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ADIPOSE TISSUE METABOLIC ALTERATIONS AND EFFECT OF MICROBIOTA

Author:
Juan Carlos Palacio

Director:
María Iturralde Navarro

Faculty of Science – Biotechnology Degree
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1. ABSTRACT

Obesity is among the top health concerns across the globe, and it has been for many years, yet the world remains unable to stop it. Overweight and obesity follow a clear uptrend pattern and that will not change unless a real battle is waged against their main causes.

The present review will explore the causes and mechanisms underlying this health crisis, focusing on what for many years has been disregarded: the active role that the adipose tissue plays in the development of the metabolic alterations regarding obesity and the undeniable implication of gut microbiota in supporting the existing mechanisms for weight gain and fat storage. The aim is to integrate most of the factors to provide a global vision of the processes happening obesity.

The review has been methodically elaborated, bringing together information from many different experts in the different fields, striving for accurate and state-of-the-art information throughout the whole review, with special emphasis in the final fragment on the other major health crisis concerning the world right now: COVID-19.

La obesidad es uno de los mayores problemas globales a nivel sanitario y lleva siéndolo varios años sin que el mundo haya podido frenarlo. La incidencia del sobrepeso y de la obesidad siguen un claro patrón ascendente que no cambiará a no ser que realmente se ataquen las principales causas.

Esta revisión bibliográfica explorará las causas subyacentes a esta crisis de salud, centrándose en lo que durante muchos años se ha descuidado: el papel activo que juega el tejido adiposo en el desarrollo de las alteraciones metabólicas de la obesidad y la innegable implicación de la microbiota intestinal en el apoyo los mecanismos existentes para el aumento de peso y el almacenamiento de grasa. El objetivo es integrar la mayoría de los factores para brindar una visión global de los procesos que ocurren en la obesidad.

La revisión ha sido elaborada metódicamente, reuniendo información de muchos expertos de los diferentes campos, buscando información precisa y de actualizada a lo largo de toda la revisión, con especial énfasis en el fragmento final sobre la otra gran crisis de salud mundial ahora mismo: COVID-19.

2. INTRODUCTION

2.1. Obesity: a deadly disease

Obesity and overweight are defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health. They are most commonly discerned and measured through the BMI or Body Mass Index, which is the result of the weight of a person divided by the square of his or her height in meters ($\frac{kg}{m^2}$). To be precise, the condition of overweight in adults ranges from a BMI equal or greater than 25 to a BMI of 30. Once the BMI is equal or greater than 30 it is classified as obesity[1].

Obesity is among the top health concerns across the globe[2] and it has been for many years, yet the world remains unable to stop it. Overweight and obesity follow a clear uptrend pattern and that will not change unless a real battle is waged against their main causes. The latest Centers and Disease Control and Prevention (CDC) report on health conditions by age shows some astonishing numbers. In the United States, from the years 1988- 1944 to the years 2017-2018, the percentage of obesity in adults has risen from 22.5% to 42.2%. The percentage in children has seen an increase of approximately 9%[3].

The problem is not exclusively of the United States. In Spain, the Agencia Española de Seguridad Alimentaria y Nutrición (AESAN) reports that 52.7% of the adult population is overweight and 17.3% is obese. In children the numbers do not improve as around 42% of them are overweight and around 18% are obese[4].

To gain some worldwide perspective on the issue, the WHO showcases a series of key facts to help understand the magnitude of obesity. According to the statistics dating 1st April 2020, worldwide obesity has tripled since 1975. This striking increase can be appreciated in comparative color-coded maps (**Fig. 1**). In 2016 more than 1.9 billion adults were overweight; of these, over 650 million were obese. This means that 39% of adults were overweight and 13% were obese. 38 million children under the age of 5 were overweight in 2019[1].

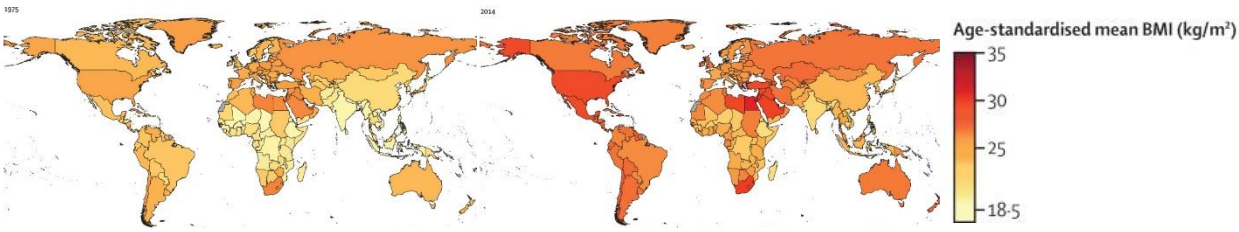

***Figure 1**. Adapted from: Age-standardized mean BMI in women by country in 1975 and 2014*[5]

This data is extremely worrying because obesity is a disease that takes a toll on both the healthcare system funds and the individual suffering from it. Besides the social disabilities resulting from the stigma associated with obesity[6], the most common health consequences of overweight and obesity are cardiovascular issues[1], especially heart disease and strokes, type 2 diabetes, for which obesity is the leading risk factor[7]. Also, musculoskeletal disorders and some cancers are acknowledged as direct consequences of obesity. More insight about the inner mechanisms will be presented later.

The rise of overweight and obesity has two main causes: certain food marketing practices and institutionally-driven reductions in physical activity. However, further investigation has revealed at least ten putative factors that may require more attention that they are receiving now. These factors are microbiota microorganisms, epigenetics, increasing maternal age, greater fecundity among people with higher adiposity, assortative mating, sleep debt, endocrine disruptors, pharmaceutical iatrogenesis, reduction in variability of ambient temperatures, and intrauterine and intergenerational effect[8].

The most remarkable and proven cause is the diet changes and the food marketing associated with certain types of products. These changes mainly involve the sweetening of the diet, especially beverages. Data shows that in the United States indicate that 74% of products in the food supply contain sweeteners. This impacts the rest of the world's supply and, although governments are taking steps in the right direction, it is suggested that they keep adapting and improving the measures, since the excessive intake of added sugars has adverse effects on the consumer's health[9].

There are several key genetic, molecular and physiological mechanisms involved in obesity, which will be discussed thereafter.

2.2 Obesity: mechanisms involved

There are several hypotheses about the genetic contribution to obesity, such as the fetal programming, which postulates that the predominant governing force is the fetal environment, meaning that if there is a maternal over or undernutrition it will provoke a corresponding postnatal response. This hypothesis would be supported by epigenetic mechanisms. Other theories involve evolutionary pressure, such as the predation release theory, which explains the contribution through the absence of predators, making obesity genes thrive in this favorable environment. Alongside these favorable environment theories are the sedentary lifestyle and the increased reproductive fitness and the assortative mating. The most plausible explanation is a complex one, combining all the others mentioned above[10]. The power of Genome-Wide Association Studies (GWAS) is revealing a large quantity of obesity related minor genes, meaning that they have a small effect size on BMI[11]. Despite of all the new technology and findings, explaining the apparent high heritability of obesity still poses a challenge.

Although the genetic contribution plays a big role, one must not forget that the origin of the obesity pandemic are indisputably the changes in diet and lifestyle.

There are other important mechanisms that revolve around the adipose tissue, how it grows in response to excessive caloric intake, how there are processes of inflammation and fibrosis taking place and how it synthesizes and secretes adipokines that act in different parts of the human body. All of these eventually cause metabolic alterations that will be further discussed.

Finally, the last type of mechanisms that have a proven impact on obesity are the ones triggered and regulated by the microbiota. The microbiota suffers changes through the process of obesity, having its composition modified and therefore the way it affects the human body is also modified.

