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Chronic Low-Grade Systemic Inflammatory State and Insulin Resistance: Implications for Metabolic Health

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Abstract:- Insulin resistance, recognized since 1936 as part of non-communicable diseases, has been an evolving topic. This work updates the scientific community on this epiphenomenon as a component of a low-grade systemic inflammatory state. Through searches in PubMed, Redalyc and Google Scholar, 368 articles were identified, 49 references were selected, of which 77.5% were published between 2020 and 2024. The historical periodization includes the initial differentiation of insulin-sensitive and insulin-insensitive diabetic patients in 1936, which laid the foundations for its study. Between 1979 and 1987, the development of the euglycemic-hyperinsulinemic clamp marked an advance in its quantification; from 1988 to 1999, its role in metabolic syndrome was consolidated, and since 2000, research has highlighted the influence of the intestinal microbiota on insulin resistance and its link to inflammation.

Keywords:- *Insulin Resistance, Low-Grade Systemic Inflammatory State, Metabolic Syndrome.*

I. INTRODUCTION

Complex diseases, also known as chronic non-communicable diseases, are those that have a multigenic genetic component and an environmental component. These types of diseases are determined by a complex system of interactions between specific genetic changes in more than one gene. In recent years, the association between environment, epigenetic changes and some of the most common complex diseases such as cancer, cardiovascular diseases, type 2 diabetes and chronic adiposity-based disease has been studied.(1)

The so-called Non-Communicable Diseases (or chronic non-communicable diseases) constitute a typical case of the need to integrate knowledge about a group of health problems "that are not transmitted" (infect) people from an infectious agent, which have an increasing prevalence in communities, especially in those with a significant population aging, where most of the main causes of death, illnesses and disabilities that afflict human beings accumulate. (2)

Non-communicable diseases are estimated to cause three-quarters of deaths worldwide today, reflecting a chronic inability to control this epidemic in most countries, despite the fact that it is well known how to reduce the risk of these diseases and their consequences, through actions to counteract factors that have been incorporated into populations as symbols of the so-called "modern life", such as excessive tobacco and alcohol consumption, decreased physical activity, inadequate diet, increasing obesity, among the most important, as well as "proven" medical interventions, especially for the management of hypertension, diabetes and cancer. (2)

When the endothelium is subjected to the aggression of different risk factors, it is considered a dysfunctional endothelium, giving a greater tendency to vasoconstriction, greater adhesion of platelets and leukocytes, uncontrolled growth of cells, especially smooth muscle cells in the vessel wall, increased passage of lipids to the sub-endothelium and a greater tendency to vascular thrombosis. From here the following questions arise, when trying to overcome the reductionist barriers of specializations and classifications: will the chronic inflammatory state of the endothelium be the final common pathway of the pathogenesis, evolution and subsequent clinical expression of many of the so-called Non-Communicable Diseases, true "systemic diseases" (or better, "systemic syndromes"?). (2)

According to the author, the systemic inflammatory state characterized by elevated levels of inflammatory markers, related to conditions such as those mentioned above, may play a crucial role in the pathogenesis of NCDs, by contributing to insulin resistance, dyslipidemia and endothelial dysfunction, which are common risk factors associated with these diseases. Furthermore, the low-grade systemic inflammatory state not only exacerbates the progression of NCDs, but may also influence their prevention and treatment. Chronic inflammation may alter the body's response to therapeutic interventions by impairing blood glucose regulation and lipid control.

In this sense, insulin resistance is considered a condition characterized by a lower insulin activity at the cellular level, which is expressed in different metabolic pathways, specifically at the level of carbohydrate, lipid and protein metabolism, where the most affected organs are the liver, muscle and adipose tissue, although it may involve other systems. Insulin resistance underlies the cardiometabolic dysfunction associated with obesity, including hypertension, metabolic syndrome, type 2 diabetes mellitus, non-alcoholic fatty liver disease, polycystic ovary syndrome, obstructive sleep apnea, as well as malignant neoplasms such as endometrial carcinoma.(3)

Finally, metabolic syndrome is described as a set of risk factors that include abdominal obesity, insulin resistance, high blood pressure, and atherogenic dyslipidemia. This condition has shown an increase in its incidence, mainly due to changes in lifestyle and the increase in the prevalence of obesity in the population worldwide. A series of genetic and environmental elements are combined in its etiopathogenesis; within the proposed mechanisms, insulin resistance, chronic inflammation, and neuronal activation play an important role in the progression of metabolic syndrome.(4)

Knowledge of the systemic inflammatory state and insulin resistance allows the researcher from the research context to identify the *main theoretical and empirical deficiencies* related to:

- Limitations in the detailed understanding of the exact molecular pathways that connect chronic inflammation to insulin resistance
- Individual variability, i.e. there is insufficient attention to genetic, environmental and lifestyle factors and their relationship with inflammation and insulin resistance
- Limitations in the translation of findings from preclinical animal models to humans, making it difficult to generalize the results
- Need for further studies evaluating the effectiveness of interventions aimed at reducing inflammation and its impact on insulin sensitivity
- There is little research in the Bolivian context on how non-communicable diseases are associated with inflammation and insulin resistance

These inconsistencies may increase morbidity and mortality due to non-communicable diseases and their complications; however, the researcher identifies the following as *potential ways to resolve this problem :*

- Cooperation projects with experts in biochemistry and molecular biology, natural and traditional medicine, endocrinology, nutrition and genetics to develop more comprehensive approaches
- Biochemistry and molecular biology research laboratory to identify biomarkers of inflammation and insulin resistance
- Proposal for long-term research evaluating the effects of interventions in diverse populations
- Possibilities of developing specific natural therapies based on the individual characteristics of patients in collaboration with other national and/or international institutions
- Local government support to strengthen education on the management of inflammation and insulin resistance in the general population and among health professionals

Despite the weaknesses identified in the knowledge about the systemic inflammatory state and insulin resistance, there are important potentials to address this problem. The integration of interdisciplinary approaches and the use of advanced technology, such as molecular biology tools, allow for a deeper and more precise analysis. In addition, longitudinal studies and the personalization of therapies provide paths to develop effective interventions. These strengths provide the researcher with a robust framework to reduce morbidity and mortality related to non-communicable diseases and define the following scientific problem:

What is the relationship between low-grade systemic inflammatory status and insulin resistance in an adult population of the National University of the East, Santa Cruz campus, during the period from 2025 to 2027?

