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REVIEW ARTICLE

Lipotoxicity: unraveling the deleterious mechanisms of free fatty acids to damage the cell

Lipotoxicidad: desenmarañando los efectos deletéreos de los ácidos grasos libres para dañar a la célula

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ABSTRACT

The development of obesity implies an excessive accumulation of triglycerides into adipose tissue, triggering the expansion of adipocytes, an increased synthesis of free fatty acids, as well as the rise of ectopic deposits of fat that appear when the storage capacity of adipocytes as well as the oxidative capability of mitochondria is exceeded. Therefore, lipids levels are increased, disrupting several cellular functions. Under such conditions, mitochondria, Golgi apparatus, and endoplasmic reticulum are the most affected cell organelles among several bioenergetics-related pathways. Oxidative stress, mitochondrial dysfunction, inflammation, and cell death activation are some of the more studied mechanisms to understand the molecular effects of lipotoxicity on cellular function; therefore, in this review, we describe the findings that explain the toxicity resulting from the excessive storage lipids on cellular metabolic pathways and organelles´ functions, pointing out those aspects that remain as open questions for future research.

Keywords: Obesity. Lipotoxicity. Mitochondrial dysfunction. Free fatty acids. Ectopic fat accumulation.

RESUMEN

El desarrollo de obesidad implica una excesiva acumulación de triglicéridos en el tejido adiposo, lo que genera la expansión de los adipocitos, un aumento en la síntesis de ácidos grasos libres, así como un aumento en los depósitos ectópicos de grasa, que aparecen cuando se superan tanto la capacidad de almacenamiento de los adipocitos como la capacidad de la mitocondria para oxidarlos. Como consecuencia, los niveles de lípidos aumentan, alterando diversas funciones celulares. Bajo estas condiciones, la mitocondria, el aparato de Golgi y el retículo endoplásmico son algunos de los organelos que sufren más alteraciones, junto con las vías implicadas en la bioenergética de la célula. El estrés oxidativo, la disfunción mitocondrial, inflamación y la activación de muerte celular son algunos de los mecanismos más estudiados para entender los efectos de la lipotoxicidad sobre la función celular; por lo tanto en esta revisión describimos los hallazgos que explican la toxicidad ocurrida por la excesiva acumulación de lípidos sobre las vías metabólicas y la función de organelos celulares, señalando aquellos aspectos que permanecen como incógnitas para ser abordados en futuras investigaciones.

Palabras clave: Obesidad. Lipotoxicidad. Disfunción mitocondrial. Ácidos grasos libres. Acumulación ectópica de grasa.

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Date of reception: 21-10-2024
Date of acceptance: 27-01-2025
DOI: 10.24875/RME.24000055

Available online: 25-09-2025
Rev Mex Endocrinol Metab Nutr. 2025;12:129-136

INTRODUCTION

Lipids and obesity

Lipids are one of the most important biological macromolecules, which fulfill structural, regulatory, and signaling functions as well as energy supplier and reserve functions. Unlike other molecules, lipids exist in many structures obtained from the diet-consumed and newly synthesized in the liver. At first, after being absorbed in the intestine, lipids are transported to the liver for being metabolized or distributed; later, free fatty acids (FFA) are synthesized *de novo* in the liver and, subsequently, transported to peripheral tissues by lipoproteins (LPs)[1].

LPs are specialized structures with a nucleus –rich in triglycerides and esterified cholesterol– covered by phospholipids, cholesterol, and apolipoproteins. Their primary function is the transportation of lipids (triglycerides and cholesterol) between organs[2].

The amount of lipids transported by LPs is directly proportional to the levels of intake and biosynthesis; therefore, an overload, given by an augmented ingestion or disruptions in their metabolism (absorption, oxidation, and synthesis), may increase the storage of triglycerides into the adipocytes, the cells constituents of adipose tissue. Eventually, and under tightly regulated mechanisms, triglycerides can be removed and distributed to be used as an energy source when the primary source is scarce.

Adipocytes have a high capacity to store triglycerides; however, if this capacity is exceeded, the release of FFA is stimulated, triggering the ectopic accumulation of fat in different organs, which may interfere with their function[3].

Fatty acids (FAs) are the simplest form of lipids and are conformed by a carboxyl group attached to a hydrocarbon chain that may contain only single bonds between carbon atoms (saturated FA) or a variable number of double bonds between carbons[4] (unsaturated FA). The FAs having only one double bond are named monounsaturated, whereas those containing two or more double bonds are known as polyunsaturated FAs.

