

Adiponectin: ceramidase activity and stress control of the endoplasmic reticle in obesity

Adiponectina: actividad ceramidasa y control del estrés del retículo endoplásmico en la obesidad

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Abstract

Adiponectin is a cytokine synthesized by adipocytes, which acts through receptors (AdipoR1, AdipoR2) and T-cadherin. Recently, it has been identified an endosomal protein, APPL1, that binds to AdipoRs to mediate signaling and nuclear factors of adiponectin. The expression of these receptors depends on the activation phenotype of the macrophages: classical activation (M1) suppresses the expression, and alternative activation (M2) maintains the expression of AdipoRs. Adiponectin regulates the metabolism of carbohydrates and lipids and reducing the production of hepatic glucose and the oxidation of fatty acids; it is also considered a biomarker of endothelial function due to its correlation with endothelial alterations, dyslipidemia, and atherosclerosis. There is a new protective function of Adiponectin against metabolic disorders and organic damage through T-cadherin that

facilitates the exosomal release of inadequately folded proteins, controls cellular stress, decreases ceramide levels, and maintains cellular homeostasis. Another essential function of adiponectin is to protect cells from apoptosis induced by endoplasmic reticulum stress and the reduction of the inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells as it blocks mitochondrial apoptosis through the activation of the pathway of the protein kinase signal. Adiponectin is a potential biochemical biomarker and an anti-inflammatory in metabolic disorders since it modulates the pathogenesis of overweight and diabetes mellitus type 2, thus considered key to the prognosis and therapeutic intervention of these pathologies.

Keywords: obesity, adiponectin, adiponectin receptors, ceramidas, endoplasmic reticulum stress

La adiponectina es una citocina sintetizada por los adipocitos, que actúa a través de los receptores AdipoRs (AdipoR1, AdipoR2) y T-cadherina, recientemente se ha identificado APPL1, una proteína endosomal que se une a los receptores AdipoRs, para mediar la señalización y los factores nucleares de la adiponectina. La expresión de estos receptores depende del fenotipo de activación de los macrófagos, activación clásica (M1) suprime la expresión y la activación alternativa (M2) mantiene la expresión de AdipoRs. La adiponectina regula el metabolismo de carbohidratos y lípidos, reduce la producción de glucosa hepática y la oxidación de ácidos grasos, además se considera un biomarcador de la función endotelial por su correlación con alteraciones endoteliales, dislipidemia y aterosclerosis. Existe una nueva función protectora de la adiponectina contra los trastornos metabólicos y el daño orgánico, a través de T-cadherina facilitando la liberación exosómica de proteínas plegadas inadecuadamente, controlando el estrés celular, disminuyendo los niveles de ceramida y manteniendo la homeostasis celular. Otra función importante de la adiponectina es la protección de las células de la apoptosis inducida por el estrés del retículo endoplásmico y la reducción de la inflamación en adipocitos, hepatocitos, células endoteliales y células beta pancreáticas bloqueando la apoptosis mitocondrial a través de la activación de la vía de la señal de la proteína quinasa. La adiponectina es un potencial biomarcador bioquímico y antiinflamatorio en los trastornos metabólicos, ya que modula la patogénesis del sobrepeso y la diabetes mellitus tipo 2, considerándose clave para el pronóstico e intervención terapéutica de estas patologías.

Palabras clave: obesidad, adiponectina, receptores de adiponectina, ceramidas estrés del retículo endoplásmico.

Adiponectin is a protein hormone synthesized by mature adipocytes. It is also known as adipocyte complement-related protein of 30-kDa (Acrp30), because its homology with the C1q complement system factor (a subcomponent of the complement 1)¹⁻³. Adiponectin is an hormone adipokine with the highest expression in adipose tissue. Its synthesis redominates in subcutaneous white adipose tissue, and it is a potential biochemical and anti-inflammatory biomarker in metabolic disorders. Adiponectin levels are negatively correlated with fat accumulation⁴⁻⁷.

Adiponectin is a protein of 244 amino acids (247 amino acids in the mouse), whose primary structure includes four distinct regions: a signal peptide, a variable region, a collagen-like domain and a globular domain. The primary structure is similar to C1q since, the basic structural unit of adiponectin is a strongly associated trimer, formed by the conjunction of three units into the globular domain. In turn, these trimers can be associated in groups of 4 to 6 through the collagen domain, forming highly ordered structures or oligomers⁸⁻¹⁰. Recently, adiponectin production has been demonstrated in cells other than adipocytes such as osteoblasts, hepatocytes, myocytes, epithelial cells, and placental tissue¹¹⁻¹⁴.

Adiponectin is synthesized as a 28-30 kDa monomer. After post-translational modifications, the adiponectin is assembled in oligomers that control its biological activity. These oligomers are found in three different molecular weights forms: low molecular weight trimer, medium molecular weight hexamer, and high molecular weight multimer^{15,16}.

Adiponectin represents 0.01% of the total serum proteins. Its concentration in plasma (5-30 µg/ml), which depends on gender, as males show lower levels compared to women¹⁷. Regarding to differences in androgen concentrations, men with hypogonadism present higher levels of adiponectin compared to men with eugonadal status^{18,19}.

Genetic factors determine around 39-70% of the variability in adiponectin levels. The primary genetic determinant of adiponectin is the ADIPOQ (Adiponectin, C1Q And Collagen Domain Containing), which is located in chromosome 3q27; it contains three exons with the start codon in exon 2 and the stop codon in exon 3 and is related to susceptibility to type 2 diabetes and metabolic syndrome²⁰⁻²². Approximately 15.8 kb and three exons form adipose most abundant transcript 1 gene (APM1), several polymorphisms of this gene have been associated with adiponectin levels and have been linked to susceptibility to metabolic syndrome, type 2 diabetes,

and cardiovascular disease²⁰⁻²³.