This study on "Chronic Low-Grade Systemic Inflammatory State and Insulin Resistance: Implications for Metabolic Health" has a relevant *scope* by examining how persistent and low-grade inflammation is associated with insulin resistance, a key factor in the development of endothelial dysfunction in cardiometabolic diseases. Investigating this relationship is fundamental to identify the underlying mechanisms and potential triggers of these diseases, by providing a framework for early interventions in the prevention and management of cardiometabolic complications.

The *importance* of this study lies in the fact that it addresses a public health problem with broad implications for morbidity and mortality. Chronic inflammation, when interacting with insulin resistance, can deteriorate general health, affect longevity and increase health care costs. The results of the research can guide professionals and legislators in the creation of preventive policies, health promotion programs and therapeutic approaches based on regulating the inflammatory state and improving insulin sensitivity, thus improving metabolic health in the population.

Research Hypothesis: *There is a positive relationship between the low-grade systemic inflammatory state and insulin resistance in the adult population of the National University of the East, Santa Cruz campus, during the period from 2025 to 2027.* This hypothesis suggests that as the level of low-grade systemic inflammation increases, an increase in the levels of insulin resistance is expected to be observed in the population studied.

II. METHODOLOGY

The search strategy was carried out by consulting recognized national and international sources in health sciences, such as PubMed, Redalyc and Google Scholar. Key descriptors such as "insulin resistance," "low-grade systemic inflammatory state" and "metabolic syndrome" were used. Of the 368 articles identified, 319 were excluded by limiting themselves to the title and abstract, selecting 49 references. Of these, 38 (77.5%) were published between 2020 and 2024, while 11 articles prior to that period were included due to their historical relevance. The analysis was based on the historical-logical method, complemented by theoretical approaches such as inductive-deductive and analysis-synthesis, ensuring an exhaustive and rigorous review of the findings. This approach made it possible to integrate contemporary and historical perspectives on insulin resistance and its relationship with inflammatory and metabolic processes.

III. RESULTS AND DISCUSSION

The connection between chronic low-grade systemic inflammatory states and insulin resistance represents a central axis in the understanding of metabolic disorders. In this section, key findings of the study are discussed, integrating historical and contemporary data that underline the relevance of factors such as gut microbiota, inflammatory biomarkers, and therapeutic interventions. The discussion contextualizes this evidence within the current metabolic health landscape, assessing its impact on the prevention and treatment of associated conditions such as obesity, metabolic syndrome, and type 2 diabetes. A periodization by stages follows.

- *Stage I. From 1936 - 1978. Differentiation into Insulin-Sensitive and Insulin-Insensitive Types in Diabetic Patients*

The article *"Trends in insulin resistance: insights into mechanisms and therapeutic strategy"* describes a chronology of key discoveries in the understanding of insulin and insulin resistance and highlights that in 1936 *Mr.* Harold Himsworth introduced the concept of Insulin Resistance, the subject of this literature review. This concept was instrumental in distinguishing between type 1 diabetes, characterized by a lack of insulin, and type 2 diabetes, in which insulin is present but the cells do not respond adequately.(5)

The importance of visceral adipose tissue, located mainly around the organs (perigonadal, perirenal and mesenteric), which differentiates it from subcutaneous adipose tissue. In 1947, the French diabetologist Jean Vague described the relationship between gender and types of obesity, and defined two types of obesity based on the location of the adipose tissue: android (abdominal obesity) and gynecoid (gluteofemoral obesity). Android obesity is characterized by the accumulation of visceral fat, in addition to subcutaneous fat in the abdominal region. It has been shown that this type of obesity confers a three-fold higher risk of cardiovascular disease, compared to gynecoid obesity. In addition, it especially favors the development of insulin resistance, type 2 diabetes mellitus. In turn, it is often accompanied by high blood pressure and dyslipidemia. (6)

The identification of the insulin receptor and the study of its signaling pathways in the 1970s marked a significant advance in the understanding of insulin action and its role in metabolism. The work of Dr. C.R. Kahn and other researchers was instrumental in characterizing the insulin receptor and beginning to delineate the intracellular pathways that are activated when insulin binds to its receptor on the cell surface.(7)

Excess free fatty acids in obesity conditions increase endoplasmic reticulum stress, which leads to the inhibition or attenuation of the insulin signaling pathway by activating two kinases which cause the phosphorylation of IRS (insulin receptor substrate) in serine residues and not tyrosine as occurs under normal conditions, nullifying the signaling cascade that should be activated by the insulin-receptor binding. (8)

The development of insulin resistance has multifactorial mechanisms, among which the most notable are a diet high in carbohydrates, mainly refined, in addition to a sedentary lifestyle, among others. It has been determined that fructose present in various foods with a high caloric intake such as soft drinks, increases the amount of hepatic triglycerides and alters the function of the leptin hormone responsible for controlling hunger and appetite, and also increases the production of uric acid by activation of the xanthine oxidase pathway, which leads to insulin resistance by inhibition of the production of endothelial nitric oxide and decreased blood flow in the tissues. (8)

According to the author of the research, insulin resistance, first defined in 1936, constitutes a central axis in the understanding of metabolic diseases. Visceral adipose tissue plays a critical role by releasing excess free fatty acids, which contributes to oxidative stress and metabolic damage. In addition, it is pointed out how the regular consumption of refined carbohydrates aggravates this condition by generating glucose spikes that favor fat storage and alter metabolic function. These factors, combined, reinforce the importance of preventive strategies that include healthy eating habits and effective control of body weight.

- *Stage II. From 1979 - 1987. Development of the Euglycemic-Hyperinsulinemic Clamp*

The euglycemic-hyperinsulinemic clamp, developed by Ralph DeFronzo and collaborators, is considered the "gold standard" for measuring insulin sensitivity. It allows the measurement of the amount of glucose needed to maintain constant blood glucose levels while insulin is being infused. Although it is an expensive and laborious procedure, it has

been key in the research of insulin resistance and its relationship with metabolic diseases.(9)

The HOMA (Homeostasis Model Assessment) method was first described in 1985 by researchers David R. Matthews and colleagues, as a practical tool to assess insulin resistance and pancreatic beta cell function, using only fasting glucose and insulin levels. This method facilitated the study of insulin resistance in large populations and has been widely adopted in clinical and epidemiological research for its simplicity and effectiveness.(10)

The HOMA-IR method is based on mathematical equations that estimate how the body regulates glucose homeostasis through the interaction between insulin and glucose production in the liver. This model has become a key tool in research into diabetes and other metabolic diseases, as it provides a noninvasive and practical estimate of insulin sensitivity and beta cell function in clinical and epidemiological studies.(10)

