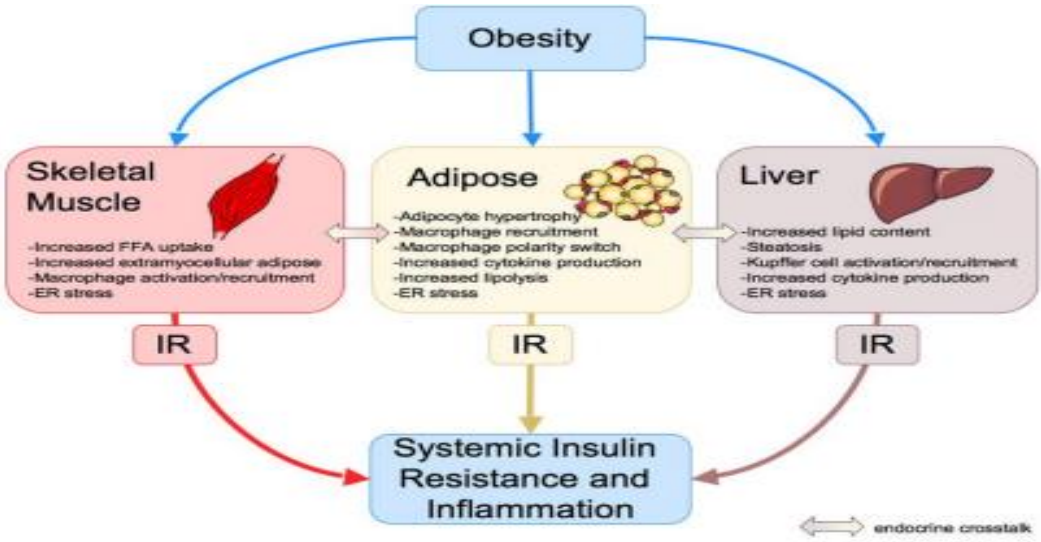

Figure 1. Obesity and development of inflammation and insulin resistance. Obesity-induced changes in skeletal muscle, adipose tissue, and liver cause inflammation and IR through autocrine and paracrine signals. Endocrine-mediated interaction between insulin and target tissues contributes to IR in distant tissues. The net results of these changes are IR and systemic inflammation (Charkviani, Thongprayoon et al. 2023)

A critical step in the progression of inflammation within the TA is represented by activating pathways that promote inflammation, such as JNK/IKK (see Figure 1). Many experimental observations support that activation of the JNK/IKK pathway triggers a cascade of 'amplifiers.'» and proinflammatory «mediators» that selectively alter insulin signaling pathways beyond the receptor, either through a direct inhibitory effect of some cytokines (e.g., TNF-a, IL-6) on serine residues in the IRS-1 molecule (or IRS-2 in the liver) or through the action of specific transcription factors that inhibit the activity of insulin. Among these, some transcription factors are from the family of suppressor signaling cytokines (SOCS).*suppressive cytokine signaling*) whose members SOC-1 and SOC-3 have a direct inhibitory effect on the action of insulin by interfering with the phosphorylation of tyrosine residues in the IRS-1 and IRS-2 molecules, which promotes their degradation within the cellular proteasome. SOC-3 also regulates the action of leptin at the level of its hypothalamic receptor, as has been demonstrated in SOC-3 haplodeficient mice, which become resistant to diet-induced Ob and IR when they receive this molecule. In addition, FABPs can also induce IR in obese mice by sequestering ligands against peroxisome proliferator-activated receptors (PPARs).*peroxisome proliferator-activated receptors*) and the retinoic acid receptor (RAR).*retinoic acid receptor*), two atypical anti-inflammatory

transcription factors that promote the uptake and metabolism of nutrients (glucose, fatty acid) by increasing the insulin sensitivity of specific tissues (Bajracharya, Katzke et al. 2023).

It must be emphasized that weight loss is correlated with decreased inflammation and that improvements in the cardioprotective effects of many of the more popular drug regimens are correlated with improvements in systemic inflammation. However, recent clinical trials have unexpectedly found that intervening in such complex and central processes without thorough knowledge may carry unexpected and undesirable risks. These findings also raise whether adipocyte-specific anti-inflammatory treatments offer an effective and safe way to prevent CVD (Virtanen, Voutilainen et al. 2019).

The most recent attempt to reconcile previous theories is the *adipocyte expandability hypothesis*, which interprets the links between Ob and its metabolic consequences (IR, FFA surplus, low-grade inflammation) based on the most exciting observations from animal models. This hypothesis tries to explain the events that occur within the obese adipocyte as an attempt to accommodate the caloric excess offered by the TA. As a proven fact, the appearance of metabolic complications (T2DM) is preceded by a period of normal metabolism during which TA expansion occurs, showing a favorable expression profile of lipid deposition and adipocytokine release. Then a cascade of effects arises local and systemic that leads to the appearance of IR and its metabolic consequences in the liver, skeletal muscle, and other organs that turn Ob into a systemic disorder with all possible adverse effects. In the context of Ob, the damage determined by genetic and epigenetic mechanisms gives rise to a deficit in the capacity of cells to cope with present metabolic disorders and inflammatory stress. This hypothesis reconciles the recently discovered biology of TA, and its role as an endocrine organ, with the low-grade inflammatory process that underlies Ob and T2DM (Potrykus, Czaja-Stolc et al. 2023).

Bottom Line: Overnutrition leads not only to BP inflammation but to β-cell stress through proinflammatory signals from "obese fat cells" that attract and activate macrophages and other immune cells, weakening the cells' defense β against toxic immune mediators; in addition to the effects of high concentrations of glucose and fatty acids. In the context of Ob, β cell damage determined by genic and epigenetic mechanisms also negatively influences its ability to cope with metabolic disorders and inflammatory stress present. Pending questions: why and how does the proinflammatory state begin in obese patients and T2DM? Why does inflammation cause IR and DMT2? Does the inflammation reflect a genetically determined failure of some intrinsic (immune) anti-inflammatory regulatory mechanisms? Will it be helpful to identify new anti-inflammatory therapeutic drugs to prevent Ob and T2DM? We do not currently have conclusive answers to these questions. An exciting challenge is further investigating the relative impact of genetic and environmental factors (e.g., genes, overnutrition, lifestyle, physical activity, and sedentary behavior) in the pathogenesis of this particular proinflammatory state that characterizes Ob-DMT2 and IR (Duangjai, Phanthurat et al. 2023).

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