The ADIPOQ gene negatively correlates with fasting glucose results and insulin sensitivity. Epigenetic modifications such as methylation in the promoter region of the DNA adiponectin gene may result in repressed transcriptional activity with low levels of adiponectin in plasma and a significant association with lower levels of adiponectin in patients with type 2 diabetes^{24,25}.

Adiponectin receptors

Adiponectin acts through two receptors: AdipoR1 and AdipoR2 in the regulation of energy homeostasis and anti-inflammatory responses. AdipoR1 is the most abundant form in skeletal muscle, whereas AdipoR2 is the most abundant form in the liver²⁶. AdipoR1 and AdipoR2 have seven transmembrane domains, which are homologous with the G protein-coupled receptors. The N-terminal is located in the cytoplasmic region of the cell while the C-terminal end is external. Besides, a zinc ion is found in the transmembrane domains, which plays a vital role in the stimulation of adenosine monophosphate-activated kinase (AMP-K) that allows the action of adiponectin. These characteristics of adiponectin receptors are being used for the development of AdipoR agonists, which may be included in the future treatment of obesity and type 2 diabetes²⁷, since adiponectin modulates the pathogenesis of overweight and diabetes mellitus type 2^{28,29}.

Adiponectin acts through AMP-K, a critical regulatory kinase of glucose and lipid metabolism, and by the activation of the peroxisome proliferator-activated gamma receptor (PPAR- γ), which inhibits gluconeogenesis and stimulates glucose uptake^{30,31}. Recent research has identified an adiponectin receptor adapter protein named Adaptor Protein, Phosphotyrosine Interacting With PH Domain And Leucine Zipper 1 (APPL1), that is an adapter protein with a Pleckstrin homology domain and a phosphotyrosine binding domain. This is an endosomal protein that binds to the AdipoR1 and AdipoR2 to positively mediate the signaling and nuclear transcription factors of adiponectin³¹.

APPL1 has three functional domains, which play essential role in the intracellular signal transduction of receptors, and it is expressed in insulin target tissues: skeletal muscles, liver, and adipose tissue. APPL1 interacts directly with adiponectin receptors mediating the actions of adiponectin in the regulation of metabolic energy and insulin sensitivity; adiponectin signaling through APPL1 is necessary to exert its anti-inflammatory as well as cytoprotective effects on endothelial cells, reducing the formation of neointima through the inhibition of smooth muscle proliferation³². The suppression of APPL1 expression in skeletal myoblast culture cells decreases adiponectin-induced glucose uptake and translocation of GLUT4 (glucose transporters 4), while its over-expression enhances the stimulatory actions of adiponec-

tin in the glucose metabolism³³.

In addition to the effects on glucose metabolism, adiponectin acts as a cardioprotective molecule, by suppressing the expression of interleukin-8 (IL-8) in human aortic endothelium cells stimulated by tumor necrosis factor Alfa (TNF α)³⁴. Also, adiponectin reduces the expression of adhesion molecules in endothelial cells, prevents the binding of monocytes, stimulates the production of interleukin-10 (IL-10), and suppresses the expression of proinflammatory mediators in monocytes and macrophages, such as TNF α and the chemo-attractant protein of monocytes 1 (MCP-1) in various cell types (macrophages derived from human monocytes -cells of the stromal vascular fraction of human subcutaneous fat pads). Furthermore, Adiponectin controls the expression of the vascular adhesion molecule-1 (VCAM-1) and TNF α in atherosclerotic lesions^{35,36}. It also prevents the transformation of the macrophage into foam cells by inhibiting the expression of the scavenger receptor and coenzyme-A: cholesterol acyltransferase, responsible for the storage of lipids and the development of atherosclerotic plaques. Adiponectin performs an anti-apoptosis activity in cardiac ventricular myocytes and a protective effect on glomerular podocytes^{37,38}. Low serum content of adiponectin is considered a biomarker of endothelial function due to its correlation with endothelial alterations, dyslipidemia, and atherosclerosis³⁹. Adiponectin suppresses the activation of M1 macrophages (classically activated macrophages) that produce proinflammatory cytokines such as TNF α , the macrophage migration inhibiting factor (MIF), interleukin 6 (IL-6), the monocyte chemotactic protein-1 (MCP-1) and promotes the proliferation of M2 macrophages (alternatively activated macrophages) that secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF- β). Adiponectin deficiency leads to a classical activated M1 macrophage phenotype, while recombinant adiponectin acts promoting an anti-inflammatory phenotype in macrophages^{40,41}. The macrophage polarization phenotype regulates the expression of adiponectin receptors (AdipoR), suppressing the expression of AdipoRs, and in M2 macrophages maintains the expression of those receptors^{42,43}.

Since the circulating levels of adiponectin, particularly the high-weight form, are elevated in mice with T-cadherin deficiency, T-cadherin has been postulated as a binding protein for adiponectin, which plays a crucial role in its signaling^{44,45}. T-cadherin has also been identified as a potent receptor for hexamers and high molecular weight oligomers of adiponectin⁴⁶; this protein is highly expressed in the vasculature and to a lesser extent, in the muscle. However, the liver, a significant target for adiponectin, does not show high expression of that protein of T-cadherin expression⁴⁷.

The active forms of multimeric and hexameric adiponectin, accumulate in tissues such as heart, vascular endothelium and skeletal muscles through

the interaction with T-cadherin. Studies in mice with T-cadherin deficiency have shown that the association of adiponectin and T-cadherin plays a protective vascular role suppressing atherosclerotic plaque formation and neointimal proliferation⁴⁸; therefore, demonstrating that T-cadherin is essential for cardiovascular protection mediated by adiponectin⁴⁹.