According to the configuration of their unsaturation, FA can be trans- or cis-. Commonly, the FAs are found in the "cis" configuration, whereas the "trans" configuration often appears in industrialized foods, with harmful effects on health[5].

Among their bioenergetics functions, FAs are fundamental constituents of biological structures, such as phospholipids and sphingolipids, the main constituents of cell membranes. On the other hand, FA has meaningful participation in regulatory tasks, being as hormone precursors or as constituents of prostaglandins, thromboxanes, and leukotrienes, molecules that participate in biological processes such as inflammation, muscle contraction, and coagulation[5].

This review was designed following the PRISMA reporting guidelines for systematic reviews (http://www.prisma-statement.org/).

LIPID METABOLISM

The digestion of lipids begins as soon as they are into the mouth, with mechanical action and exposition to a salivary lipase as the first step. Later, intestinal lipase and bile salts emulsify the ingested lipids to form micelles that are absorbed in the small intestine, mainly as FFA, monoacylglycerol, and cholesterol. Once these lipids are in the enterocytes, triglycerides are synthesized *de novo* and, among cholesterol, bind to apoproteins A and B48 to assemble chylomicrons and release into the bloodstream through the lymph. In blood vessels, lipases hydrolyze triglycerides from chylomicrons[6].

As mentioned above, FFA can be obtained either by synthesis from carbohydrates (lipogenesis) or by lipolysis through the action of lipases on storage triglycerides; lipolysis is upregulated by hormones such as glucagon, epinephrine, norepinephrine, and adrenaline, whereas insulin stimulates lipogenesis[7].

FAs and triglycerides are synthesized in the liver, adipose tissue, and mammary glands. Their synthesis begins with the releasing of Acetyl-CoA from the mitochondria to the cytosol, for being carboxylate by Acetyl-CoA carboxylase to form Malonyl-CoA, which is subjected to the cycling binding of two carbon atoms

through condensation and reduction reactions catalyzed by the FAs synthase, until reaching a chain long of 16 carbons, the palmitic acid[8]. The FAs with more than 16 carbons are synthesized (by elongation) in the mitochondria and develop a myriad of functions as structural compounds for membranes, as signaling molecules, hormone precursors, or also can be stored as constituents of triglycerides[8].

The removal of adipose tissue occurs under energy demand. First, lipases release FA from triglycerides to feed the β-oxidation into the mitochondria for adenosine triphosphate (ATP) production. To this end, the FA must be activated in the endoplasmic reticulum (ER) or on the outer mitochondrial membrane through the binding of an Acetyl-CoA molecule, a reaction catalyzed by the Acyl-CoA-synthase[9]. After that, the Acyl-CoA will be modified to Acyl-carnitine to cross freely from cytosol to the mitochondrial matrix. Once in the matrix, carnitine palmitoyltransferase II (CPTII) binds the FA to a CoA, forming new Acyl-CoA that enters the β-oxidation, where each cycle brings a molecule of acetyl-CoA, FADH2, and NADH. Finally, a mole of acetyl-CoA will generate 12 moles of ATP through the Krebs cycle and oxidative phosphorylation[10].

MAIN ASPECTS OF LIPOTOXICITY

The development of obesity implies an excessive accumulation of triglycerides into adipose tissue, triggering the expansion of adipocytes, the increased synthesis of FFA, and the emergence of ectopic deposits of fat that appear when the storage capacity of adipocytes as well as the oxidative capability of mitochondria are exceeded[11]. The toxic effects of a higher concentration of FFA in the cell occur through the activation of non-oxidative metabolic pathways that produce toxic metabolites, leading to a state of lipotoxicity, which induces cellular dysfunction and death[12].

In this sense, lipotoxicity is strongly related to the presence of insulin resistance and its progression to diabetes due to the ectopic accumulation of fat in muscle tissue, which reduces the translocation of type 4 glucose transporters (Glut-4) and affects mitochondrial function with a drop of its oxidative capacity[13].