3. OBJECTIVES

The aim of this work is to show which are the most important mechanisms involved in obesity as well as to highlight the role of the adipose tissue. For years this tissue has been thought to have little activity, however recently its implication in body mass regulation cannot be ignored. Some aspects of the implication of microbiota are also discussed and lastly the possible association between obesity and severity of COVID-19 cases.

4. METHODOLOGY

In a review, the bibliographic search must be thorough, objective and reproducible. These three characteristics are desirable in any work; although there must be a balance between the number and the relevance of the articles selected. There should be enough material to properly inform the researcher but not so much that the researcher cannot process it[12].
The selection criteria for this work have been:

- Publishing date, aiming for recent studies, with few exceptions regarding already fully characterized mechanisms.

- Keywords, such as “obesity”, “adipocytes”, “adipokines”, “microbiota”, “COVID-19” and several more that appear throughout the work. The search of these words and their combinations has been proven vital in order to find suitable results.

- Database in which the article is published, selecting only those coming from verified databases such as PubMed or Nature.

5. ADIPOSE TISSUE

The classic concept of the adipose tissue as an inert fat storage has been forgotten and replaced by a new updated vision. The adipose tissue is a very dynamic endocrine organ capable of having an impact on the metabolism of the whole body[13]. This is possible thanks to the hormones it produces and secretes, the adipokines. However, it does not always work as it should, causing what is known as an adipose tissue dysfunction. This condition has been proposed to be the underlying cause of metabolic alterations such as type 2 diabetes[14].

5.1. White, brown and beige adipocytes

Traditionally, adipocytes have been divided in two categories attending to morphology and function: white and brown. On one hand white adipocytes are big rounded cells with a unilocular lipid droplet, surrounded by a thin layer of cytoplasm, few mitochondria and a flattened nucleus (**Fig. 2a**). Their main functions are energy storage, heat insulation and secretion of adipokines. White adipose tissue is distributed mostly in the subcutaneous compartment but can also be found covering organs such as the liver, the kidneys and even muscle. On the other hand, brown adipocytes are smaller, polygonal shaped, with multiple lipid droplets, several mitochondria and a central nucleus (**Fig. 2b**). They are responsible for the adaptive thermogenesis through the UCP-1 protein. Brown adipose tissue can also store energy and secrete adipokines, although less efficiently than white adipose tissue. Contrary to white adipocytes, brown ones have very specific locations: cervical, supraclavicular, periaortic, paravertebral and suprarenal[15].

In 2010 a third type of adipose cells was described, the beige adipocytes (**Fig. 2c**). These are brown-like adipocytes inside white adipose tissue, their importance lies in two main reasons, understanding how environmental factors control cell fate specification and the possibility of them being a new therapeutic target in the treatment of obesity and other metabolic

disorders[16]. The acquisition of this phenotype is brought by factors such as cold exposure[17], stimulation of β-adrenergic receptors and peroxisome proliferator-activated receptor-γ (PPAR-γ). This phenotype acquisition process is known as fat browning[15]. Similar to brown adipocytes, they are defined by their multilocular lipid droplet morphology, high mitochondrial content and the expression of a core set of brown fat–specific genes[18].

Despite of how similar beige and brown may seem at first glance, since both have the common ability to undergo thermogenesis, there are several differences that set them apart as distinct cell types. For instance, they derive from different embryonic precursor, there are also a number of quantitative trait loci associated with the induced development of beige but not brown, which suggest a different regulation of these cell types.

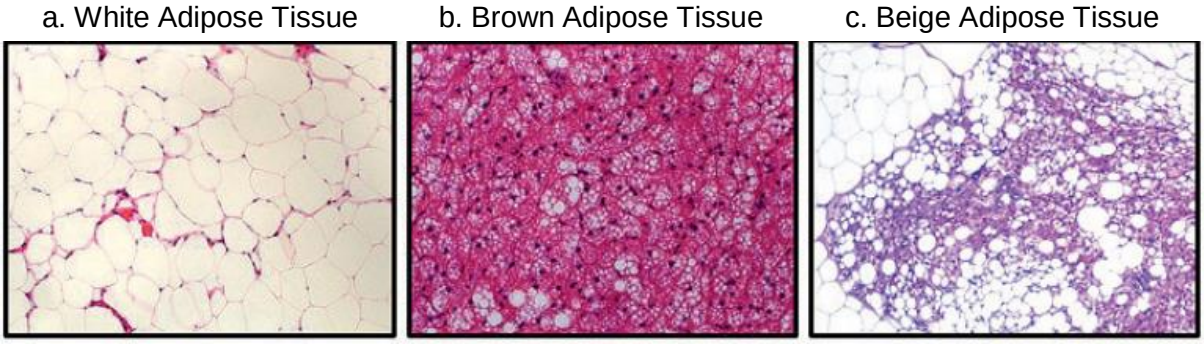

***Figure 2**. White, brown and beige adipose tissue. Representative histologic sections of mice tissue. Hematoxylin and eosin staining, 100X [15].*

Beige adipocytes express several differential genetic markers like CD137, TMEM26, TBX1 or SHOX2[15] as well. Moreover, a notorious difference exists between how both of these cell types regulate the expression of the uncoupling protein-1 (UCP1). Brown adipocytes express high levels of UCP1 in basal or unstimulated conditions whereas beige adipocytes do not. In order for the beige adipocytes to express UCP1, they need certain stimuli or activators such as agonists of the β-adrenergic receptors or PPAR-γ[18].

The UCP1 is a protein located in the internal membrane of the mitochondria which confers the protons permeability to pass through that membrane, thus causing the uncoupling of the respiratory chain from the oxidative phosphorylation process. This phenomenon shifts the energy that the respiratory chain uses to establish a proton gradient into producing heat instead of producing ATP. This heat production process called thermogenesis needs a large oxidation rate to be sustained, for this purpose there is a big intake of metabolic substrates, fundamentally fatty acids and glucose from the bloodstream[19].

In conclusion, brown and beige adipocytes can undergo thermogenesis, therefore consuming a lot of metabolites and helping prevent overweight and obesity. The remarkable difference is that beige can be induced and brown cannot. As previously stated, new experiments are on the way to determine whether they can be used as a therapeutic target or not. It is key to understand the roles of each type of adipocyte to further comprehend the mechanisms that will be described below.

5.2. Adipogenesis

Adipogenesis refers to the process of differentiation of pre-adipocytes into mature fat cells, in other words, the development of adipose tissue. It varies a little depending on age and sex, however the determinant factor for fat accumulation is the balance between fat synthesis or lipogenesis and fat breakdown or lipolysis. Fat synthesis occurs when the balance is altered in favor of high caloric intake, in this situation, the body must store the leftover energy.

The molecular basis for adipogenesis can be looked at as a process divided in two phases. The first phase is the commitment phase, where a fibroblast-like cell such as a mesenchymal precursor commits to the adipocyte lineage without any morphological changes, forming what is known as a preadipocyte. The main factors involved in this phase are the bone morphogenic proteins 2 and 4 (BMP2 and BMP4)[20]. They drive adipocyte commitment through their receptor, which simultaneously activates a new transcription factor family called Small Mothers Against Decapentaplegic (SMAD). When the heterodimers SMAD1, SMAD5 and SMAD8 are activated they activate SMAD4 (also known as DPC4)[21]. Finally, this part of the signaling pathway is completed when SMAD4 stimulates the expression of peroxisome proliferator-activated receptor-γ (PPARγ), which truly is the master regulator of the adipogenesis process.