Recent research in mice vascular tissue helped to establish a new function for adiponectin mediated by T-cadherin in the regulation of exosomal release. The importance of this function is based on the fact that exosomes are vesicles that intervene in cell-to-cell communication under normal and pathological conditions by transferring active proteins, mRNA and small non-coding RNAs. They also serve as an alternative way for the elimination of lysosomes of inadequately folded proteins; this exosomal release controls cell stress and maintains homeostasis by exporting various unnecessary or harmful materials. In this regard, adiponectin decreases ceramide levels establishing a protective function, since the intracellular accumulation of ceramides is implicated in the pathogenesis of insulin resistance and endothelial dysfunction and leading to the creation of new therapeutic strategies⁵⁰.

Ceramidase activity of adiponectin

Adiponectin induces ceramidase activity through its receptors resulting in the hydrolysis of ceramide to form sphingosine and free fatty acid. Sphingosine produced in this reaction is further phosphorylated by sphingosine kinase to produce sphingosine 1-phosphate (S1P). This molecule functions as an essential signaling molecule in several different cellular processes. The ceramidase activity induced by activation of AdipoR1 and AdipoR2 determines the adiponectin activity in the metabolism of sphingolipids⁵¹.

In transgenic mice with overexpression of adiponectin receptor isoform (AdipoR1, AdipoR2) was demonstrated that adiponectin could induce ceramidase activity, which produced increment in hepatic sphingosine-1-phosphate levels and improves hepatic steatosis in adult mice with diet-induced obesity⁵².

The degradation of ceramide in the liver by adiponectin is a local phenomenon leading to decreased hepatic lipid absorption and expression of lipogenic. In addition, the effects of adiponectin mediated through AdipoR1 and AdipoR2 within adipocytes, contribute to greater local lipid purification to protect adipocytes from excess exposure to lipids⁵²⁻⁵³.

The receptors of adiponectin decrease the length of the chain of ceramides in obesity, suggesting a possible novel therapeutic objective, since ceramide metabolism influences predominantly in the sensitizing effects to insulin by adiponectin in the liver and adipose tissue. In other words, overexpression of AdipoR1 and AdipoR2

increases the activity of ceramidase in visceral adipose tissue. When sphingosine kinase phosphorylates Sphingosine, it produces sphingosine 1-phosphate (S1P), which it acts as a signaling molecule⁵⁴. Other groups have shown that overexpression of S1P avoids the accumulation of ceramide and improves muscle insulin resistance in mice fed with a high-fat diet⁵⁵. Overexpression of S1P acid ceramides seems to have the same effect on adipose tissue preventing hepatic steatosis and systemic insulin resistance⁵⁶.

Ceramides are a critical factor in understanding the regulation of weight gain and intolerance to glucose, as they increase during obesity and promote insulin resistance. Ceramides are synthesized by the enzyme ceramide synthetase (CerS)^{56,57}. Overexpression of CerS correlates with insulin resistance and CerS deficient mice are protected from high-fat diet induced obesity and glucose intolerance⁵⁸.

The accumulation of ceramide in skeletal muscles is associated with altered insulin sensitivity, so the concentration of ceramide decreased by adiponectin may be a mechanism to increase insulin sensitivity in skeletal muscle⁵⁹.

Adiponectin through the activity of ceramidase can avoid apoptosis. It has been considered that the reducing activity of ceramide is an important mechanism of adiponectin to fight metabolic diseases and protect against organ damage⁶⁰. This finding was supported by the induction of AdipoRs overexpression in the liver, which was accompanied by better glucose metabolism. The crystalline structures of AdipoR2 sphingosine have provided additional support for the concept of ceramides in the action of adiponectin⁶¹.

T-cadherin can regulate the cellular content of ceramide in response to the multimeric adiponectin of high molecular weight, as an additional mechanism for the adiponectin/AdipoR axis that improves the biogenesis and secretion of exosome leading to decrease of cellular ceramides⁶². Adiponectin actions in the metabolism of carbohydrates and lipids in adipose tissue, adiponectin increases basal glucose uptake and glucose uptake through AMP-activated protein kinase (AMPK) activation, which plays a vital role in the regulation of cellular lipid metabolism and systemic adipose deposits regulating lipolysis, fatty acid transport and β -oxidation⁶³.

Adiponectin not only inhibits lipolysis, but also preferentially promotes fat storage in adipocytes of subcutaneous adipose tissue, instead of visceral or ectopic adipose tissue in the liver and avoids subcutaneous morphological alterations of fat (adipocytes hypertrophy, degenerative changes, infiltration of macrophages, and necrosis of adipocytes). Consequently, circulating levels of adiponectin and infiltration of macrophages in adipose tissue are among the most potent clinical predictors of insulin sensitivity in obese individuals^{64,65}.

Rabbit blastocysts cultured *in vitro* with adiponectin, showed that the insulin-like growth factor-I receptor (IGF1R) and insulin receptor were up-regulated after incubation with adiponectin. These results imply an increase in the availability and sensitivity of insulin, due to a more significant expression of the receptor as a response to adiponectin⁶⁶.

Anti-inflammatory actions of adiponectin could contribute to the “metabolically healthy obese,” a subpopulation of obese individuals with normal insulin sensitivity since there is information regarding to high level of adiponectin in obese women with a profile standard metabolic⁶⁷.

Adiponectin regulates the metabolism of carbohydrates and lipids, reduces the production of hepatic glucose and improves the oxidation of fatty acids in skeletal muscle. Unlike most other adipokines, circulating adiponectin levels are typically reduced in obesity, type 2 diabetes, and associated conditions. Besides, mice lacking adiponectin or humans with polymorphisms that compromise adiponectin production a metabolic dysfunction and type 2 diabetes. Therefore, therapeutic strategies to reverse hypoadiponectinemia are attractive⁶⁸. The growing evidence indicates that resistance to adiponectin also contributes to the development of metabolic and cardiovascular diseases⁶⁹.