The article by Matthews and his collaborators is widely cited and has been fundamental to the advancement of endocrinology and the study of metabolic diseases, by allowing the evaluation of insulin resistance in large populations without the need for complex methods such as the hyperglycemic, euglycemic clamp test, which is more accurate but also more expensive and difficult to perform.(10)

The diagnosis of insulin resistance is made by direct methods, such as the hyperinsulinemic-euglycemic *clamp* , or by indirect methods, such as HOMA-IR, fasting insulin measurement, and the oral glucose tolerance test. The gold standard for diagnosis is the *clamp* , but its determination is complex, expensive, and not available at the primary care level. (11)

Insulin resistance consists of a decreased response in peripheral tissues to the action of insulin, causing compensatory hyperinsulinism. As a result, both elevated concentrations of insulin or fasting glucose indicate the presence of this entity. The HOMA-IR index allows the evaluation of insulin resistance; to calculate it, it is necessary to obtain the levels of glycemia and insulinemia. (12)

The World Health Organization (WHO) has defined insulin resistance with this method as the highest quartile of HOMA-IR in non-diabetics, also defined as the lowest decile of insulin sensitivity in a normal subgroup of non-diabetic population, although it is recognized that these methods are not suitable for daily clinical practice, in some countries with large populations cut-off points have already been created, such as China, where the HOMA-IR value of 1.4 defines alteration in glycemic metabolism. In Chile, the National Consensus on Hyperinsulinism published by the Chilean Endocrinology Society defines type 2 diabetes mellitus as a HOMA-IR value>2.6. (3)

In addition to the measurement of insulin resistance by means of paraclinical tests, the International Diabetes Federation has proposed that screening of people at risk be the first step in the prevention of type 2 diabetes mellitus. To this end, it is suggested that screening instruments be used and that blood tests be performed on those identified as being at high risk. Among the questionnaires that serve this purpose is the Finnish Risk Assessment Instrument for Type 2 Diabetes Mellitus (FINDRISC), first described in 2001, which is validated and has been used as a screening instrument for risk assessment for the development of diabetes and prediabetes.(11)

The FINDRISC risk assessment instrument evaluates eight indicators, with a possible score between 0-21 points, and includes: age, body mass index (BMI), waist circumference (WC), physical activity > 30 minutes per day, frequency of consumption of fruits or vegetables, medications for the treatment of hypertension, history of impaired fasting glucose and family history of type 2 diabetes mellitus in first- or second-degree relatives. The level of risk for diabetes is evaluated in five categories: low risk (score < 7 points), slightly elevated (7-11 points), moderate (12-14 points), high risk (15-20 points) and very high risk (> 20 points).(11)

Recently, Guerrero-Romero et al. proposed and validated a new index for early recognition of insulin resistance in young adults, the triglyceride-glucose (TyG) index. The cut-off point for diagnosis of insulin resistance of the TyG index was 4.55 for women and 4.68 for men. The TyG index is defined as the natural logarithm of the product of triglyceride concentration by fasting glucose concentration over two: {TyG = [Ln (Fasting triglycerides, mg/dL x Fasting glucose, mg/dL) / 2]}. This index has advantages since it results from routine laboratory analysis and does not require insulin quantification. (13)

The TyG index is an adequate predictor of insulin resistance when compared with the HOMA-IR and the euglycemic-hyperinsulinemic clamp method in individuals with different degrees of adiposity and glucose levels, and has shown a positive and significant correlation with the percentage of glycosylated hemoglobin in patients with type 2 diabetes mellitus. In addition, the TyG has the advantage that both triglyceride and glucose concentrations are cheaper than insulin and are routinely measured, so they can be widely used in clinical practice. (13) Other studies that have determined insulin resistance through the triglyceride/glucose index have considered a value of 4.68 as the cut-off point to diagnose insulin resistance. This indicator was previously validated in the Mexican population.(11)

The assessment of insulin resistance is a very important tool in the definition and management of patients in risk groups. A significant correlation has been demonstrated between insulin resistance and triglyceridemia. This fact

agrees with the pathogenetic explanation that has been given to the Insulin Resistance Syndrome, which supposes that the biological characteristics of the perivisceral adipocyte, in addition to contributing as has been said to insulin resistance, also have a metabolic activity that leads to a greater lipolytic behavior, with an increase in the supply of fatty acids to the liver and consequently, a greater synthesis and secretion of very low density lipoproteins, together with a lower catabolism. (14)

As a research regularity, the author of this work considers that tools such as the euglycemic-hyperinsulinemic clamp, recognized as the standard method for accurately measuring insulin sensitivity, have been fundamental in understanding metabolic mechanisms. In parallel, the HOMA (Homeostasis Model Assessment) method offers a more accessible alternative for assessing insulin resistance in clinical settings. Likewise, the FINDRISC instrument stands out as a key tool for identifying people at risk of developing diabetes and prediabetes, facilitating early interventions. Finally, the triglyceride and glucose index emerges as an important marker for assessing cardiometabolic risk associated with insulin resistance and metabolic dysfunction. These instruments, together, reinforce the diagnostic and preventive capacity in the management of metabolic diseases.

- *Stage III. From 1988 - 1999. Insulin Resistance In Metabolic Syndrome*

In his 1988 Banting Lecture, published in *Diabetes* under the title *"Role of* Insulin Resistance in Human Disease," Dr. Gerald Reaven introduced the term "Syndrome X," now known as metabolic syndrome. In this work, Reaven described how insulin resistance is not only linked to type 2 diabetes, but is also associated with other conditions such as hypertension, dyslipidemia (abnormal blood lipid levels), abdominal obesity, and an increased risk of cardiovascular disease. (15)

Reaven argued that insulin resistance is the underlying mechanism that links these factors, forming a set of interrelated conditions that significantly increase the risk of developing cardiovascular disease. By identifying this group of disorders as a "syndrome," Reaven pioneered the understanding that these were not isolated conditions, but rather a set of interconnected metabolic abnormalities with important clinical consequences.(15)

Metabolic Syndrome was first known in the early 80's and was called until then as syndrome X, later it was also called insulin resistance syndrome, cardiovascular dysmetabolic syndrome, quartet of death and finally metabolic or cardiometabolic syndrome, currently known and studied by the WHO since 1999 (5). According to the WHO, the criteria included are the following: triglycerides greater than or equal to 150 mg / dL, HDL less than 40 mg / dL in men and 50 mg / dL in women, blood pressure greater than 130 / 85 mmHg, insulin resistance (IR), high body mass index (BMI) and microalbuminuria, two of these risk factors make the diagnosis (16)

Another consideration regarding the definition of metabolic syndrome is the manifestation of three of the following signs: central obesity, hypertension, dyslipidemia, hyperinsulinemia, impaired fasting glucose and insulin resistance. (17) However, from the point of view of clinical practice, in the opinion of the author of the research, the WHO reference will be used.