The second phase is the differentiation phase; it starts from PPARγ. PPARγ is indispensable for the differentiation since it activates C/EBPα (CCAT-enhancer-binding protein-α) and together they fully activate the transcription of mature adipocyte specific genes such as the insulin receptor gene, the adiponectin gene and the Adipocyte Protein 2 (aP2) gene, also known as Fatty Acid Binding Protein 4 (FABP4)[22].

Some other studies make the point that this process has three steps, adding one in the middle of the two described above. This intermediate step would be the mitotic clonal expansion, involving DNA replication and duplication of cells[23].

Certain extracellular factors influence whether an adipocyte differentiates or not. There are signaling molecules that include including insulin[24], glucocorticoids[25] and bone morphogenetic proteins (BMPs) that directly activate PPARγ, thus facilitating the differentiation. On the other hand, there are also ligands that cause insulin resistance and prevent the precursor cells from undergoing differentiation such as interleukin 1β (IL-1β) and interleukin 6 (IL-6), transforming growth factor-β (TGF-β) or tumor necrosis factor (TNF).

There also exist physiological states and cues that are integrative of the whole body and influence the regulation of adipogenesis. Among these are inflammation, which will be detailed later; the circadian rhythm, which if disrupted, increases the risk of obesity[26] due to a deregulation of the cyclic expression of PPARγ; and lastly the reactive oxygen species (ROS), if they exceed the limit that the cells can process, they can cause what is known as oxidative damage[27] since they oxidize lipids and amino acids, ultimately leading to inefficient ATP production and metabolic dysfunction[28].

This increase or expansion of the adipose depots can be either in size (hypertrophy) or in number (hyperplasia). Hyperplasia is usually considered the healthiest of the two, for it allows the tissue to maintain proper vascularization and adipokine levels[14]. On the other hand, hypertrophy is linked to hypoxia in the tissue due to a massive size increase (**Fig. 3**). The

response to hypertrophy carried out by the adipose tissue involves hypoxia-inducible factor 1 or HIF-1, it is however insufficient to induce enough vascularization.

Instead, the hypoxic adipose tissue cells increase the expression of pro-fibrotic genes, leading to tissue fibrosis. In this process, the hypoxic adipose tissue can go as far as undergoing necrosis, which leads to posterior infiltration by immune cells and consequently tissue inflammation[28]. All of the previous factors pile up to end up decreasing adipose tissue function, causing high levels of sugars and lipids in the blood circulation and thus contributing to lipotoxicity and other metabolic alterations such as diabetes.

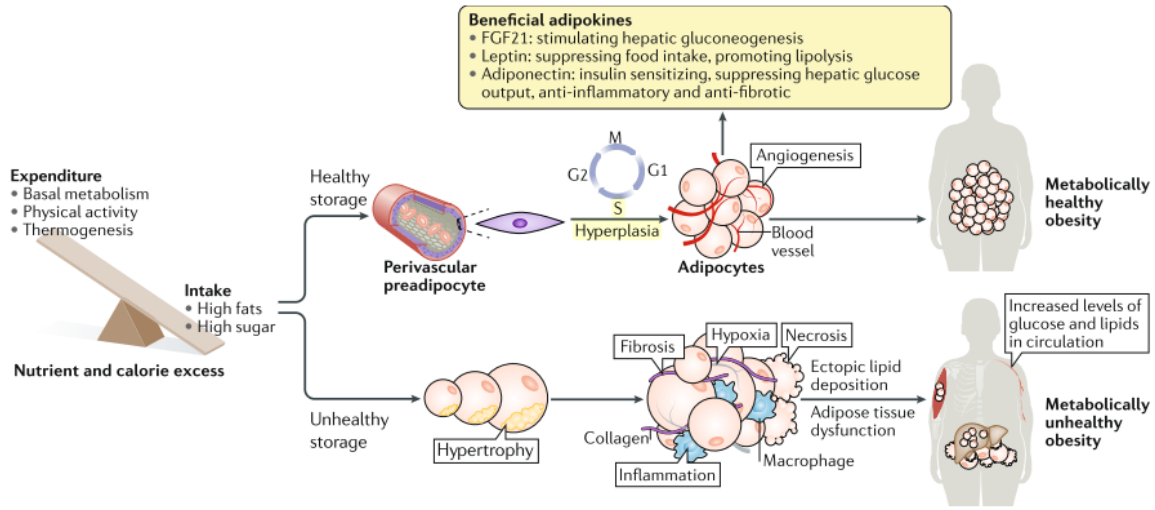

***Figure 3**. Mechanisms of adipose tissue expansion. When the balance between expenditure and intake tips in favor of the intake, leftover energy needs to be stored. On the one hand, hyperplasia is associated with healthy storage, proper vascularization and no circulating abnormalities. On the other hand, hypertrophy is linked to fibrosis, hypoxia, inflammation and even necrosis of the adipose tissue, as well as increased concentrations of lipids and glucose in circulation [28].*

5.3. Inflammation and fibrosis

As previously discussed, the adipose tissue can grow in an unhealthy fashion. This causes an adipose dysfunction characterized by inflammation and fibrosis processes.

Inflammation is defined as a protective tissue response to injury or destruction of tissues. Triggered by hypoxia, chronic inflammation is a characteristic feature of obesity and metabolic alterations. This kind of inflammation aims for the proliferation of blood vessels to fight against the hypoxic state, and it includes the presence of lymphocytes and macrophages. It is also associated with certain inflammatory adipokines. The main inflammatory markers are interleukin 6 (IL-6) and C-reactive protein (CRP); in opposition to these and as the main anti-inflammatory marker the human body produces adiponectin[29]. All of these play a huge role as links between inflammation and obesity.

Interleukin 6 is a pro-inflammatory cytokine produced not only by the white adipose tissue but also by other cell types such as immune cells. This is a special cytokine because its effects occur at sites different from its origin. The mechanism involves the interleukin 6 receptor (IL-6R), which is also expressed in the hypothalamus, controlling appetite and energy intake[30].

Macrophages are the main cell type infiltrating the adipose tissue and raise the levels of IL-6. Increased IL-6 levels cause a series of complications, especially related to cardiovascular diseases, different kinds of cancer and other diseases such as pulmonary hypertension, chronic renal diseases and even depression.

C-reactive protein (CRP) is a sensitive marker of systemic inflammation that is synthesized by the liver. Although it is not obesity specific, it is obesity related. Many analyses have found strong evidence that links every degree of obesity directly to CRP[31]. This correlation is not affected by ethnicity characteristics and sex. The physiological mechanism is well described for this association. The liver drains free fatty acids and triacylglycerol, inducing the release of cytokines such as IL-6 by the adipose tissue. This event triggers expression and release of CRP by the hepatocytes, which explains the elevated levels. This mechanism also links IL-6 and CRP as pro-inflammatory markers related to obesity[29].

Opposing the inflammatory effects of IL-6 and CRP is the adiponectin. Adiponectin is a protein hormone derived from adipocytes. It has been identified as having a positive impact on not only inflammation but also atherosclerosis, type 2 diabetes and insulin resistance; all of them being possible consequences derived from obesity. It circulates at fairly high serum concentrations (2–20 µg/ml) in healthy individuals.

It plays an important autocrine role helping fat tissue mass grow in a hyperplasic way rather than in a hypertrophic way[32]. Other important local effect is the increase of local nitric oxide production and the inhibition of plaque initiation and thrombosis. This offers protection against endothelial dysfunction and reduced oxidative stress. Adiponectin also has effects in the liver, improving insulin sensitivity, reducing gluconeogenesis and increasing the oxidation process. All of the previous actions amount to a substantial positive impact on metabolic alterations. In obesity, adiponectin levels in the serum are found to be significantly reduced[33], and it is assumed that the high levels of inflammatory markers such as IL-6 are the cause for the reduction of synthesis and secretion of adiponectin.

