Lipotoxicity and kidney

Lipotoxicidade e rim

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ABSTRACT

Lipotoxicity could be defined as the deleterious effects exerted by lipids on plasma (normally as non-esterified molecules) on cell and tissues. Lipotoxicity is closely linked to obesity, although it can be observed in some lean individuals. Therefore, as overweight becomes more prevalent worldwide, the pathological effects mediated by lipotoxic molecules will have a greater impact in healthcare systems.

Ectopic deposition of lipids into non-adipose tissues, such as the kidney, can lead to accumulation of toxic metabolites that lead to mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis and renal dysfunction. Pro-inflammatory mediators are released by visceral adipose tissue in response to injury: adipocytokines (leptin, resistin, vistatin, adiponectin), chemokines (IP-10, IL-8, RANTES and MCP-1), interleukins (IL-1, IL-6) and growth factors (TNFa).

Visceral adiposity plays an important role in inflammation and insulin resistance in obesity. Oxidative processes are pivotal events in injury to renal tubular and epithelial cells exposed to ox-LDL. In type 2 diabetes, ox-LDL and free fatty acids damage podocyte function, structure and tubulointerstitial tissue.

The mechanisms by which obesity causes nephron injury are not fully understood but likely involve a combination of haemodynamic, metabolic and inflammatory changes. Most of the research has been done on its effects in cardiovascular disease, but lipotoxicity is also a major contributor to the development of chronic kidney disease (CKD). The understanding of the adipogenesis should provide new opportunities for therapeutic intervention.

In this paper the current state of causes, consequences and possible therapeutic intervention is summarized, providing an insight on the contribution of lipotoxic molecules to renal disease.

Key-Words: Lipotoxicity, obesity, visceral adipose tissue, adipocytokines, insulin resistance

RESUMO

A lipotoxicidade define-se pelos efeitos deletérios causados pelos lipídios plasmáticos em circulação (usualmente sob a forma de moléculas não-esterificadas) nas células e nos tecidos. A lipotoxicidade está intimamente relacionada com a obesidade, embora possa ser observada em alguns indivíduos magros. Com o aumento da prevalência da obesidade por todo o mundo, também os efeitos patológicos mediados pelas moléculas lipotóxicas terão maior impacto na população.
LIPOTOXICITY

Circulating non-esterified fatty acids (NEFA) in obesity and diabetes

Among the lipids that could induce cell damage, non-esterified fatty acids (NEFA) are the most abundant and, therefore, their production and actions are well known, constituting in most cases a synonym of lipotoxicity. NEFA are the preferential energy source of some highly metabolic organs, such as the myocardium or the liver. Physiological lipolysis of triglycerides occurs in adipose tissue (mainly subcutaneous) and its regulation depends on energy requirements. NEFAs are transported bound to albumin molecules (which have a half-life of 4-6 min)1.

Serum NEFA concentrations are very variable and affected by gender, fasting state and psychological stress (causing concentrations as high as > 1700 μmol/L) and can be suppressed by high-carbohydrate diets2. But in those physiological conditions, plasma NEFA concentrations remain relatively stable as removal by muscle increases to match adipose tissue lipolysis1,3. In conditions like obesity, the increase in adipose tissue is expected to correlate with NEFA plasma concentration and, although several studies seem to indicate a direct relationship, recent systematic review shows no apparent correlation between both parameters4. But, due to the variation of NEFA concentration with physiological parameters, further studies will require homogenous measurements taking into account circadian rythms, fasting time and gender.

In type 2 diabetes, data from clinical studies are clearer. The first observation of the correlation between NEFA and diabetes occurred in a native American population, in the mid 1990s5. This observation was later confirmed in larger cohorts, such as the Paris Prospective Study, in which fasting NEFA concentration correlated with tolerance to glucose deterioration, independently of previous insulin resistance or insulin secretion defects6. Thus, a high serum NEFA concentration can be considered a pathognomonic sign in type 2 diabetes7 and some authors consider that it is an independent risk factor of insulin resistance in obese patients. A high concentration of NEFA on fasting is related with the amount of visceral adipose tissue.

Adipose tissue dysfunction

Adipose tissue is an important endocrine organ, in addition to its role as an energy storage organ, secreting a large number of cytokines (adipokines). White adipose tissue (WAT) is composed by lipid-laden mature adipocytes, various stromal cells, such as...
pre-adipocytes, endothelial cells, fibroblasts and immune cells that may be involved in adipose tissue functions. Macrophages represent a major source of proinflammatory cytokines, which contribute to chronic inflammatory response. Brown adipocytes are specialized for energy expenditure, glucose oxidation and insulin sensitivity. Beige adipocytes share many of the oxidative properties of the brown adipocytes1, 8.