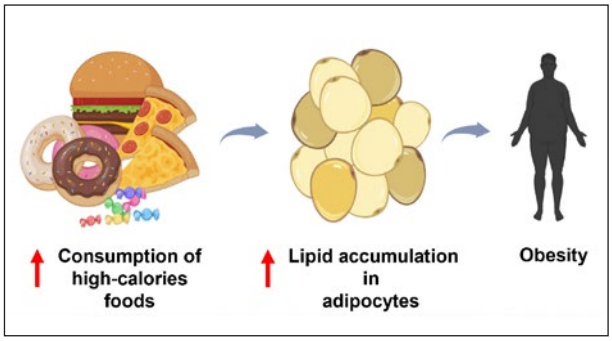

Figure 1. Obesity. One of the main factors for the appearance of overweight and obesity is the intake of hypercaloric food, driving lipids accumulation in adipocytes, increasing their size and, therefore, increasing the body fat mass in the individual.

Although there is still controversy regarding the detailed mechanisms for fat accumulation in adipose and non-adipose tissues, evidence indicates that consuming high-fat and high-carbohydrate diets favors such a condition[14] (Fig. 1).

Lipotoxicity is driven by lipids such as long-chain acyl-CoA, ceramides, and diacylglycerols with the ability to disturb the function of enzymes, altering metabolic pathways and leading to the activation of cell death pathways[15].

Lipid metabolism is highly regulated by sterol regulatory element-binding proteins (SREBPs). These transcription factors rest inactively attached to the ER membranes and, to a lesser extent, to the mitochondria[16]. For their activation, SREBPs are cleaved in the reticulum before being transported to the nucleus to trigger the transcription of proteins involved in the synthesis of lipids. In this sense, high levels of serum glucose may induce overexpression of SREBP and, therefore, the activation of downstream genes implicated in either an increased *de novo* synthesis of FFA or lipid storage[17].

Likewise, FFA increases the expression of peroxisome proliferator-activated receptors (PPARs) α/γ, inducing an imbalance in lipid uptake, oxidation, storage, and syntheses, favoring lipid accumulation[17].

Recent reports indicate that alterations in PPARγ function also affect the phosphatidylinositol 3-kinase pathway PI3k/akt by inducing either structural changes in insulin receptor substrates 1 and 2 (IRS-1, IRS-2) or inhibiting Glut-4 translocation to the cytoplasmic membrane, as occurs in skeletal muscle under insulin resistance[18].

In addition, PPARγ stimulates peroxisome proliferator response elements, increasing, as a result, lipogenesis, fat deposits, and the concentration of circulating FFA, accompanied by an increase in the expression of FAs binding proteins (aP2), FA transporters, Acyl-CoA synthetase, and LP lipase; all of them take part in the metabolism and transport of FAs[17].

Alterations in PPARα also modify the constitutive expression of mitochondrial enzymes that participate in FFA catabolism, such as constituents of the β-oxidation pathway, and downregulate mitochondrial components of the electron transport chain, favoring their accumulation and establishment of a cytotoxic state[19].

The PPARs coactivator γ-1α (PGC-1α), a transcription factor with central participation in lipid metabolism and mitochondrial biogenesis, is affected under a lipotoxicity state. The regulation of PGC-1α occurs through the activation of the mitogen-activated protein kinase (MAPK) ERK/MAPK[20].

The CD36 receptor activation depends on Na+/K+ ATPase (the sodium and potassium adenosine triphosphatase). Activation of CD36 by oxidized low-density lipoprotein (LDL) occurs through phosphorylation of Fyn and Lyn with the intervention of Na+/K+ ATPase, which activates MAPK, whereas ERK and p38 activate akt or NFκβ kinase, which triggers proinflammatory cytokine production and activates apoptotic signaling pathways; this represents a particular aspect of lipotoxicity[21], compromising lipid metabolism and activating inflammatory pathways as occurs in atherosclerosis with endocytosis of the oxidized LDL by macrophages, leading them to differentiate into foam cells.

LIPOTOXICITY AS ACTIVATOR OF APOPTOSIS

FFA-mediated apoptosis is one of the main causes of obesity-related cell death. It occurs when non-adipose tissues are exposed to high concentrations of FFA, which stimulates both the intrinsic and extrinsic apoptotic pathways; in addition, it was reported that perforin/granzyme and common execution pathways can be stimulated[22].

The accumulation of FFA may activate the pro-apoptotic protein Bax, leading to apoptosis through the intrinsic pathway through the action of Bim and JNK. Once activated, Bax translocates to and increases the permeability of the inner mitochondrial membrane, allowing the release of cytochrome C from intermembrane space to cytosol to participate in the assembly of the apoptosome complex, which leads to activation of procaspase 9[23,24].