During the 1990s, researchers discovered that chronic low-grade inflammation, characterized by elevated levels of proinflammatory cytokines such as TNF-alpha and IL-6, contributes to insulin resistance. This discovery changed the perception of insulin resistance, showing that it is not only a metabolic problem but also an inflammatory one.(18)

, *adiponectin and its role in insulin sensitivity* were identified . Adiponectin is a hormone produced by adipose tissue that improves insulin sensitivity and has anti-inflammatory effects. The identification of this hormone in 1995 helped to clarify the role of adipose tissue in insulin resistance and its link to obesity and metabolic syndrome.(19)

Furthermore, obesity and metabolic diseases contribute to liver damage, which can elevate liver enzyme levels and in turn exacerbate insulin resistance, leading to the development of type 2 diabetes mellitus over time. Studies have independently linked elevated levels of glutamic oxaloacetic transaminase with type 2 diabetes mellitus, suggesting a predictive role for this enzyme in metabolic syndrome, independent of body weight. Furthermore, gamma glutamyl transpeptidase has been associated with oxidative stress and chronic inflammation, both key factors in the pathogenesis of type 2 diabetes mellitus. (20)

Inflammation, a physiological protective response of the organism, occurs to control physical, chemical or biological aggressions, and is characterized by an elevated number of leukocytes and/or an increase in the levels of proinflammatory cytokines in the circulation or in the tissues. There is experimental and clinical evidence indicating that obesity induces alterations in adipose, hepatic and muscular tissue that lead to a chronic low-grade inflammatory response, which contributes to insulin resistance and systemic metabolic dysfunction.(21)

In the state of obesity there is an increase in the accumulation of lipids, particularly in adipose tissue, which causes an increase in the size of adipose cells, expansion of adipose tissue and alteration in the secretion of adipokines and proinflammatory cytokines, as well as the aberrant release of free fatty acids. These and proinflammatory cytokines act on metabolic tissues, such as liver and muscle tissue, modifying the inflammatory response, as well as lipid metabolism, thus contributing to metabolic syndrome. In addition, it has been

shown that obesity increases macrophage infiltration in adipose tissue and that this contributes substantially to the production and secretion of cytokines in response to obesity. (21)

The increased size of the adipocyte (hypertrophy/hyperplasia), together with a concomitant inflammatory state, conditions its functioning: altering its secretory profile with a greater production of leptin and less adiponectin, which inhibits its expression by inflammatory factors such as tumor necrosis factor alpha (TNFα), causing a lower sensitivity to insulin, leading to a worse mitochondrial function and greater endoplasmic reticulum stress, producing greater basal lipolysis, altering the cellular cytoskeleton, and causing less de novo lipogenesis. The increase in the flow of free fatty acids, together with inflammatory factors, converts a situation of insulin resistance and local inflammation into a state of systemic insulin resistance and chronic low-grade inflammation. (22)

Dysfunctional adipose tissue and the change in its secretome establish a state of low-grade inflammation that promotes an increase in the infiltration and polarization of M1 macrophages and other cells of the immune system. At the same time, these exacerbate the systemic inflammatory state by producing an increase in the release of cytokines such as TNF-α, interleukin (IL)-6, IL-12, IL-1β, among others. In addition, the visceral adipose tissue of obese patients is characterized by fibrosis, altered angiogenesis and endothelial dysfunction, thus worsening the state of hypoxia, inflammation and necrosis of the tissue. In this sense, obesity has been established as the starting point of various cardiovascular diseases such as atherosclerosis.(23)

A recent definition proposes to identify “metabolically healthy” obese individuals according to the diagnosis of obesity and the following criteria: serum triglycerides ≤150 mg/dl, HDL (low-density lipoprotein) cholesterol concentrations >40 mg/dl in men or >50 mg/dl in women, systolic blood pressure ≤130 mmHg, diastolic blood pressure ≤85 mmHg, no antihypertensive treatment, fasting blood glucose ≤100 mg/dl and no treatment with hypoglycemic agents. (6)

Chronic low-grade inflammation, also called metabolic inflammation or meta-inflammation, is associated primarily with obesity and is chronic and systemic. It occurs in the absence of apparent infection or frank autoimmune disease and is distinguished from chronic inflammation by the absence of functional disturbance, by not inducing injury, and by its gradual progression, most likely involving intricate signaling between multiple organs. (24)

In the development of chronic low-grade systemic inflammation, an increase in inflammatory molecules (IL-1b, IL-6, IL-17, TNFa, C-reactive protein) and immune cells (macrophages and T lymphocytes) has been detected in the infiltrated tissue, although at the same time it does not exhibit structural alterations or impotence in its primary functions. Given the capacity of the intestinal microbiota to secrete inflammatory mediators, it plays a central role in both metabolic inflammation and inflammation of aging, in addition to contributing to the regulation of the circadian rhythm and participating in the intercommunication between organs. (24)

It is noted that in the inflammatory response there is a change in the concentration of serum proteins and the need for cells, leading to an overproduction of leukocytes, which is called leukocytosis. In the laboratory, the number and type of blood cells and some molecules associated with the inflammatory process such as high-sensitivity C-reactive protein, albumin, IL-6, fibrinogen, procalcitonin, D-dimer and the erythrocyte sedimentation rate test can be measured to evaluate the inflammatory process. (24)

Chronic low-grade inflammation is characterized by elevated circulating levels of inflammatory cytokines and infiltration of macrophages into peripheral tissues. This process does not induce injury or loss of functionality of the infiltrated tissue. Mainly, low-grade systemic inflammation is associated with the development of cardiometabolic diseases in patients with obesity, so this immune evolution is considered as metainflammation. (25, 26)

The evidence presented suggests that low-grade systemic disease plays an essential role in the development of metabolic diseases, such as dyslipidemia, atherogenesis, type 2 diabetes mellitus and systemic arterial hypertension. This meta-inflammation causes the activation of intracellular signals that lead to the release of local and systemic substances. The inflammatory factors that feed back and interconnect are related to proinflammatory cytokines and macrophage ROS (reactive oxygen species), which reach adipose, muscle and liver tissue. Once established, low-grade systemic inflammation promotes and perpetuates metabolic changes establishing a vicious circle that leads to pathological processes, such as insulin resistance, atherosclerosis and endothelial dysfunction. Breaking the circle, therefore, depends on simultaneously controlling the metabolic and inflammatory components. (27)