The three molecules described are key when it comes to understanding the inflammatory process that the adipose tissue goes through in obese conditions. However, they are not the only ones, the mechanism controlling inflammation is complex and it involves local and central levels of regulation.

Fibrosis is defined as the accumulation of excessive extracellular matrix (ECM). It is a process that can occcur in the liver, heart, kidney and also in the adipose tissue. It is likely that they all have equal negative impact on systemic metabolic alterations. This phenomenom happens in rapidly expanding adipose tissue, where the hypoxia caused by hypertrophy leads to the induction of the expression of the triggering molecule, the hypoxia-inducible factor 1α (HIF-1α). Among other functions realted to the inflammation pathway, HIF-1α leads to a profibrotic transcriptional program in the adipose tissue[34].

ECM is mainly constituted by fibronectin and collagens. Type I collagens account for most of the framework necessary to sustain ECM, however it is type IV collagen which stabilizes the complex. Studies suggest that the excess of type IV collagen is a determinant factor in metabolyc dysregulations[35]. Also the presence of lysyl oxidase (LOX) is crucial for collagen fibre crosslinking and thus for fibrosis development[36].

Adipose tissue cells encapsulated in ECM lose their functions and undergo necrosis more frequently. The remaining lipid droplets stay in the tissue for weeks and along with surrounding dysfunctional adipose tissue cells, they induce the infiltration of macrophages and other white cells, thus enabling a pro-inflammatory environment (**Fig. 4.1**). Other studies suggest that HIF-1α by itself is a direct inducing factor of different pro-inflammatory molecules, for example IL-6 which has been previously described and causes white cell infiltration ultimately producing fibrotic components (**Fig. 4.2**).

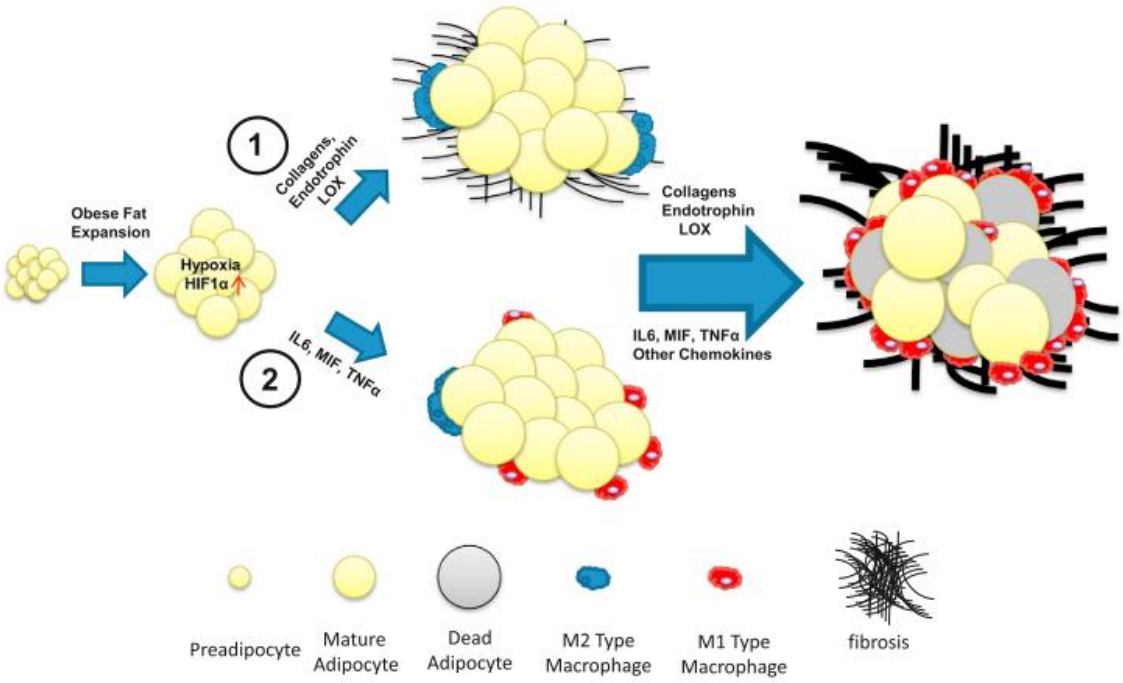

Figure 4. *Proposed models for the sequential steps leading to adipose tissue fibrosis and metabolic dysfunction. Obese fat pad expansion quickly leads to a hypoxic state. As a result, HIF1a is induced. The first hypothesis proposes that the adipose cells encapsulated in excessive extracellular matrix lose their functions and undergo necrosis, leaving behind remaining lipid droplets, which along with dysfunctional adipocytes surrounding them recruit macrophages, leading to a pro-inflammatory state and ultimately causing fibrosis. The second hypothesis suggests that HIF-1 α by itself has the capacity of inducing pro-inflammatory molecules, causing the macrophage infiltration and therefore ending in fibrosis. Both hypothesis reach the same outcome in the end and both seem plausible, the reality is keen to be a combination of the two.*

Fibrosis has not only been associated with dysfunctional adipose tissue but also to insulin resistance and it is a substantial risk factor that can lead to type 2 diabetes along with the inflammation[14]. They both play big roles in the complications known to derive from obesity.

5.4. Adipokines

Adipokines can be defined as the specific cytokines of adipocytes. They are associated with the progression of obesity and linked consequences. Adipokines have hormone function, act as growth factors that modulate insulin resistance, and act on the fat and glucose metabolism while also participating in pro and anti-inflammatory responses; they act in paracrine and endocrine manners. When there is an excess of adiposity and adipose tissue dysfunction,

adipokines are also deregulated, influencing in a negative fashion other cytokine and chemokine secretions and interfering with glucose and lipid metabolism[37].

The main adipokines include leptin, adiponectin, resistin, tumor-necrosis factor (TNF), interleukin 6 (IL-6), chemokine ligand 2 (CCL2), interleukin 10 (IL-10) and transforming growth factor-β (TFG-β). IL-6 has already been detailed and the rest will be further explained below *(**See annexe**).*

Leptin is a peptide hormone, product of the LEP gene and secreted by white adipocytes[38]. Once released into the circulation, has central and peripheral effects by binding to the leptin receptor, which activates the JAK/STAT pathway. In the hypothalamus, where this receptor is widely expressed, it acts appetite-regulating factor that induces a decrease in food intake and an increase in energy consumption by inducing anorexigenic factors and suppressing orexigenic neuropeptides. Leptin also has effects on the periphery, increasing basal metabolism, influencing insulin secretion and reproductive function and being absolutely crucial for the modulation of the innate and the adaptive immunity[39].

Adiponectin is encoded by the ADIPOQ gene, and it binds to two receptors, AdipoR1 and AdipoR2, involved in the increase of expression of adenosine monophosphate kinase and PPARγ respectively. As previously described, it reduces inflammation and increases insulin sensitivity, the latter especially in the liver[40].

Resistin (RETN) differs from others because in humans it is secreted by macrophages. Its name comes from its capacity to interfere with the action of insulin. Decorin, a connective tissue extracellular matrix protein, has been deemed to be the probable receptor for murine RETN. No receptors in humans have been clearly identified at this time and the molecular mechanism by which RETN carries out its effects is not yet clear. Interestingly there are studies that suggest no correlation between RETN levels in obesity, meanwhile others report a notable increase of RETN levels associated with obesity[40]. What it is known is that, at least in rodent models, it activates pro-inflammatory cytokines via NFκB pathway and also activates the suppressor of cytokine signaling 3 (SOCS-3), which is acknowledged for reducing insulin signaling in adipose tissue and other tissues[41]. It is worth noting that NFκB is a well-known factor involved in diet-induced obesity, insulin resistance and the inflammation related to unhealthy adipose-tissue expansion.