FFA's capability to interact with Toll-like receptors allows it to bind lipopeptides that stimulate proinflammatory responses through upregulation of nuclear factor kappa B and as positive regulators for tumor necrosis factor α and interleukins 3 and 6, triggering inflammatory processes, cell stress, and apoptosis[25].

On the other hand, perforin and granzyme can be released from the ER into the cytosol under states of lipotoxicity and oxidative stress, triggering the activation of Caspases 9. This, in turn, activates Procaspases 3, 6, and 7, which, as active Caspases, carry out protein degradation, chromatin condensation, and DNA degradation[26,27].

Long-chain FA in excessive concentrations also favors the synthesis of complex lipids as ceramides and cholesterol esters through upregulation of both the ceramide precursor, dihydrosphingosine, and the serine palmitoyl transferase, which catalyzes the condensation of Palmitoyl-CoA and serine as a first step in the biosynthesis of sphingolipids. The increase in ceramides' production, simultaneously with the overproduction of reactive oxygen species (ROS) under a state of lipid saturation, leads to the activation of the apoptotic signaling pathways[28]. These processes are related to the appearance of diseases such as atherosclerosis, cardiomyopathy, retinopathy, nephropathy, neuropathy, and endothelial dysfunction[29].

CELLULAR MECHANISM FOR LIPOTOXICITY

Mitochondrial lipotoxicity

For correct functionality, mitochondria depend on the organization and composition of their two membranes, which are mainly composed of phosphatidylcholine, phosphatidylethanolamine, cardiolipin,

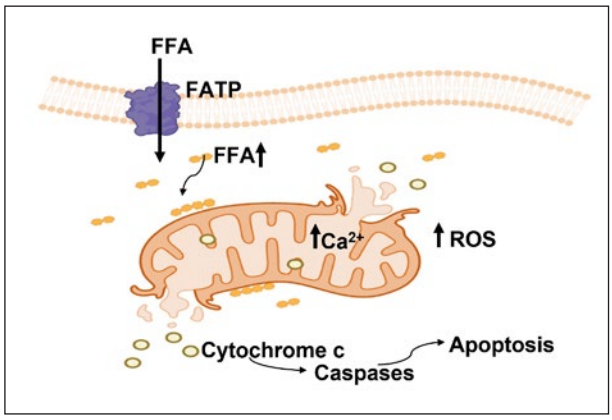

Figure 2. Mechanism of lipotoxicity to induce mitochondrial apoptosis. FFA enter the cell through FATP, FA leading to their accumulation in mitochondrial membranes, increasing ROS production, lipid peroxidation, and modifying the mitochondrial membranes permeability, which allows the intra-mitochondrial accumulation of calcium and mitochondrial swelling. The outer membrane breaks out, with the consequent release of cytochrome c and other pro-apoptotic factors that activate diverse processes of apoptosis and the caspases pathway, which is known as the intrinsic pathway of apoptosis. FFA: free fatty acid; FATP: fatty acid transporter protein; ROS: reactive oxygen species.

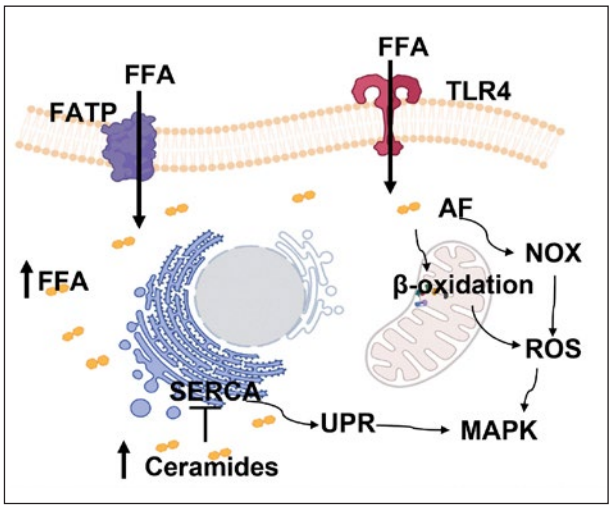

Figure 3. Schematic representation of mechanism for mitochondrial and endoplasmic reticulum lipotoxicity. FFA enters the cell through fatty acid-transporting proteins or Toll-like receptors 4. Intracellular FFA accumulation induces the reactive oxygen species over-production by stimulating B-oxidation or triggering activation of NOX. Once a state of oxidative stress is established, serine kinases such as MAPK are activated, and the production of ceramides in the endoplasmic reticulum is increased, with the consequent activation of UPR that also activates MAPK. FFA: free fatty acid; TR4: type 4 Toll-like receptor; UPS: unfolded protein response; MAPK: mitogen-activated protein kinase; SERCA: sarco endoplasmic reticulum Ca2+ ATPase.

phosphatidylinositol, lysophosphatidylethanolamine, and cholesterol[30]. According to previous reports, mitochondrial membranes contain lipid rafts that carry out critical regulatory functions on transport and signaling[31].