Adiponectin is a well-described anti-inflammatory adipokine very abundant in serum. Previous reports have found that adiponectin deficiency promotes cardiovascular and metabolic dysfunction in murine models while its overexpression is protective⁷⁰. In addition to the circulatory system, skeletal muscle is a peripheral target for adiponectin to exert its anti-inflammatory metabolic effects by improving the utilization of glucose and the oxidation of fatty acids in myocytes and by increasing the uptake of glucose in skeletal muscle through the translocation of glucose transporter 4 (GLUT-4). AdipoR1 is the most abundant adiponectin receptor in skeletal muscle, and globular adiponectin has a high affinity to AdipoR1; for this reason, most of the effects of adiponectin in skeletal muscle are carried out by the globular form⁷¹.

Recent research in obese mice demonstrated that adiponectin improves the oxidation of fatty acids in muscle cells by stimulating the transcriptional activity of PPAR γ (peroxisome proliferator-activated gamma receptor), a nuclear receptor that modulates the transcription of multiple genes. This receptor intervenes in the effect of adiponectin on glucose and the metabolism of fatty acids in skeletal muscle to decrease the content of muscular lipids as a controlling mechanism of insulin resistance⁷².

Adiponectin reduces endoplasmic reticulum stress

The endoplasmic reticulum is an organelle that participates in the storage of intracellular calcium, in assembly, folding and post-translational modifications of proteins that must then be adequately folded through special proteins called chaperones⁷³.

When endoplasmic reticulum homeostasis is altered, three events known as the stress of the reticulum occur: accumulation of misfolded proteins in the lumen, decrease of protein transport towards the Golgi apparatus and depletion of calcium. This stress triggers a repair process called “unfolded protein responses (UPR)”⁷⁴.

In order to protect the cell and restore cellular homeostasis. The signals capable of activating reticule stress include calcium availability, presence of pathogens or alterations in nutrients. In addition, the endoplasmic reticulum is a sensor in the detection of cellular and metabolic alterations⁷⁵.

The reticulum stress produces an inflammatory response through the activation of NF- κ B (nuclear factor enhancer of the light chains kappa of activated B cells) and translocation to the nucleus, promoting the expression of a variety of genes involved in the expression of inflammatory cytokines such as TNF- α , IL-1 β and IL6, which induce lipogenesis, low-grade inflammatory status in obesity, insulin resistance and hepatic steatosis⁷⁶. In addition to the inflammatory process, the interaction between the endoplasmic reticulum and the mitochondria, plays a vital role in metabolic homeostasis and oxidative stress, in the case that those adaptation mechanisms were insufficient to restore the activity of the endoplasmic reticulum, and the cell suffers apoptosis⁷⁷.

Adiponectin protects cells from endoplasmic reticulum stress-induced apoptosis and reduces inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells. These actions block mitochondrial apoptosis through the activation of protein kinases pathway signal and the suppression of transcription activating transcription factor-2 (ATF2), which plays a crucial role in the regulation of apoptosis and lipogenesis^{76,77}. Adiponectin improves the cellular availability of Ca²⁺ and eliminates the deposit of free fatty acids induced by endoplasmic reticulum stress in adipocytes, decreases mitochondrial apoptosis and improves the cellular activity of the reticulum⁷⁸⁻⁸⁰.

AdipoR1 and AdipoR2 receptors have seven transmembrane domains, which are homologous with the G protein-coupled receptors, a zinc ion that plays a fundamental role in the stimulation of the adenosine monophosphate-activated kinase, which allows the action of adiponectin. These characteristics of adiponectin receptors are being used for the development of AdipoR agonists, which may be included for the treatment of obesity and type 2 diabetes in the future since adiponectin modulates the pathogenesis of overweight and diabetes mellitus type 2, and it is considered a prognostic marker and a therapeutic intervention.

Recent research has helped to identify an adaptor protein of adiponectin receptors called APPL1, which binds to AdipoR1 and AdipoR2, to positively mediate the signaling and nuclear factors of adiponectin and the actions of adiponectin in the regulation of energy metabolism and insulin sensitivity. Adiponectin signaling through APPL1 is necessary to exert its anti-inflammatory and cytoprotective effects on endothelial cells so reducing the formation of arterial neointima via a dependent inhibition of the oligomerization of smooth muscle proliferation.

The ceramidase activity of AdipoR1 and AdipoR2 determines the hydrolysis of ceramide to form sphingosine 1-phosphate, which acts as an adiponectin signaling molecule. The latter allows lipid clearance by protecting adipocytes from their excess in visceral adipose tissue and decreases the absorption of hepatic lipids and the expression of lipogenic genes. This suggests that it is a possible novel therapeutic objective as the metabolism of ceramide predominantly influences the insulin-sensitizing effects of adiponectin in the liver and adipose tissue.

Recent research using vascular tissue of mice established a new function for adiponectin through T-cadherin in the exosomal release to control cell stress and maintain homeostasis by exporting several unnecessary or harmful materials. This adiponectin protective function against metabolic disorders and organ damage can lead to the creation of new therapeutic strategies.

Adiponectin protects cells from endoplasmic reticulum stress-induced apoptosis and reduces inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells by blocking mitochondrial apoptosis through the activation of the signal pathway of the protein kinases and suppression of activating transcription factor ATF2, which has a vital role in the regulation of apoptosis and lipogenesis.