The number of adipose tissue macrophages increases in obesity and participates in inflammatory pathways that are activated in the adipose tissues of obese individuals. Exposure to antigens derived from food and the intestinal microbiota causes macrophages to establish themselves in adipose tissue as main actors of the inflammatory process; however, an inflammatory response in the intestine seems to precede adipose tissue inflammation in diet-induced obesity. (28)

The Systemic Immune Inflammation Index is a novel indicator of inflammation that combines neutrophil, lymphocyte, and platelet counts in peripheral blood to reflect the inflammatory and immunological status of the body. Numerous studies have identified this index as an important prognostic biomarker for various types of cancer. In addition, it has strong diagnostic and prognostic values for diseases associated with inflammation induced by immune dysfunction.(29)

Higher scores indicate a constantly activated immune system and thus a higher risk of chronic inflammation, which can impair glucose metabolism and metabolic balance. Inflammatory mediators are often detected in the adipose tissue of obese individuals, and chronic low-level inflammation is the main feature of obesity. Some studies have detected higher plasma concentrations of inflammatory mediators, including C-reactive protein, interleukin-6, and tumor necrosis factor-α, in obese individuals. (30)

Insulin resistance is frequently associated with elevated levels of total cholesterol and LDL-C (low-density lipoprotein). This occurs because insulin, under normal conditions, inhibits cholesterol production in the liver. However, in a state of insulin resistance, this inhibition is reduced, leading to an increase in hepatic cholesterol synthesis and, therefore, to elevated levels of LDL-C in the blood. In addition, insulin resistance contributes to lipoprotein dysfunction, promoting the formation of smaller, denser LDL particles, which are more atherogenic, i.e., more likely to contribute to plaque formation in the arteries. (31)

Insulin resistance is also strongly related to elevated triglyceride levels. In situations of insulin resistance, the ability of this hormone to inhibit lipolysis is reduced, resulting in an increase in free fatty acids in the blood. These fatty acids are transported to the liver, where they are converted into triglycerides, which are then released into the circulation via very low-density lipoproteins (VLDL). This results in hypertriglyceridemia, a common marker of insulin resistance and an important risk factor for cardiovascular disease (31).

C-reactive protein (CRP), especially high-sensitivity CRP (hs-CRP), has been recognized as a good marker of cardiovascular diseases as its elevated levels are associated with adverse outcomes of acute coronary syndrome. In addition, it plays an important role in the initiation and development of atherosclerotic plaques. In addition, hs-CRP is considered an independent risk factor and predictor of cardiovascular events, in addition to being widely used to establish the effectiveness of anti-inflammatory treatments. (26)

In particular, it has been used as a useful biomarker in clinical practice for various diseases such as: insulin resistance, obesity, sleep apnea, cancer and cardiovascular disease. For laboratory measurement of hsCRP, the cut-off point proposed by the American College of Cardiology for cardiovascular risk stratification was used, in which it is classified as: low risk (< 1 mg/L), moderate risk (≥ 1 mg/L) and high risk (≥ 3 mg/L). A value ≥ 10 mg/L is considered as an acute phase inflammatory response.(32)

The focus on the prevalence of Metabolic Syndrome and the magnitude of risk factors for type 2 Diabetes Mellitus, Cardiovascular Disease and other problems such as fatty liver, cholesterol gallstones, polycystic ovary syndrome, obstructive sleep apnea and gout is vast. However, there is little information about atherogenic, inflammatory and adiposity markers in patients with metabolic disease in Mexico. (33)

The introduction of drugs such as metformin and thiazolidinediones (e.g., rosiglitazone and pioglitazone) provided new tools for the treatment of type 2 diabetes, focusing on improving insulin sensitivity. These drugs will help establish the treatment of insulin resistance as a key goal in diabetes management.(34)

Metformin increases levels of 5 Activated Protein Kinase (AMPK), decreases gluconeogenesis by inhibiting glycerophosphate dehydrogenase in the mitochondria and increases muscle uptake, decreased levels and turnover of free fatty acids, reduced visceral obesity and plasma triglyceride levels with improvement of proinflammatory and prothrombotic state. (3)

According to the researcher, the so-called "Syndrome X", also known as metabolic or cardiometabolic syndrome, has been the subject of study since its formal recognition by the WHO in 1999 due to its relevance to global health. This syndrome is closely associated with chronic low-grade inflammation, also called metabolic inflammation or meta-inflammation, which, being chronic and systemic, is mainly linked to obesity. As part of the advance in diagnostic indicators, the Systemic Immune Inflammation Index emerges as an innovative tool that combines neutrophil, lymphocyte and platelet counts to assess the inflammatory status. In addition, C-Reactive Protein (CRP) remains a reliable and widely recognized marker of cardiovascular diseases, underlining its relevance in the identification and management of cardiometabolic risks.

- *Stage IV. From 2000 to the Present. Effect of the Intestinal Microbiota on Insulin Resistance*

Intestinal dysbiosis is mainly characterized by a decrease in the diversity and abundance of bacteria and fungi, especially those associated with dysfunction and various pathologies that are related to metabolic, immunological, cardiovascular and neuronal disorders through the influence of bile acid metabolism, inflammatory state, insulin resistance and incretin secretion. (35)

The foods consumed alter the diversity of the gut microbiome, both in the short and long term, suggesting that bacterial composition is directly related to the type of diet, which could determine certain types of diseases such as type II diabetes and obesity, secondary to a low-grade inflammation process, called metabolic endotoxemia.(16) The gut microbiome is an important factor in chronic systemic inflammation secondary to endotoxemia caused by the release of endotoxins after bacterial death. The gut microbiome likely affects host metabolism through several pathways involving energy extraction, gut barrier integrity, production of metabolites affecting satiety, insulin resistance, bile acid metabolism, and subsequent changes in metabolic signaling.(35)

It has been determined that dysbiosis can change the functioning of the intestinal barrier and the lymphoid tissues associated with the intestine by allowing the passage of structural components of bacteria, such as lipopolysaccharides, which activate inflammatory pathways that can contribute to the development of obesity and metabolic diseases, altering the production of gastrointestinal peptides related to satiety, resulting in increased food intake. (36)

In recent years, the gut-brain axis has been studied because it is an important mediator of the complex neuroendocrine regulation of appetite and energy homeostasis. Intestinal hormones appear to communicate from the gastrointestinal tract to appetite-regulating centers within the central nervous system through metabolites. The microbiota could be involved in the modulation of chemical transmitters and intestinal dysbiosis could trigger an altered production of neurotransmitters, leading to increased appetite, overeating and weight gain as a consequence of obesity. (36)