Mitochondria are highly active organelles delimited by two membranes that generate two subcompartments: the intermembrane space and the mitochondrial matrix, the space where ATP synthesis and the β-oxidation of FAs occur[32,33]. Mitochondria also play a key role in regulating apoptosis[30].

Under pathological conditions, FFA accumulation in the vicinity of the mitochondria may occur, shifting the structural organization of the mitochondrial membranes and triggering the accumulation of calcium inside the organelle, compromising its oxidative capacity and triggering oxidative stress (Fig. 2). Ectopic fat accumulation is related to mitochondrial dysfunction and ROS overproduction, which induces lipid peroxidation and oxidative damage to mitochondrial DNA and proteins[20,33].

FFA is transported from the cytosol into the mitochondria through both the fat/CD36 transporter and the carnitine transport pathway. Therefore, a deficiency of the least difficult of the FFA ingress into the mitochondria affects the efficiency of lipid oxidation[19,25] and contributes to their intracellular accumulation.

In the absence of optimal oxidative capacity of mitochondria, excessive FFA accumulates in this organelle, promoting ceramide synthesis, which is related to toxicity and activation of apoptosis[29]. This effect was described first to palmitate and stearate, which inhibits both the oxidation of ceramides and the activity of CPT-I, increasing intracellular concentration of ceramides and inhibiting the complex III of the electron transport chain, with the subsequent releasing of cytochrome C.

In addition, palmitate overload saturates ER membranes with phosphatidylcholine and triglycerides, increasing the calcium stores in both the reticulum and mitochondria (Fig. 3), triggering loss of the mitochondrial membrane potential and activating apoptosis[34,35]. As an additional mechanism, ceramides may assemble large channels in the mitochondrial outer

membrane, releasing proapoptotic factors. There is also a relationship between proapoptotic proteins and ceramides that modify mitochondrial membrane permeability, linking mitochondrial dysfunction and activation of apoptosis with lipotoxicity.

The increase in acyl-CoA interferes with the mitochondrial synthesis of ATP by inhibiting the electron transport chain, decreasing the mitochondrial membrane potential, and causing the oxidation of lipid molecules. The exacerbated oxidative damage impaired mitochondrial functions in adipose and muscle tissue, where the accumulation of saturated FFA in mitochondria disrupts the PI3K/Akt pathway[21,36].

The literature reports that consuming obesogenic diets for up to 8 weeks does not trigger detectable mitochondrial damage, although it does cause a significant increase in adipose tissue; however, prolonging the consumption of diets until 18 weeks represents a threshold for the appearance of mitochondrial dysfunction, with disrupted structure and function in the liver, kidneys, and muscle[37].

On the other hand, in rat models of diet-induced obesity, the organisms' adaptability has been observed. When the administration of obesogenic diets, rich in carbohydrates or fat, starts at an early age, metabolic alterations or cellular damage, such as the accumulation of fatty tissue, mitochondrial dysfunction, and insulin resistance, can be detected after a longer time of consumption of diets, compared to animals whose intake begins in adulthood. Another important finding is that mitochondrial damage usually appears after the establishment of a metabolic alteration, which occurs due to the accumulation of adipose tissue, including FFA[38].

Models of studies with obesity due to genetic manipulation in rats in combination with consumption of diets rich in fat or carbohydrates have shown the increased accumulation of fatty tissue, an elevated profile of FFA and circulating triglycerides, as well as the presence of ectopic deposits in the liver, kidney, and muscle tissue. At the mitochondrial level, morphological aberrations, among decreased expression of genes involved in mitochondrial metabolism, such as PGC1 α and other regulators of oxidative phosphorylation genes, lead to a reduction in ATP production[39,40].