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References

1. Abou-Samra M, Selvais CM, Dubuisson N, Brichard SM. Adiponectin and Its Mimics on Skeletal Muscle: Insulin Sensitizers, Fat Burners, Exercise Mimickers, Muscling Pills ... or Everything Together? *Int J Mol Sci.* 2020; 21(7):2620. doi: 10.3390/ijms21072620.
2. Achari AE, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int J Mol Sci.* 2017 Jun 21; 18(6):1321. doi: 10.3390/ijms18061321.
3. Adams CJ, Kopp MC, Larburu N, Nowak PR, Ali MMU. Structure and Molecular Mechanism of ER Stress Signaling by the Unfolded Protein Response Signal Activator IRE1. *Front Mol Biosci.* 2019; 6:11. doi: 10.3389/fmolb.2019.00011.
4. Alimi M, Goodarzi MT, Nekoei M. Adiponectin gene polymorphisms and risk of type 2 diabetes: an updated evidence for meta-analysis. *Diabetol Metab Syndr.* 2021;13(1):133. doi: 10.1186/s13098-021-00749-x.
5. Almabouada F, Diaz-Ruiz A, Rabanal-Ruiz Y, Peinado JR, Vázquez-Martínez R, Malagón MM. Adiponectin receptors form homomers and heteromers exhibiting distinct ligand binding and intracellular signaling properties. *J Biol Chem.* 2013;288(5):3112-25. doi: 10.1074/jbc.M112.404624.
6. Bhattarai KR, Riaz TA, Kim HR, Chae HJ. The aftermath of the interplay between the endoplasmic reticulum stress response and redox signaling. *Exp Mol Med.* 2021;53(2):151-167. doi: 10.1038/s12276-021-00560-8.
7. Camastra S, Ferrannini E. Role of anatomical location, cellular phenotype and perfusion of adipose tissue in intermediary metabolism: A narrative review. *Rev Endocr Metab Disord.* 2022;23(1):43-50. doi: 10.1007/s11154-021-09708-3.
8. Camino T, Lago-Baameiro N, Pardo M. Extracellular Vesicles as Carriers of Adipokines and Their Role in Obesity. *Biomedicines.* 2023;11(2):422. doi: 10.3390/biomedicines11020422.
9. Cavaliere G, Cimmino F, Trinchese G, Catapano A, Petrella L, D'Angelo M, Lucchin L, Mollica MP. From Obesity-Induced Low-Grade Inflammation to Lipotoxicity and Mitochondrial Dysfunction: Altered Multi-Crosstalk between Adipose Tissue and Metabolically Active Organs. *Antioxidants (Basel).* 2023;12(6):1172. doi: 10.3390/antiox12061172.
10. Chakarov S, Blériot C, Ginhoux F. Role of adipose tissue macrophages in obesity-related disorders. *J Exp Med.* 2022; 219(7):e20211948. doi: 10.1084/jem.20211948.
11. Choi HM, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. *Int J Mol Sci.* 2020 Feb 12;21(4):1219. doi: 10.3390/ijms21041219.
12. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, Martín-Rodríguez A, Martínez-Guardado I, Navarro-Jiménez E, Laborde-Cárdenas CC, Tornero-Aguilera JF. The Role of Adipokines in Health and Disease. *Biomedicines.* 2023;11(5):1290. doi:

13. Cobos-Palacios L, Ruiz-Moreno MI, Vilches-Perez A, Vargas-Candela A, Muñoz-Úbeda M, Benítez Porres J, Navarro-Sanz A, Lopez-Carmona MD, Sanz-Canovas J, Perez-Belmonte LM, Mancebo-Sevilla JJ, Gomez-Huelgas R, Bernal-Lopez MR. Metabolically healthy obesity: Inflammatory biomarkers and adipokines in elderly population. *PLoS One*. 2022;17(6):e0265362. doi: 10.1371/journal.pone.0265362.
14. Correnti J, Lin C, Brettschneider J, Kuriakose A, Jeon S, Scorletti E, Oranu A, McIver-Jenkins D, Kaneza I, Buyco D, Saiman Y, Furth EE, Argemi J, Bataller R, Holland WL, Carr RM. Liver-specific ceramide reduction alleviates steatosis and insulin resistance in alcohol-fed mice. *J Lipid Res*. 2020;61(7):983-994. doi: 10.1194/jlr.RA119000446.
15. Dalamaga M, Diakopoulos KN, Mantzoros CS. The Role of Adiponectin in Cancer: A Review of Current Evidence. *Endocrine Reviews*. 2012;33(4):547-94. doi:10.1210/er.2011-1015.
16. Estienne A, Bongrani A, Reverchon M, Ramé C, Ducluzeau PH, Froment P, Dupont J. Involvement of Novel Adipokines, Chemerin, Visfatin, Resistin and Apelin in Reproductive Functions in Normal and Pathological Conditions in Humans and Animal Models. *Int J Mol Sci*. 2019;20(18):4431. doi: 10.3390/ijms20184431.
17. Fayyaz S, Japtok L, Kleuser B. Divergent role of sphingosine 1-phosphate on insulin resistance. *Cell Physiol Biochem*. 2014;34(1):134-47. doi: 10.1159/000362990.
18. Field BC, Gordillo R, Scherer PE. The Role of Ceramides in Diabetes and Cardiovascular Disease Regulation of Ceramides by Adipokines. *Front Endocrinol (Lausanne)*. 2020;11:569250. doi: 10.3389/fendo.2020.569250.
19. Fukuda S, Kita S, Obata Y, Fujishima Y, Nagao H, Masuda S, Tanaka Y, Nishizawa H, Funahashi T, Takagi J, Maeda N, Shimomura I. The unique prodomain of T-cadherin plays a key role in adiponectin binding with the essential extracellular cadherin repeats 1 and 2. *J Biol Chem*. 2017 ;292(19):7840-7849. doi: 10.1074/jbc.M117.780734.
20. García Robles Mayra Judith, Camarillo Alba Jaqueline, Valenzuela Gurrola Manuel de Jesús, López Jesús Adrián, Ramírez de los Santos Saúl. ADIPQ gene polymorphism rs266729 (-11377 C>G) and metabolic syndrome risk in a Mexican population of western Mexico. *Nutr. Hosp.* [Internet]. 2021; 38(1):67-72. Disponible en: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212-16112021000100067&lng=es.
21. Ghoshal K, Bhattacharyya M. Adiponectin: Probe of the molecular paradigm associating diabetes and obesity. *World J Diabetes*. 2015 Feb 15;6(1):151-66. doi: 10.4239/wjd.v6.i1.151.
22. Green CD, Maceyka M, Cowart LA, Spiegel S. Sphingolipids in metabolic disease: The good, the bad, and the unknown. *Cell Metab*. 2021;33(7):1293-1306. doi: 10.1016/j.cmet.2021.06.006.
23. Hajduch E, Lachkar F, Ferré P, Fougelle F. Roles of Ceramides in Non-Alcoholic Fatty Liver Disease. *J Clin Med*. 2021;10(4):792. doi: 10.3390/jcm10040792.
24. Han W, Yang S, Xiao H, Wang M, Ye J, Cao L, Sun G. Role of Adiponectin in Cardiovascular Diseases Related to Glucose and Lipid Metabolism Disorders. *Int J Mol Sci*. 2022;23(24):15627. doi: 10.3390/ijms232415627.
25. Holland WL, Xia JY, Johnson JA, Sun K, Pearson MJ, Sharma AX, Quittner-Strom E, Tippetts TS, Gordillo R, Scherer PE. Inducible overexpression of adiponectin receptors highlight the roles of adiponectin-induced ceramidase signaling in lipid and glucose homeostasis. *Mol Metab*. 2017;6(3):267-275. doi: 10.1016/j.molmet.2017.01.002
26. Hong X, Zhang X, You L, Li F, Lian H, Wang J, Mao N, Ren M, Li Y, Wang C, Sun K. Association between adiponectin and newly diagnosed type 2 diabetes in population with the clustering of obesity, dyslipidaemia and hypertension: a cross-sectional study. *BMJ Open*. 2023;13(2):e060377. doi: 10.1136/bmjopen-2021-060377.
27. Howlader M, Sultana MI, Akter F, Hossain MM. Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. *Heliyon*. 2021;7(8):e07851. doi: 10.1016/j.heliyon.2021.e07851.
28. Imierska M, Zabielski P, Roszczyc-Owsiejczuk K, Sokołowska E, Pogodzińska K, Kojta I, Błachnio-Zabielska A. Serine Palmitoyl-transferase Gene Silencing Prevents Ceramide Accumulation and Insulin Resistance in Muscles in Mice Fed a High-Fat Diet. *Cells*. 2022;11(7):1123. doi: 10.3390/cells11071123.
29. Ishida M, Tatsumi K, Okumoto K, Kaji H. Adipose Tissue-Derived Stem Cell Sheet Improves Glucose Metabolism in Obese Mice. *Stem Cells Dev*. 2020;29(8):488-497. doi: 10.1089/scd.2019.0250.
30. Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T. Adiponectin/AdipoR Research and Its Implications for Lifestyle-Related Diseases. *Front Cardiovasc Med*. 2019 14;6:116. doi: 10.3389/fcvm.2019.00116.
31. Khoramipour K, Chamari K, Hekmatikar AA, Ziyaiyan A, Taherkhani S, Elguindy NM, Bragazzi NL. Adiponectin: Structure, Physiological Functions, Role in Diseases, and Effects of Nutrition. *Nutrients*. 2021;13(4):1180. doi: 10.3390/nu13041180.
32. Kiernan K, MacIver NJ. The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. *Front Immunol*. 2021;11:622468. doi: 10.3389/fimmu.2020.622468.
33. Kirichenko TV, Markina YV, Bogatyreva AI, Tolstik TV, Varaeva YR, Starodubova AV. The Role of Adipokines in Inflammatory Mechanisms of Obesity. *Int J Mol Sci*. 2022;23(23):14982. doi: 10.3390/ijms232314982.
34. Lei X, Qiu S, Yang G, Wu Q. Adiponectin and metabolic cardiovascular diseases: Therapeutic opportunities and challenges. *Genes Dis*. 2022;10(4):1525-1536. doi: 10.1016/j.gendis.2022.10.018.
35. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal Transduct Target Ther*. 2022;7(1):216. doi: 10.1038/s41392-022-01073-0.
36. Li WH. Targeting Ceramides and Adiponectin Receptors in the Islet of Langerhans for Treating Diabetes. *Molecules*. 2022 ;27(18):6117. doi: 10.3390/molecules27186117.
37. Li X, Ren Y, Chang K, Wu W, Griffiths HR, Lu S, Gao D. Adipose tissue macrophages as potential targets for obesity and metabolic diseases. *Front Immunol*. 2023;14:1153915. doi: 10.3389/fimmu.2023.1153915.
38. Liang W, Qi Y, Yi H, Mao C, Meng Q, Wang H, Zheng C. The Roles of Adipose Tissue Macrophages in Human Disease. *Front Immunol*. 2022 Jun 9;13:908749. doi: 10.3389/fimmu.2022.908749.
39. Liu Y, Vu V, Sweeney G. Examining the Potential of Developing and Implementing Use of Adiponectin-Targeted Therapeutics for Metabolic and Cardiovascular Diseases. *Front Endocrinol (Lausanne)*. 2019;10:842. doi: 10.3389/fendo.2019.00842.
40. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, Beguinot F, Miele C. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. *Int J Mol Sci*. 2019;20(9):2358. doi: 10.3390/ijms20092358.