Various factors, including obesity, unbalanced diet, the use of antibiotics and other drugs, cause progressive damage to the morphology and function of the intestine, and the microbiota becomes less diverse and more dynamic. These variations in the intestinal microbiota can deteriorate to a state of “dysbiosis,” which is defined as a reduction in microbial diversity and a combination of the loss of beneficial bacteria and an increase in symbiotic bacteria that become pathogenic under certain conditions. This intestinal dysbiosis is a key factor that mediates the appearance of endothelial dysfunction, loss of the intestinal barrier, metabolic disorders, increased cytokines, oxidative stress, malabsorption of nutrients, and increased toxins. All of these factors have been linked to the progression of chronic diseases such as chronic kidney disease, diabetes, high blood pressure, autoimmune diseases, among others. (37)

The microbiota increases inflammation-induced vascularization and mucosal blood flow, which increases nutrient absorption. The gut microbiota is able to promote a state of low-grade systemic inflammation, insulin resistance, and increase cardiovascular risk through mechanisms that include exposure to bacterial products, in particular, lipopolysaccharides derived from gram-negative bacteria. This is called metabolic endotoxemia. (1)

Several studies have shown that sleep deprivation and poor sleep quality are associated with increased insulin resistance. Research indicated that sleep deprivation negatively affects glucose regulation and insulin secretion, leading to increased interest in the relationship between sleep, metabolism, and metabolic health. (34) Elevated levels of free fatty acids have been shown to interfere with insulin signaling and affect glucose uptake, as well as promote inflammation, which has expanded the understanding of the metabolic mechanisms underlying insulin resistance. (38)

Short-chain fatty acids influence carbohydrate metabolism by stimulating the secretion of peptides in the intestine, such as glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2). These hormones, also called incretins, are produced by enteroendocrine cells in the digestive tract. As incretins, they exert a strong influence on gastric emptying, promote satiety, protect β-cells from apoptosis, and maintain glucose homeostasis. Under stimulation by incretins, insulin is secreted only in cases of hyperglycemia, which helps prevent persistent hyperinsulinemic states.(39)

Another factor that also modifies the composition of the microbiota is fasting because it induces high concentrations of postprandial insulin, which is associated with increased fat oxidation, which determines metabolic inflexibility, low-grade inflammation states and alteration of glucose homeostasis. Likewise, late food intake has been linked to a higher risk of obesity and coronary heart disease.(16) The increase in circulating concentrations of free fatty acids, particularly saturated ones, in pathological conditions such as obesity, indicates insulin resistance through different biochemical mechanisms.(40)

The acute nature of the obesity epidemic requires obesogenic environmental factors, including: nutritional factors related to qualitative alterations in lipid composition and macronutrient processing; sedentary habits characteristic of advanced and aged societies; other more speculative aspects could be the epigenetic programming of intake and expenditure mechanisms in the intrauterine environment and in early life, and more recently it has been suggested that the intestinal flora could interact with nutrients and the biology of the individual by modifying the risk of obesity and diabetes. It has been suggested that obese patients have a specific bacterial endowment that releases lipid-type bioactive compounds that interact with energy balance control mechanisms. (41)

The alteration of the symbiotic relationship between intestinal bacteria and the host promotes the development of metabolic diseases, through low-grade inflammation. Increase in short-chain fatty acids (SCFA) through increased fermentation of non-digestible carbohydrates. SCFA bind to intestinal endocrine cell receptors (GRP43 and GRP41) that increase peptide YY, which slows intestinal transit, increasing nutrient absorption and leptin levels. (42)

The intestinal microbiota is also related to the development of cardiovascular diseases, and a mechanism of relationship between the two is found again in a state of dysbiosis. The greater the number of gram-negative bacteria, the greater the amount of lipopolysaccharides and these endotoxins are considered proatherogenic compounds. Lipopolysaccharides promote the oxidation of low-density lipoproteins, the generation of proinflammatory cytokines, the increase in oxidative stress, the decrease in nitric oxide and the elevation of endothelin-1, situations that together lead to vasoconstriction and increased blood pressure. (39)

The intestinal microbiota contributes to the generation of uremic toxins. In states of impaired renal function, they accumulate and induce an inflammatory response and increased mortality. Several factors contribute to dysbiosis in patients with kidney disease, including: slow intestinal transit, reduced protein absorption, lower dietary fiber intake, iron treatment, and frequent use of antibiotics. The pathways that link uremic toxins to the development of cardiovascular disease are complex, including low-grade systemic inflammation, oxidative stress, endothelial dysfunction, modulation of signaling pathways, and altered mitochondrial energy metabolism. (42)

In 2019, an estimated 463 million people were suffering from diabetes worldwide; these numbers are expected to continue to rise to 578 million patients by 2030. Type 2 diabetes mellitus is often preceded by insulin resistance, a condition in which insulin actions in peripheral tissues, including skeletal muscle, liver, and adipose tissue, are impaired. The authors of this article propose based on current evidence, modulation of inflammation through the gut microbiota could be a target for new therapies in reducing the current diabetes pandemic. (43)

A classic topic within Naturopathic Medicine is digestive leucocytosis, postprandial leucocytosis or postprandial hyperleucocythemia, which consists of the increase in white blood cells when food is ingested that has been subjected to a certain temperature or has been industrially processed. Current knowledge allows us to affirm that the intestinal barrier is subject to multiple aggressors that cause it to lose selectivity in absorption. The passage of macromolecules and microorganisms in a permeable intestinal mucosa would be involved in the appearance of inflammatory, allergic, autoimmune diseases and cancer. (44)

For the comprehensive treatment of overweight and obesity, treatment should be given according to the WHO cut-off points, which is multidisciplinary and individualized for each patient. The treatment includes non-pharmacological, pharmacological, surgical, laparoscopic, psychological and nutritional treatment mainly. An assessment by another service may be used, however, this should only be done if the patient warrants such an assessment. (45)

Therapeutic strategies should be individualized and aimed primarily at reducing the risk of cardiovascular disease and type 2 diabetes mellitus. A reduction in body weight of 7-10% is recommended. and lifestyle changes (individualized dietary advice, physical activity and giving up toxic habits). It is suggested that losing just 5% of the initial weight has the beneficial effect of increasing insulin sensitivity and reducing serum triglycerides, low-density lipoproteins and blood pressure levels.(16)