TNF is an inflammatory adipokine originally synthesized as a transmembrane monomer (TNFm) and is later processed by the TNF-converting enzyme resulting in soluble TNF (TNFs). Both forms have biological effects, however TNFm is thought to mediate autocrine actions and TNFs is responsible for the endocrine actions[42].

TNF is the factor originated from the adipose tissue linking obesity, inflammation and diabetes. The main source of TNF in obese individuals are not the adipocytes but the macrophages, that is the cause why elevated levels of TNF are observed in these individuals with metabolic syndrome[43]. The association between high levels of TNF and metabolic syndrome is the effect TNF has in mediating insulin resistance. The mechanism is not fully elucidated, but there is evidence that several downstream mediators of different inflammatory and metabolic diseases intersect. It is also known that TNF is involved in expression of other pro-inflammatory adipokines such as IL-6, CCL2 and TNF itself, through NFκB activation[44].

CCL2 is a chemokine produced mainly by macrophages and endothelial cells that participates in inflammation by recruiting monocytes toward the inflammatory site ref69. Studies have demonstrated that CCL2 expression has direct correlation with an increase of infiltration of pro-inflammatory cells in adipose tissue, therefore influencing insulin resistance and other metabolic disorders in obese humans[40].

IL-10 is produced by different types of immune cells and also adipocytes, creating an anti-inflammatory environment in the adipose tissue under physiological conditions. ref 54. This adipokines plays a key role limiting inflammation through several mechanisms, such as inhibition of macrophage activity and inhibition of the synthesis of some pro-inflammatory cytokines, for example TNF which has been previously detailed. It does so by suppressing two subunits of NFκB, inducing an overall anti-inflammatory state and helping restore insulin sensitivity[40].

TGF-β is a global cytokine which almost all cells can produce and respond to. It regulates several cellular processes including but not limited to differentiation, proliferation, death and migration. TGF-β levels on adipose tissue are correlated to obesity[45], however the exact role in obesity and adipogenesis has not been described yet.

The main takeaway is that the adipose tissue is an incredible dynamic tissue, with a complex regulation and an extremely important endocrine function that affects the whole body. All of the processes that occur are connected at some point (**Fig. 5**) and form a delicate equilibrium that if disrupted, causes dysfunction and ultimately leads to obesity and metabolic alterations.

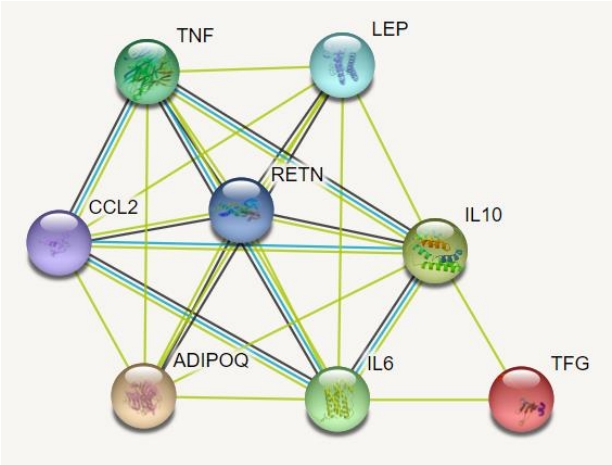

Figure 5. *STRING protein network interaction portraying the main adipokines described and their connections. Based on strong evidence of interaction, the network suggests a functional cluster formed by TNF, IL-10, IL-6, CCL2 and RETN. It can also be inferred that leptin, resistin and adiponectin work closely to carry out their function*[46].

6. METABOLIC ALTERATIONS

When the obesity related alterations presented above take a toll on the body, they are considered metabolic alterations or diseases. These are the cause why many obese individuals have a decreased quality of life or even die. They are all direct consequences derived from obesity, therefore preventable in many cases. The main diseases induced by

obesity include but are not limited to: cardiovascular diseases (CVDs), type 2 diabetes (T2DM), dyslipidemia, hypertension[47] and in some cases different types of cancer.

6.1 Obesity and CVDs

CVDs are the leading cause of mortality among obese population, the excess of adipose tissue creates a pro-inflammatory profile due to adipokine deregulation, as previously discussed in this work. Its importance lies in the fact that this profile causes a relevant increase in CDVs risk regardless of other pathologies. Studies suggest that it may even alter myocardium structure and function[48]. This situation also influences dyslipidemia, T2DM, and hypertension, accelerating their progression and increasing their severity. Although adipokine profiles oscillates between individuals, the overproduction of pro-inflammatory is especially favored in obesity.

Substantial weight gain and excess of adipose tissue is pernicious to metabolic health and a serious risk factor for the development of CVDs. Particularly in children, it causes abnormal glucose metabolism (hyperglycemia) and dyslipidemia, making them predisposed to develop CVDs and T2DM, which will severely impact their later stages of life[37]. Experimental studies have strongly associated increases in BMI with augmented risk of suffering from CVDs in the years to come; even the smallest increase in BMI has posterior consequences[49].

6.2 Obesity and T2DM

Obesity is a primary cause of T2DM a chronic and metabolic disease characterized by elevated levels of blood glucose, which leads over time to damage to the heart, vasculature, eyes, kidneys and nerves. It is a condition marked by deficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance and an inadequate compensatory insulin secretory response. The progression of this disease makes insulin secretion unable to maintain glucose homeostasis, which produces hyperglycemia. Individuals suffering from T2DM are mostly obese. In this condition.

Insulin is a hormone produced in the β cells of the islets of Langerhans in the pancreas. It is released into the bloodstream in situations of hyperglycemia. The main regulator of insulin is glucose, however it can also be influenced by amino acids, ketones, incretins or different neurotransmitters.

When the glucose transporter 2 (GLUT2) allows glucose into the β cells of the pancreas the signaling cascade is generated and ends with the secretion of insulin into the bloodstream. Insulin will travel through the circulation, being recognized by receptors of the tyrosine kinase family, whose binding and recognition will result in increased expression of glucose transporter proteins in the cell membrane[50]. As glucose regulates insulin, insulin is the key regulator of the metabolic balance of glucose. Low concentrations of insulin decrease liver and muscle glycogen synthesis and glucose uptake by sensitive tissues, while increasing lipolysis and gluconeogenesis. On the contrary, high concentrations of insulin cause a rapid uptake, use and storage of glucose by most of the tissues of the body, inducing protein, glycogen and protein synthesis. High levels of insulin also partake in the regulation of various genes in cells that respond to insulin, and inhibit hepatic gluconeogenesis[51].

Insulin resistance (IR) can be defined as resistance to effects on glucose uptake, metabolism, or storage. Manifestations include but are not limited to decreased glucose transport and metabolism especially in adipocytes and muscle tissue; and diminished suppression of hepatic glucose output. Insulin affects primarily the metabolism of lipids and carbohydrates, however it is not dilucidated whether it affects protein metabolism or not. Different older studies have suggested it does[52] but more recent ones have challenged this claim[53], providing the sufficient scientific evidence to prove their stand.

One of the most affected or influenced tissues is the adipose tissue since adipocytes are one of the most highly insulin-responsive cell types[54]. Recent studies suggest that defective signaling from insulin receptors is associated to the insulin resistance in obese individuals. The cause behind it might be an increased expression and activity of several protein tyrosine phosphatases (PTPs), with a dephosphorylating function, therefore terminating signaling propagated through tyrosine phosphorylation and not allowing GLUT4 to translocate and take glucose in (**Fig. 6**).