41. Luo L, Liu M. Adipose tissue in control of metabolism. *J Endocrinol.* 2016;231(3):R77-R99. doi: 10.1530/JOE-16-0211.
42. Mahdinia E, Shokri N, Taheri AT, Asgharzadeh S, Elahimanesh M, Najafi M. Cellular crosstalk in atherosclerotic plaque microenvironment. *Cell Commun Signal.* 2023;21(1):125. doi: 10.1186/s12964-023-01153-w.
43. Mahmoud AM. An Overview of Epigenetics in Obesity: The Role of Lifestyle and Therapeutic Interventions. *Int J Mol Sci.* 2022 Jan 25;23(3):1341. doi: 10.3390/ijms23031341.
44. McLaughlin T, Medina A, Perkins J, Yera M, Wang JJ, Zhang SX. Cellular stress signaling and the unfolded protein response in retinal degeneration: mechanisms and therapeutic implications. *Mol Neurodegener.* 2022;17(1):25. doi: 10.1186/s13024-022-00528-w.
45. Molina-Vega M, Muñoz-Garach A, Damas-Fuentes M, Fernández-García JC, Tinahones FJ. Secondary male hypogonadism: A prevalent but overlooked comorbidity of obesity. *Asian J Androl.* 2018;20(6):531-538. doi: 10.4103/aja.aja_44_18.
46. Moura J, Madureira P, Leal EC, Fonseca AC, Carvalho E. Immune aging in diabetes and its implications in wound healing. *Clin Immunol.* 2019;200:43-54. doi: 10.1016/j.clim.2019.02.002. Epub 2019 Feb 5
47. Nguyen TMD. Adiponectin: Role in Physiology and Pathophysiology. *Int J Prev Med.* 2020;11:136. doi: 10.4103/ijpvm.IJPVM_193_20.
48. Obata Y, Kita S, Koyama Y, Fukuda S, Takeda H, Takahashi M, Fujishima Y, Nagao H, Masuda S, Tanaka Y, Nakamura Y, Nishizawa H, Funahashi T, Ranscht B, Izumi Y, Bamba T, Fukusaki E, Hanayama R, Shimada S, Maeda N, Shimomura I. Adiponectin/T-cadherin system enhances exosome biogenesis and decreases cellular ceramides by exosomal release. *JCI Insight.* 2018;3(8):e99680. doi: 10.1172/jci.insight.99680.
49. Orecchioni M, Ghosheh Y, Pramod AB, Ley K. Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages. *Front Immunol.* 2019;10:1084. doi: 10.3389/fimmu.2019.01084.
50. Ouyang Z, Zhong J, Shen J, Zeng Y. The cell origins of foam cell and lipid metabolism regulated by mechanical stress in atherosclerosis. *Front Physiol.* 2023;14:1179828. doi: 10.3389/fphys.2023.1179828.
51. Parida S, Siddharth S, Sharma D. Adiponectin, Obesity, and Cancer: Clash of the Bigwigs in Health and Disease. *Int J Mol Sci.* 2019;20(10):2519. doi: 10.3390/ijms20102519.
52. Park CY, Lee SK, Kim J, Kim D, Choe H, Jeong JH, Choi KC, Park HS, Han SN, Jang YJ. Endoplasmic reticulum stress increases LECT2 expression via ATF4. *Biochem Biophys Res Commun.* 2021;585:169-176. doi: 10.1016/j.bbrc.2021.11.038.
53. Perrotta F, Nigro E, Mollica M, Costigliola A, D'Agnano V, Daniele A, Bianco A, Guerra G. Pulmonary Hypertension and Obesity: Focus on Adiponectin. *Int J Mol Sci.* 2019 Feb 20;20(4):912. doi: 10.3390/ijms20040912.
54. Pham DV, Nguyen TK, Park PH. Adipokines at the crossroads of obesity and mesenchymal stem cell therapy. *Exp Mol Med.* 2023;55(2):313-324. doi: 10.1038/s12276-023-00940-2.
55. Pilon M. Paradigm shift: the primary function of the "Adiponectin Receptors" is to regulate cell membrane composition. *Lipids Health Dis.* 2021;20(1):43. doi: 10.1186/s12944-021-01468-y.
56. Polito R, Monda V, Nigro E, Messina A, Di Maio G, Giuliano MT, Orrù S, Imperlini E, Calcagno G, Mosca L, Mollica MP, Trinchesi G, Scarinci A, Sessa F, Salerno M, Marsala G, Buono P, Mancini A, Monda M, Daniele A, Messina G. The Important Role of Adiponectin and Orexin-A, Two Key Proteins Improving Healthy Status: Focus on Physical Activity. *Front Physiol.* 2020;11:356. doi: 10.3389/fphys.2020.00356
57. Qiu W, Wu H, Hu Z, Wu X, Tu M, Fang F, Zhu X, Liu Y, Lian J, Valverde P, Van Dyke T, Steffensen B, Dong LQ, Tu Q, Zhou X, Chen J. Identification and characterization of a novel adiponectin receptor agonist adipo anti-inflammation agonist and its anti-inflammatory effects in vitro and in vivo. *Br J Pharmacol.* 2021;178(2):280-297. doi: 10.1111/bph.15277. Epub 2020 Dec 18.
58. Qu J, Zou T, Lin Z. The Roles of the Ubiquitin-Proteasome System in the Endoplasmic Reticulum Stress Pathway. *Int J Mol Sci.* 2021;22(4):1526. doi: 10.3390/ijms22041526.
59. Ramos-Ramírez P, Malmhäll C, Tliba O, Rådinger M, Bossios A. Adiponectin/AdipoR1 Axis Promotes IL-10 Release by Human Regulatory T Cells. *Front Immunol.* 2021;12:677550. doi: 10.3389/fimmu.2021.677550.
60. Reibe-Pal S, Febbraio MA. Adiponectin serenades ceramidase to improve metabolism. *Mol Metab.* 2017 Feb 1;6(3):233-235. doi: 10.1016/j.molmet.2017.01.011.
61. Ren Y, Zhao H, Yin C, Lan X, Wu L, Du X, Griffiths HR, Gao D. Adipokines, Hepatokines and Myokines: Focus on Their Role and Molecular Mechanisms in Adipose Tissue Inflammation. *Front Endocrinol (Lausanne).* 2022;13:873699. doi: 10.3389/fendo.2022.873699.
62. Roy B, Palaniyandi SS. Tissue-specific role and associated downstream signaling pathways of adiponectin. *Cell Biosci.* 2021;11(1):77. doi: 10.1186/s13578-021-00587-4.
63. Roy PK, Islam J, Lalhlenmawia H. Prospects of potential adipokines as therapeutic agents in obesity-linked atherogenic dyslipidemia and insulin resistance. *Egypt Heart J.* 2023;75(1):24. doi: 10.1186/s43044-023-00352-7.
64. Rubina KA, Semina EV, Kalinina NI, Sysoeva VY, Balatskiy AV, Tkachuk VA. Revisiting the multiple roles of T-cadherin in health and disease. *Eur J Cell Biol.* 2021 Sep-Nov;100(7-8):151183. doi: 10.1016/j.ejcb.2021.151183.
65. Ryu J, Loza CA, Xu H, Zhou M, Hadley JT, Wu J, You H, Wang H, Yang J, Bai J, Liu F, Bialowas C, Dong LQ. Potential Roles of Adiponectin Isoforms in Human Obesity with Delayed Wound Healing. *Cells.* 2019;8(10):1134. doi: 10.3390/cells8101134.
66. Schindler M, Pendzialek M, Grybel KJ, Seeling T, Gürke J, Fischer B, Navarrete Santos A. Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocysts. *Hum Reprod.* 2017;32(7):1382-1392. doi: 10.1093/humrep/dex087.
67. Srivastava RA, Pinkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res.* 2012;53(12):2490-514. doi: 10.1194/jlr.R025882.
68. Sun P, Liu L, Chen J, Chen Y, Shi L, Imam MU, Chen Y, Pei X, Xu Y, Guo Y, PingZ, Fu X. The polymorphism of rs266729 in adiponectin gene and type 2 diabetes mellitus: A Meta-Analysis. *Medicine (Baltimore).* 2017;96(47):e8745. doi:10.1097/MD.0000000000008745.
69. Tanaka Y, Kita S, Nishizawa H, Fukuda S, Fujishima Y, Obata Y, Nagao H, Masuda S, Nakamura Y, Shimizu Y, Mineo R, Natsukawa T, Funahashi T, Ranscht B, Fukada SI, Maeda N, Shimomura I. Author Correction: Adiponectin promotes muscle regeneration through binding to T-cadherin. *Sci Rep.* 2020;10(1):12219. doi: 10.1038/s41598-020-66545-1.
70. Wang T, Zhang X, Li JJ. The role of NF-kappaB in the regulation of cell stress responses. *Int Immunopharmacol.* 2002;2(11):1509-20.