Exercise , together with the consumption of dietary fiber, are key elements in maintaining a healthy microbiota. In relation to *exercise*, the following mechanisms have been pointed out: increased production of butyrate, hormones, neurotransmitters and decreased release of intestinal bile acids. Regarding fiber consumption, it is suggested that it reduces postprandial glycemia, total cholesterol, low-density lipoproteins and triglycerides, therefore preventing the accumulation of visceral fat and obesity. It has also been described that it generates substrates such as short-chain fatty acids (acetate, propionate and butyrate) that fulfill important local and systemic functions, which contribute to the modulation of the intestinal microbiota. It has been proven that the administration of soluble fibers such as oligofructose and long-chain inulin correct the alteration of the microbiota or dysbiosis, also controlling intestinal permeability and endotoxemia, processes related in part to the pathophysiology of obesity and diabetes mellitus; likewise, the consumption of diets with low fiber content is associated with an increase in body weight and loss of the diversity of the intestinal microbiota.(16)

The *reducing diet and the use of synbiotics* determine changes in the microbiota and in the concentration of zonulin. Positive changes in the number of selected intestinal bacterial genera that make up the intestinal microbiota and improve the tightness of the intestinal barrier, which is related to the decrease in the concentration of zonulin in fecal samples of patients from the synbiotic group (46)

Metabolic Syndrome is more common in adulthood and results in lost years of healthy life, decreased life expectancy, and increased premature mortality and disability. Although the cause-effect relationship of biochemical factors is known, social determinants of health also participate in its genesis. The use of alternative therapies will allow the patient the opportunity to improve their quality of life and in many cases

reverse pathological conditions. Natural medicine is part of these alternatives, among which the following stand out: cinnamon (cinnamomum verum), improves insulin sensitivity, decreases lipids and reduces systolic blood pressure. Turmeric (curcuma longa), decreases blood sugar, improves insulin sensitivity, reduces body weight and is antihyperlipidemic. Garlic (allium sativum) improves all the components of the Metabolic Syndrome and green tea (camellia sinensis) reduces body weight, reduces blood sugar and insulin and is antihypertensive.(47)

Short chain fatty acids produced from prebiotic fibers, particularly propionate, can bind to receptors on the surface of epithelial cells, thereby promoting secretion of incretins and PYY with their respective impact on modulating hunger and satiety. Other foods considered prebiotics are artichokes, bananas, beans, lentils, potatoes, onions, leeks, soybeans, wheat, raw oats and barley. (39)

There are foods that contain probiotics, such as dairy products, which have been shown to have beneficial effects as regulators of blood pressure. In particular, there is talk of fermented dairy products, more specifically those that contain strains of Lactobacillus helveticus, and their inhibitory effects on the angiotensin converting enzyme (ACE), which, added to their hypocholesterolemic effects, contribute to the hypotensive effect of this strain. (39)

Akkermansia can be consumed as a probiotic or prebiotics can be used to selectively induce its growth. Among the foods that would support an increase in this strain are nopal, chia seeds, soy protein or supplementation with pomegranate extract, resveratrol, polydextrose, EpiCor or sodium butyrate. (39)

Coconut oil has shown potential benefits in the treatment of Candida infections, particularly in the digestive tract. Its antifungal properties, attributed to medium-chain fatty acids such as lauric acid, inhibit the growth and spread of Candida Albicans in the digestive system. In addition, its anti-inflammatory capacity can contribute to reducing the inflammation caused by these infections. These characteristics position it as an ally in the management of Candida from a natural perspective. Additionally, coconut oil promotes intestinal balance by promoting the development of beneficial bacteria in the microbiota, which makes it difficult for Candida to expand. It could also strengthen the immune system, facilitating a better response against infections. Finally, its inclusion in the diet can relieve common symptoms of these infections, such as abdominal pain, flatulence and diarrhea. (48)

Psychological interventions have been shown to be effective in treating emotional or mental disorders. Therefore, psychological management may benefit treatment especially for patients with obesity and anxiety. The cognitive-behavioral treatment used in all the studies analyzed is usually focused primarily on promoting healthy eating habits, physical activity, such as acceptance and commitment therapy, although they usually include habit modification techniques, typical of behavioral intervention, to improve changes at the cognitive and psychosocial level. (47)

Acupuncture involves the insertion of needles into specific points on the body to stimulate “Qi” and has been proposed to influence obesity in several ways, including regulating appetite and satiety through modulation of the autonomic nervous system and the release of neurotransmitters such as insulin and ghrelin. In addition, acupuncture may affect hormonal activity, influencing the release of key hormones such as insulin, leptin, and cortisol, and improving insulin sensitivity. It has also been suggested to stimulate the lymphatic system and reduce fluid retention. (47)

On the other hand, auriculotherapy is based on the stimulation of specific points on the external ear and has been shown to be effective in reducing weight and BMI in overweight or obese people, being an inexpensive treatment with few side effects. It can be used alone or in combination with other approaches to the treatment of obesity, such as nutritional interventions and physical exercise, although proper interpretation of research findings is required. (47)

Other current strategies used to modulate the microbiota include the administration of probiotics and prebiotics. The former are live microorganisms that, when ingested in sufficient quantities, exert benefits on the host, with lactobacillus spp., bifidobacteria and saccharomyces being the most commonly used. Prebiotics are non-digestible substances that, when consumed in sufficient quantities, stimulate the reproduction and activity of certain types of microorganisms. Examples of this group are oligosaccharides, fructooligosaccharides and inulin. It has been shown that the administration of lactobacillus and bifidobacteria, among others, is associated with a higher concentration of gram-positive bacteria and a decrease in gram-negative bacteria in stools, with the consequent decrease in circulating liposaccharide levels, which decreases the development of endotoxemia, obesity and insulin resistance. (16)

Intestinal microbiota transplantation is another therapeutic strategy to correct intestinal dysbiosis. It is a procedure in which the feces of a healthy donor are placed in the gastrointestinal tract of another patient to change the composition and obtain a therapeutic benefit. Several studies have demonstrated its usefulness in multiple extragastrointestinal diseases, among which obesity and metabolic syndrome stand out, demonstrating a significant increase in insulin sensitivity once the treatment is finished. According to current evidence, there is no contraindication to perform the procedure, however it is essential to explain the