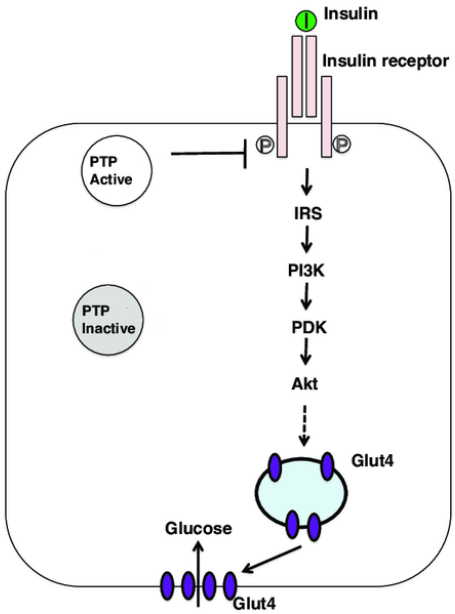

***Figure 6**. Adapted from: Insulin signaling pathway[55]. Insulin binds to the insulin receptor located in the plasma membrane in tissues, such as liver, fat and muscle. The insulin-signaling pathway is activated and the glucose transporter GLUT4 is translocated to the plasma membrane. When PTP is active it stops the cascade at the very first step. PI3K, phosphatidylinositol-3-kinase; IRS, insulin receptor substrate; PKD, protein kinase D; Akt, protein kinase B.*

Adipose tissue promotes IR through various inflammatory mechanisms, including increased free fatty acid (FFA) release and adipokine deregulation as described in the previous chapter. Evolving data suggests that adipokine deregulation, inflammation, abnormalities in gut microbiota, immune dysregulation, and inflammation have emerged as important pathophysiological factors in the development of T2DM[56]. There are both environmental factors such as diet changes or sedentary lifestyle and genetic factors which are of polygenic nature, with certain patterns of IR, reduced insulin secretion and altered insulin processing revealed by GWAS over the last decade.

T2DM has several complications or outcomes, all negative for the system. A dyslipidemic profile consisting of elevated levels of triglycerides and low density lipoproteins (LDLs) and of

diminished levels of high density lipoproteins (HDLs) is tied to T2DM. Lipoprotein production, metabolism, and clearance are usually efficient processes. However, T2DM and IR are the most important disruptors of these processes and they give rise to impaired metabolism and clearance of these lipoproteins, ultimately leading to atherosclerosis[57].

One of the primary abnormalities in IR is impaired adipose tissue fat storage, resulting from insulin's inability to inhibit hormone-sensitive lipase (HSL). This results in constitutive free fatty acids (FFA) release from the intracellular TG stores of adipocytes (**Fig. 7**). These FFA's final destinations vary among undergoing β-oxidation in hepatocytes mitochondria, being used to assemble new lipoprotein particles, partaking in gluconeogenesis leading to a worsening of already existing hyperglycemia and being stored[58].

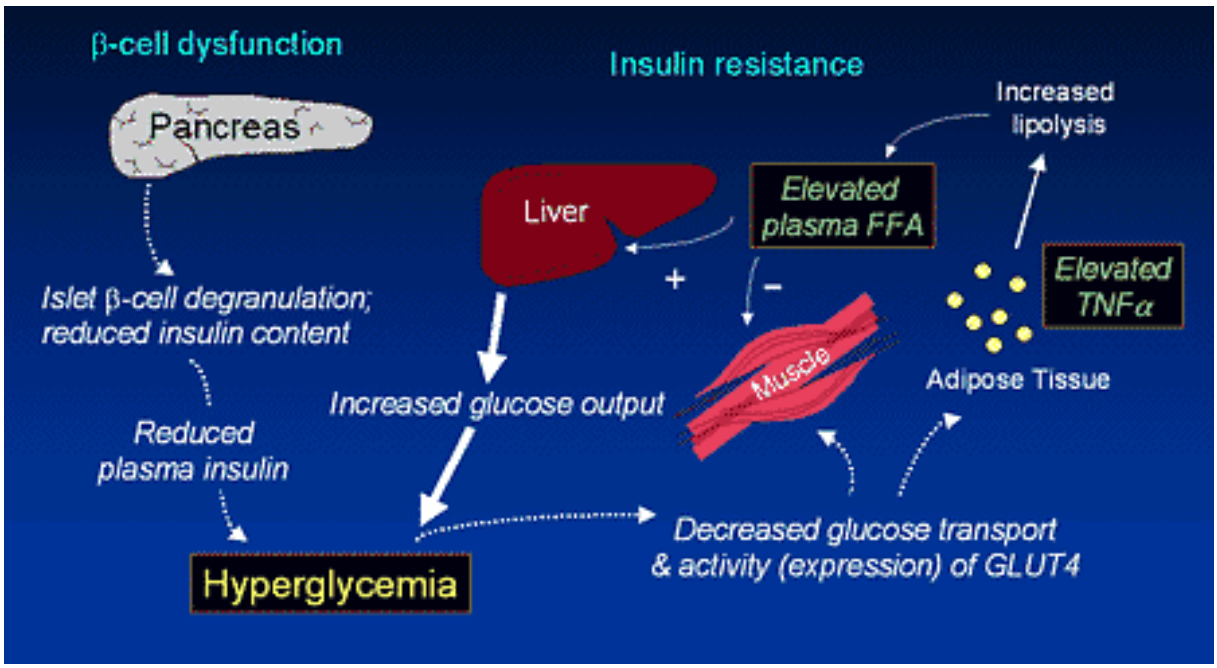

***Figure 7**. Image depicting the communication between the liver and muscle and adipose tissue in an insulin resistance situation[59]. The adipose tissue causes the elevated plasma FFA levels when altered, affecting the liver and muscle leading to hyperglycemia. The pancreas tries to keep up with the insulin production and eventually there is a loss of β.-cell function.*

6.3 Progression of T2DM increasing the risk of CVD

The increase in production of very low density lipoproteins (VLDLs) by the liver is a crucial feature of diabetic dyslipidemia, and it circles back to insulin resistance. These particles are synthesized bound to apoB100, and the production and secretion of the VLDL-apoB100 tandem is directly inhibited through the inhibition of the transcription of the microsomal transfer protein (MTP)[60]. This protein is responsible for the assembly of lipoproteins with apoB100, which generates an immature VLDL-apoB100 that will need to be processed by the

phospholipase D1 (PLD1). By inhibiting MTP insulin stops this process, therefore stopping the overproduction of lipoproteins in a fed state. In IR condition MTP expression is not modified, since the acute insulin-mediated inhibition of apoB100 secretion is not working as it should[61].

The reduced HDL levels are due to an insulin response element in the gene that codes for apoA-I, which is the main apolipoprotein component of the HDL particles. The more insulin resistant the liver becomes, the less apoA-I is produced, meaning that there will be a shortage in the synthesis of HDL particles. Moreover, in the milieu of IR, HDL particles are not only in low concentrations, but they are also often dysfunctional. This prevents HDL from performing basic functions such as reversal of cholesterol transport and inhibition of oxidative and inflammatory processes[62] (**Fig. 8**).