doi: 10.1016/s1567-5769(02)00058-9.

71. Wang Y, Zhao M, Liu S, Guo J, Lu Y, Cheng J, Liu J. Macrophage-derived extracellular vesicles: diverse mediators of pathology and therapeutics in multiple diseases. *Cell Death Dis.* 2020;11(10):924. doi: 10.1038/s41419-020-03127-z.
72. Wen X, Zhang B, Wu B, Xiao H, Li Z, Li R, Xu X, Li T. Signaling pathways in obesity: mechanisms and therapeutic interventions. *Signal Transduct Target Ther.* 2022;7(1):298. doi: 10.1038/s41392-022-01149-x.
73. Wong SK, Ramli FF, Ali A, Ibrahim N'. Genetics of Cholesterol-Related Genes in Metabolic Syndrome: A Review of Current Evidence. *Biomedicines.* 2022;10(12):3239. doi: 10.3390/biomedicines10123239.
74. Wu FY, Yin RX. Recent progress in epigenetics of obesity. *Diabetol Metab Syndr.* 2022;14(1):171. doi: 10.1186/s13098-022-00947-1.
75. Wu H, Zhang Y, Li Y, Xu J, Wang Y, Li X. Chemical Synthesis and Biological Evaluations of Adiponectin Collagenous Domain Glycoforms. *J Am Chem Soc.* 2021 May 26;143(20):7808-7818. Doi: 10.1021/jacs.1c02382.
76. Yanai H, Yoshida H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. *Int J Mol Sci.* 2019;20(5):1190. doi: 10.3390/ijms20051190
77. Yu H, Chhabra KH, Thompson Z, Jones GL, Kiran S, Shangguan G, Low MJ. Hypothalamic POMC deficiency increases circulating adiponectin despite obesity. *Mol Metab.* 2020 May; 35:100957. doi: 10.1016/j.molmet.2020.01.021
78. Zhou Z, Tao Y, Zhao H, Wang Q. Adipose Extracellular Vesicles: Messengers From and to Macrophages in Regulating Immunometabolic Homeostasis or Disorders. *Front Immunol.* 2021; 12:666344. doi: 10.3389/fimmu.2021.666344.
79. Zocchi M, Della Porta M, Lombardoni F, Scrimieri R, Zuccotti GV, Maier JA, Cazzola R. A Potential Interplay between HDLs and Adiponectin in Promoting Endothelial Dysfunction in Obesity. *Biomedicines.* 202; 10(6):1344. Doi: 10.3390/biomedicines10061344.
80. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications. *Int J Mol Sci.* 2020;21(10):3570. doi: 10.3390/ijms21103570