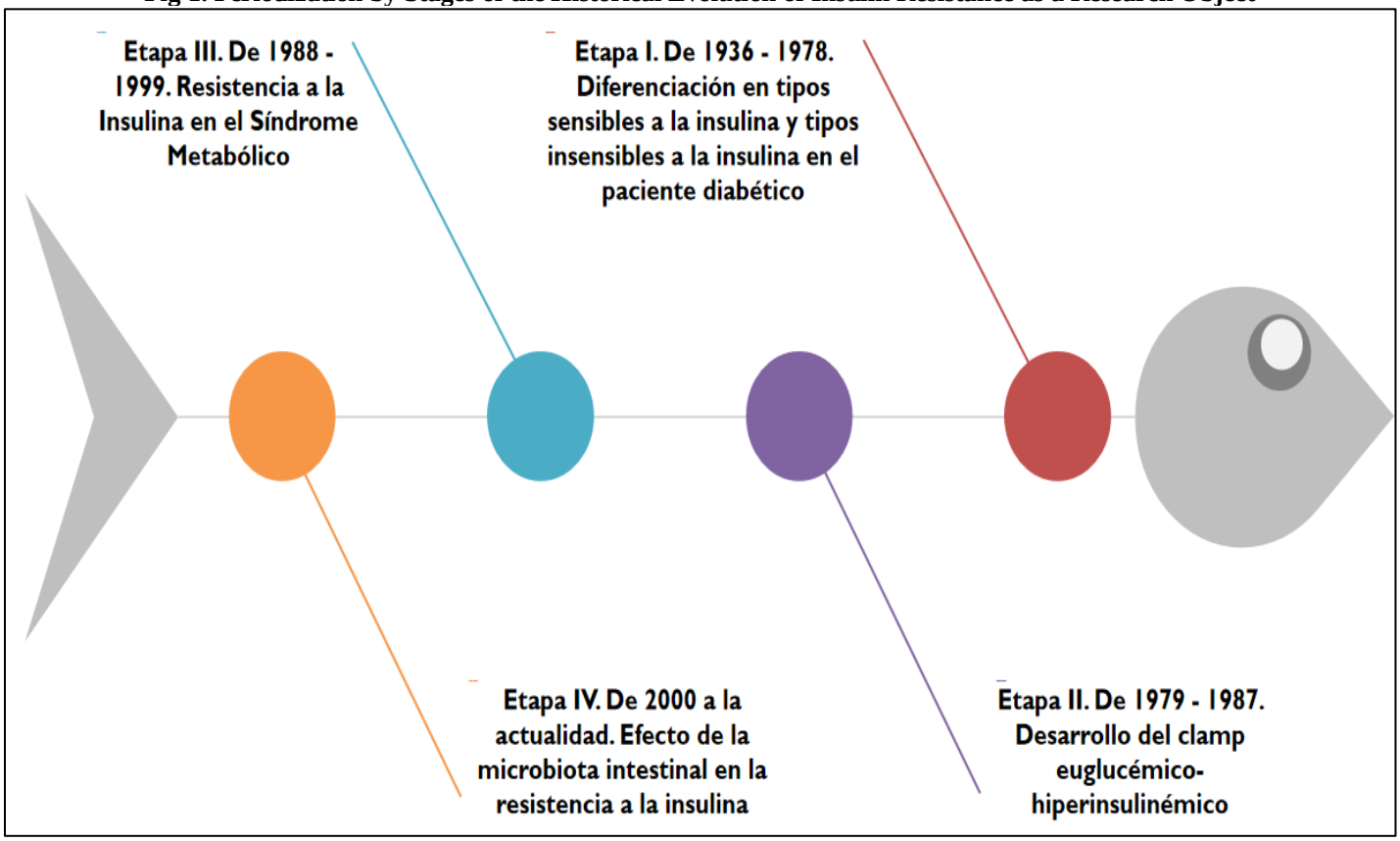
benefits, risks and the process, always obtaining informed consent from all patients before the procedure. (16)

Supplementing Fecal Matter Transplant with excellent foods such as special yogurts or exclusive meal plans could be of great help in the future when it comes to innovating personalized treatments for type 2 diabetes, as research is currently being done on how our genes can change the mix of little living things in our belly, this plan consists of making certain bacteria create useful substances or change the chemical processes of the body to help with the treatment. This technology is still new, but it could really help with treatments for T2DM. (49)

According to the author of the research, intestinal dysbiosis, defined as an imbalance in the composition and function of the intestinal microbiome, has profound implications for health. The foods consumed directly influence the diversity of the microbiota, affecting the gut-brain axis and, therefore, general well-being. The microbiota, by increasing inflammation-induced vascularization and mucosal blood flow, optimizes nutrient absorption, highlighting its role in metabolic processes. In addition, short-chain fatty acids, produced by the fermentation of dietary fiber, have a positive impact on intestinal and systemic health. In this context, physical exercise, together with a diet rich in fiber, emerges as a fundamental pillar to maintain a balanced and functional microbiota, highlighting the interrelationship between healthy habits and intestinal well-being.

Below is a summary of the four investigative stages represented in Figure 1.

Fig 1. Periodization by Stages of the Historical Evolution of Insulin Resistance as a Research Object



Source: own elaboration

The figure represents a timeline illustrating the evolution of our understanding of insulin resistance, divided into four key stages. The first stage (1936–1978) marks the initial recognition of the difference between insulin-sensitive and insulin-insensitive types of diabetic patients, a fundamental advance in understanding variations in glucose regulation. During the second stage (1979–1987), the development of the euglycemic–hyperinsulinemic clamp allowed accurate measurement of insulin sensitivity, a decisive step in metabolic research.

The third stage (1988-1999) consolidated insulin resistance as a central factor in metabolic syndrome, associating it with obesity, dyslipidemia and increased cardiovascular risk. Finally, in the fourth stage (2000 to the present), the focus was expanded to the effects of the intestinal microbiota on insulin resistance, highlighting how microbial

alterations contribute to inflammation and opening new therapeutic avenues. These stages reflect a continuous advance from clinical observation to molecular and ecological study.

IV. CONCLUSIONS

- Differentiation between insulin-sensitive and insulin-insensitive types has been essential to understanding the various forms of diabetes and the key role of insulin in glucose control. It has also facilitated the identification of molecular mechanisms involved in insulin resistance, improving the understanding of its pathophysiology.
- The euglycemic-hyperinsulinemic clamp is considered the gold standard for measuring insulin sensitivity due to its accuracy, although its complexity limits its use. In contrast, the HOMA index represents a more accessible alternative for assessing insulin resistance in clinical settings.
- Insulin resistance is a central component of metabolic syndrome, linked to obesity, dyslipidemia and hypertension, which increases the risk of cardiovascular diseases. Early identification allows for the design of preventive strategies focused on lifestyle changes.
- Alterations in the intestinal microbiota contribute to insulin resistance by enhancing inflammation and metabolic imbalance. The FINDRISC test facilitates the detection of people at risk of diabetes and prediabetes, thus allowing for early and personalized interventions.

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