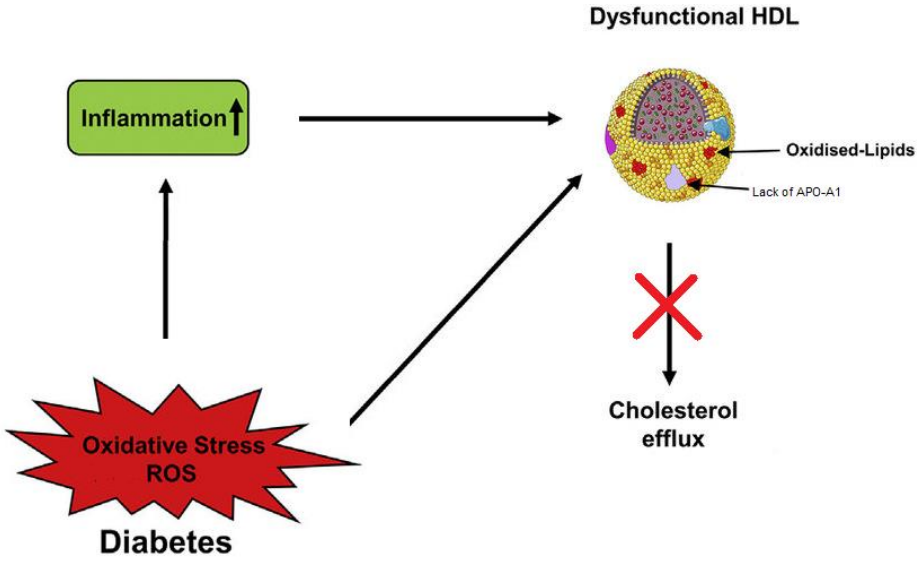

***Figure 8**. Adapted from: Image depicting how diabetes alters HDL composition and function[63]. In diabetes, high levels of oxidative stress and reactive oxygen species (ROS), induce direct or indirect compositional changes in HDL particles, rendering them dysfunctional. Thereby HDL is less effective in extracting cholesterol from cells.*

This dyslipidemic profile is closely linked to the development and progression of atherosclerosis and is a clear contributor of CVDs (**Fig. 9**). In fact, CVD is responsible for at least half of the mortality in the population suffering from T2DM[64].

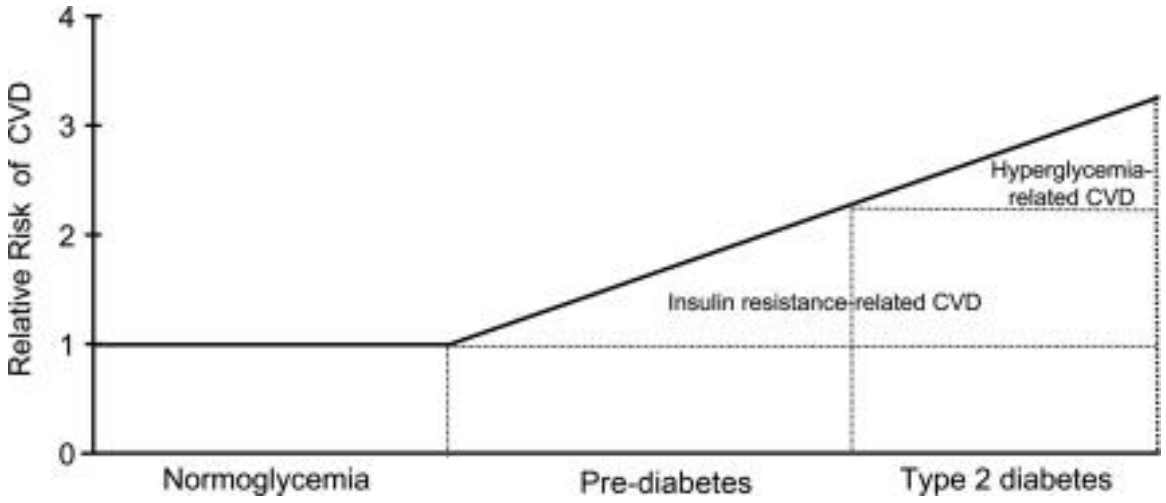

***Figure 9**. Relative risk of CVD in normoglycemia, pre-diabetes, and type 2 diabetes[65]. As T2DM progresses, issues such as IR and hyperglycemia become increasingly more severe, reaching the point of the risk of CVD being slightly over three-fold the standard risk.*

7. CHANGES IN MICROBIOTA

Obesity is closely related to the gut microbiota. The study of the gut microbiome suggests a new line of treatment by reconstructing the gut microbiota of obese individuals.

The gut microbiota comprises up to 100 trillion symbiotic microbes. For the sake of comparison, this number is ten times the number of living cells that form the body. Their sources of nutrients are food residues not digested by the human body, mucus secreted by the gut and dead cells that occasionally detach from the gut itself.

The importance of gut microbiota lies in the many active and beneficial substances that it produces in healthy state, such as vitamins, short-chain fatty acids, anti-inflammatory, analgesic, and antioxidant products. However it has the potential of producing harmful substances such as neurotoxins, carcinogens, and immunotoxins[66]. All of these can access the bloodstream directly from the gut, therefore an imbalance in the gut microbiota, also known as dysbiosis, regulates many processes and can cause metabolic disorders, increase central appetite and ultimately lead to an obese state[67].

Modern technologies of 16S RNA sequencing have allowed in-depth study of the gut microbiota. So far 6457 different taxa have been identified by the gutMEGA database[68]. The standard gut microbiota of the healthy individual is mainly composed of *Firmicutes*, *Bacteroides*, *Proteus*, *Actinomycetes*, *Fusobacteria*, and *Verrucomicrobia*. Out of all of them, *Firmicutes* and *Bacteroides* stand out as the dominating phyla. Signs of healthy microbiota include a flexible equilibrium or resilience, meaning the ability to recover from alterations and return to a healthy state; diversity, as demonstrated by the many phyla that share livelihood in the gut and also the adequate metabolization of polysaccharides, production of SCFA (or short chain fatty acids) and production of vitamins and essential amino acids[69]. The role of SCFA is not yet clear, they stand as a double-edged sword. Although they often protect against diet—induced obesity, it is suggested that an excessive quantity could promote obesity due to being used as a source of energy themselves[67].

Firmicutes/Bacteroides is a ratio that is often used a biomarker for obesity, however there is some controversy on the relevance of this *Firmicutes/Bacteroides* ratio when it comes to its direct correlation to obesity. Some studies show a direct correlation in the increase of *Firmicutes* over *Bacteroides* with BMI[70], whereas other studies find no difference in this ratio when comparing it in healthy and obese individuals[71]. More research is needed in order to determine the precise association between this ratio and obesity.

There are however many genera with established relation to obesity. *Christensenellaceae* is a recently described family in the *Firmicutes* phylum, which throughout several different populations and studies has proven to have an inverse correlation to host BMI. It is in fact the most robust link reported to date[72]. Other genera like *Akkermansia muciniphila* has proven to improve metabolic parameters in obese individuals[73]. *Lactobacillus* and *Bifidobacterium* have traditionally been used as probiotics due to their effectiveness in improving the balance of the gut microbiota.

Several obesity mechanisms have been found to be induced by the gut microbiota, including but not limited to: energy absorption, central appetite, fat storage, chronic inflammation and circadian rhythm alterations.

Different studies with mice have demonstrated that individuals with obese gut microbiota profiles have, in fact, an increased capacity of extracting energy from the diet. This information was confirmed by multiomics analysis, reaching the conclusion that obese type microbiota increases lipid absorption in the host[74][75]. This situation predisposes the individual to excessive energy accumulation, finally resulting in weight gain.

The gut-brain axis is a strong connection that modulates the interactions between both of them. The communication happens through endocrine, immune, and neural pathways. The central nervous system affects the composition of gut microbiota, as well as the microbiota can influence and regulate brain function when it comes to appetite. It participates in this regulation through serotonin, lactate, which is produced by *Lactobacillus* and *Bifidobacterium* and can extend the duration of satiety[76]; and anorexic hormones such as peptide YY and pancreatic polypeptide. In general, the metabolites of a proper working microbiota are associated to a satiety feeling.