ER LIPOTOXICITY

The endoplasmic reticulum (ER) is an organelle comprising a network of interconnected tubules, vesicles, and membranous sacs extending through the cytoplasm to form cristae. According to their different characteristics and functions, two substructures are identified: (1) The smooth ER consists of a network of membranes responsible for the synthesis of lipids such as phospholipids, cholesterol, and ceramides; also providing intercellular transport through vesicles, besides its functions as a calcium reservoir for the contractile mechanism. (2) The rough ER consists of elongated and stacked membranous tubules with attached ribosomes that appear as flattened cisterns, where protein synthesis and post-translational modifications occur[41]. Together, the Golgi apparatus (GA) and the ER are involved in the synthesis, transport, and distribution of proteins and lipids[42].

As the ER is responsible for the synthesis and transport of proteins and lipids, in a state of lipotoxicity, their production and assembly are altered, disrupting the proper folding of proteins. On the other hand, the accumulation of misfolded proteins activates both the stress signaling in the ER through the action of IRE, protein kinase R RS (PERK), and factor of transcription 6 (ATF6) and the increase in the expression of markers such as phosphorylated eif2A, with the activation of MAPK, activating stress and apoptosis pathways. It is important to note that membrane-associated proteins may also be affected, thus altering mechanisms for calcium transport[43,44].

Calcium homeostasis is affected by an increase in FFA; since the Ca2+ ATPase (SERCA) is inactivated in the sarcoplasmic reticulum (Fig. 3), inducing the overexpression of proteins such as glucose-regulated protein 78 and C/EBP homologous protein that, in turn, activates oxidative phosphorylation, through activation of the PERK, the ATF6 and the protein of the requirement of inositol 1, involved in the processes of apoptosis. These alterations were associated with the processes of lipotoxicity on smooth muscle and cardiac cells[45].

Another important role of the ER is the synthesis of ceramides, acylcarnitine, and diacylglycerols, which are overregulated by FFA accumulation. Ceramides have important toxicity, with implications at the level of the cell cycle, differentiation, a myriad of signaling

pathways, and apoptosis. Ceramides are classified according to the length of the FAs they contain, being more toxic as their acyl chains are long. Ceramide accumulation is one of the pathological factors linked to the development of diabetes, liver disease, and insulin resistance in muscles[26].

LIPOTOXICITY IN THE GA

The GA is a membranous organelle composed of tubules and vesicles located on the periphery of the nucleus near the ER. This organelle participates in important processes such as the synthesis, storage, and distribution of lipids and proteins.

The FFA is precursors for the production of glycolipids and LP. In addition, vesicles of the GA, such as in the rest of biological membranes, are mainly made up of phospholipids and may contain lipid rafts that function as signaling platforms to interact with their target organelles[46,47]. The profile of lipids that constitutes the lipid rafts has a profound impact on their function and could be affected under a state of lipotoxicity and oxidative stress. However, it is still an important topic for research.

The structure of GA is linked to the ER and mitochondria. The mechanism of lipotoxicity in this organelle is not well understood; however, reports indicate that the increase in ceramides in the ER increases its transit to the GA, exceeding its capacity and causing stress that, together with excessive ROS production, leads to the activation of apoptotic pathways through the activation of the transcription factor cAMP response element-binding protein 3, which increases the transcription of ADP-ribosylation factor 4, ultimately causing stress-induced apoptosis[47,48].

CONCLUSION

Lipotoxicity is a term more often used in pathology. It is mainly associated with obesity, the consumption of obesogenic diets, and related metabolic disturbances. The accumulation of FFA and other lipids induces cell damage by the misregulation of a myriad of signaling pathways.

Studies have shown that the accumulation of FFA triggers structural and functional changes in mitochondria, which mainly compromise ATP synthesis and, consequently, the whole cell function. On the other hand, the ER and GA, both involved in the synthesis and processing of lipids and proteins, also undergo alterations in their functions in response to lipid accumulation, although the related mechanisms are not well described. In all the above-mentioned pathological environments, oxidative stress, inflammation, and activation of apoptosis are implied.

Similarly, lipotoxicity, obesity, and diabetes are closely related; therefore, it is essential to clarify the underlying mechanisms linking the toxic accumulation of lipids with common human diseases such as diabetes, fatty liver, and insulin resistance to improve existing treatments or find strategies for the management and control of these diseases.

FUNDING

The author CMMA was supported by a fellowship from the National Council of Science and Technology (CONAHCYT), Mexico, to accomplish PhD studies in Doctorado en Ciencias Biomédicas program from Universidad Juárez Autónoma de Tabasco, Tabasco, Mexico, with CVU # 909241.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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