As gut microbiota increases the absorption of glucose in the intestine, it increases the level of serum glucose, thereby promoting the expression of two factors that promote lipogenesis and fat storage: ChREBP (carbohydrate response element binding protein) and SREBP-1 (sterol regulatory element binding protein)[67].

A healthy microbiota synthesizes the right amounts and kinds of SCFAs, meaning that it will produce butyrate, an anti-inflammatory metabolite not only known for suppressing pathways leading to the production of pro-inflammatory cytokines but also for the stimulation of energy consumption, thus having a double action against the development of obesity[77]. However, as mentioned before, SCFAs do not have a one-sided role, and the perfect example is acetate. On the one hand, acetate can be used as a substrate for cholesterol synthesis, thus helping to raise serum cholesterol levels, which can increase the risk of obesity. On the other hand, acetate has been reported to suppress appetite and reduce the risk of obesity[67].

Studies regarding gut microbiota and its ties to obesity are often limited by the many factors conditioning obesity, highlighting as well that variability among individuals and bacteria strains could explain the contradicting results. Despite what has been stated, the fact that a clear relation exists between gut microbiota and obesity is acknowledged worldwide[67].

All of the above perfectly exemplifies how gut microbiota is very much involved in regulating and modulating certain obesity mechanisms such as energy uptake and management or inflammation (**Fig. 10**). Further investigation will be needed to shed light into these and many other molecular mechanisms that interconnect creating a complex yet precise regulation network, which can result in obesity and its associated consequences when genetic and environmental factors combine for the worst.

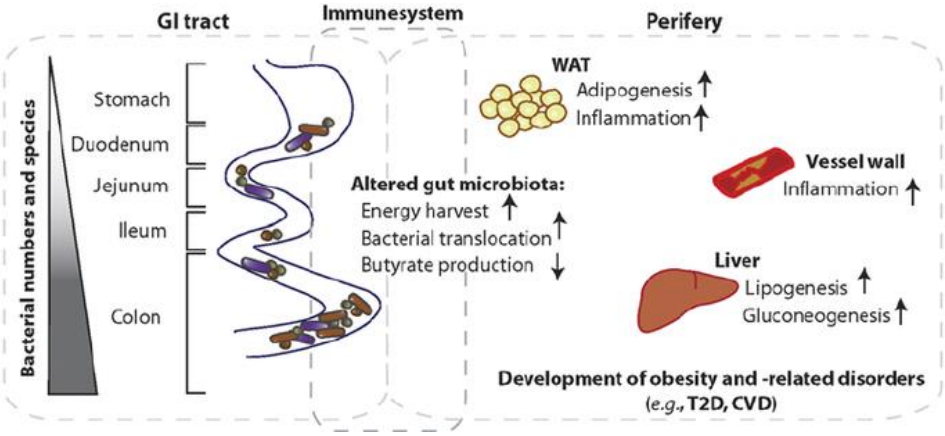

***Figure 10**. Adapted from: illustration depicting the load of microbiota along the gastrointestinal (GI) tract[78]. In obese subjects, alterations in gut microbiota composition result in increased enhanced harvest from the diet, increased bacterial translocation, and a decrease in butyrate production. This induces several metabolic changes in peripheral tissues, including increased lipogenesis, gluconeogenesis, adipogenesis and inflammation. The immune system plays a key role in mediating metabolic effects of the gut microbiota.*

8. OBESITY AND COVID-19

In December 2019, a new virus was identified in Wuhan, China. It was named SARS-CoV-2 (short for severe acute respiratory syndrome coronavirus 2). SARS-CoV-2 causes different respiratory symptoms, ranging from non-severe cold-like symptoms to acute pneumonia. It has widely and rapidly expanded throughout the whole globe, causing a public health and economic crisis. Similar to other respiratory diseases, and according to the WHO, COVID-19 is often more severe in people older than 60 years or in those individuals who have health conditions like lung or heart disease, T2DM or conditions that affect their immune system[79].

As previously discussed in detail, T2DM is very closely related to obesity, so the question arises if obesity and severity of COVID-19 or higher mortality are linked in any way. It has been attempted to answer by systematic reviews and meta-analysis, finally reaching the conclusion through careful processing of the data that obesity is, in fact, associated with a more severe COVID-19 disease course (**Fig. 11**). Obese patients are 1.7 times more likely to be hospitalized and 1.3 times more likely to be admitted to the intensive care unit (ICU). It is not however demonstrated that obesity increases the mortality associated to COVID-19[80].

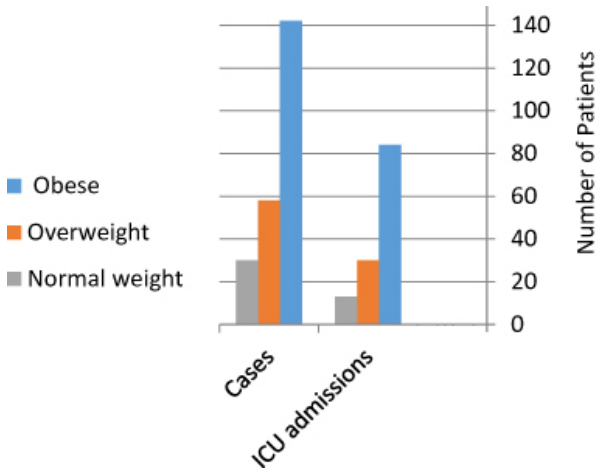

***Figure 11**. Adapted from: weight disaggregated data of patents of a study of 230 Egyptian COVID-19 patients*[81].

9. FUTURE AND PRESENT RESEARCH

There are plethora of mechanisms and processes that are not fully understood yet, meaning more investigation needs to be carried out in the field in order to elucidate these missing details and find solutions to existing problems. These investigation lines are: the excess of type IV collagen as a determinant factor in metabolyc dysregulations, steps that occur since the expression of HIF-1 α and lead to the fibrosis of the adipose tissue, correlation between levels of resistin and obesity, precise role of SCFAs and their mechanisms of action and finally taking advantage of gut microbiota sequencing to design new lines of treatment for obese patients.

10. CONCLUSSIONS

- Obesity is not just turning, but it is already a serious problem in the first world countries. The causes are genetic and environmental, meaning that at part of it is definitely preventable, therefore individuals and health officials must take a step forward in fighting this disease.

- Obesity is not a simple disease, it is in fact multifactorial and extremely hard to comprehend to the last detail. It is known however that the adipose tissue, thought to be just for fat storage not so long ago, plays a key role in the regulation and development of obesity through its increase in size, secretion of cytokines and inflammation and fibrosis processes.

- The consequences of obesity are not to be taken lightly, since they impair obese patients in several different ways. It is not only about the difficulty to perform everyday tasks, but it is about the internal conditions the body is exposed to, such as hyperglycemia, dyslipidemia and insulin resistance. These take a huge toll on the system and end up having serious consequences such as the increased risk of CVDs, the development of T2DM and many other different complications including the elevated risk of developing cancer as well.

- The gut microbiota also plays an active role in regulating energy extraction from the diet and mediation of chronic inflammation through metabolites such as butyrate and

SCFAs. The gut-brain axis works both ways, the gut influencing satiety sensation and the brain being able to shape the microbiota. It is key to maintain a healthy gut microbiota and preserve the existing flexible equilibrium, because not only helps the processes mentioned above, but also keeps the immune system fully functional and operational.

- There exists a proven increased risk of suffering complications and having a tougher time while suffering from COVID-19 if the patient is obese. This risk is of considerable magnitude and it ought not to be underestimated by the risk groups, which include individuals suffering from T2DM, therefore including a major percentage of obese population.

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12. ANNEXE

Table 1. *Molecular effectors of adipokines.*