In the last decade, adipose tissue has been considered to play a central role on insulin resistance and diabetes. The distribution of adipose tissue is also of special importance to both insulin resistance and type 2 diabetes. It is widely accepted that visceral adipose tissue is metabolically highly active and plays a major role in the pathogenesis of insulin resistance8,9. Since visceral WAT is resistant to the antilipolytic actions of insulin, it releases NEFA via portal circulation. Adipose tissue becomes dysfunctional due to its rapid expansion or contraction10. Several factors have been postulated to play a role on adipocyte dysfunction: the lipotoxicity itself, lipid-mediated Toll-like receptor (TLR) activation11; hypoxia12 and endoplasmic reticulum (ER)-stress on hypertrophic cells which leads to immune recruitment into the stressed tissue13.. This inflammation pattern results from the interaction between parenchymal and stromal cells in response to stress leading to "adipose tissue remodeling", which can be defined as the dynamic histological changes observed in adipose tissue14. Evidence suggests that the interaction between mature adipocytes and stromal cells plays a crucial role in the regulation of adipocytokine production15.

Under appropriate stimulation adipose precursor cells can acquire some phagocytic capacity and, thereby, become macrophage-like16. Many pro-inflammatory mediators are released by visceral adipose tissue in response to injury: adipoctokines (leptin, resistin, visfatin, adiponectin), chemokines (IP-10, IL-8, RANTES and MCP-1), interleukins (IL-1, IL-6) and growth factors (TNFα)11, 14. There is a paracrine regulation of adipose tissue involving saturated fatty acids and TNFα derived from adipocytes and macrophages, respectively, which establishes a vicious cycle that augments chronic inflammatory changes. The net effect is T cell and macrophage recruitment into the adipose tissue promoting its activation14,16.

Macrophages are of central importance and there are two kinds during the inflammatory process: M1 macrophages, responsible for the chronic inflammation and M2 macrophages in the interstitial space that can be polarized into M1 by stimulation with cytokines. In obese patients, phenotypic change from M2 to M1 macrophages also accelerates adipose tissue inflammation14,16. Usually in obese individuals, the number of M1 macrophages is higher in visceral fat than subcutaneous fat, one of the reasons for a more proinflammatory profile of visceral fat16. Infiltration and activation of monocytes/macrophages into the adipose tissue not only drives to induction and secretion of proinflammatory chemokines as well as increases fibrosis14-16.

Other immune cells involved in the inflammatory process are neutrophils, eosinophils, lymphocytes, natural killer cells and mast cells14, 16. Two subsets of T cells have been identified: CD8+ T cells, increased in the earlier stages of obesity, their depletion results in improvement of adipose tissue inflammation and insulin resistance. CD4+ T cells and regulatory T cells which are decreased in the advanced stage of obesity16. An imbalance of T cell subpopulations may also contribute to adipose tissue inflammation. Some antidiabetic drugs are known to modulate adipocyte-associated inflammation. Thiazolidinedione showed to be capable to improve the unbalanced M1/ M2 phenotype of adipose tissue macrophages in diet-induced obese mice17. But still, visceral WAT inflammation may be a promising therapeutic target to prevent or treat obesity-induced adipose tissue inflammation.

### Lipotoxicity and insulin resistance

In early stages of obesity, insulin action is still preserved or even enhanced as well as its action on lipogenesis and adipogenesis. In obese individuals, insulin secretion increases with insulin resistance and patients who are predisposed to diabetes fail to compensate for greater insulin requirements and tend to develop type 2 diabetes15, 18. However, even in the absence of diabetes, patients with renal dysfunction exhibit insulin resistance with hypertriglyceridemia more frequently than age and BMI-matched control subjects. Insulin resistance is believed to contribute to the burden of CKD on the cardiovascular outcome of these patients18,19.

There is a well-known relation between lipid excess and insulin resistance, particularly regarding
intramyocellular lipid content. Traditionally, it has been explained via the glucose-fatty acid cycle, also known as the Randle cycle. This regulatory pathway involves the cross-inhibition of glucose and fatty acids over the opposite catabolisms. Thus, the high level of Acetyl-CoA that results from FA degradation acts as an allosteric regulator of pyruvate dehydrogenase, leading to the inhibition of glycolysis.

Recently, Shulman has reviewed the relationship between lipid accumulation and insulin resistance showing that much of the data gathered in the last 15 years do not fit the classical theory. On the contrary, magnetic resonance spectroscopy studies have shown a decrease on the level of intramuscular glucose and glucose-6-phosphate after i.v. lipid infusion. Using lipid-infused rodents to characterize the mechanism involved, these studies have identified transient increases in muscle diacylglycerol (DAG) content. High intracellular DAG levels trigger the novel protein kinase C theta (PKCθ) isoform, which is known to be active in the absence of Ca²⁺ which, when present in skeletal muscle, drives the serine phosphorylation of several substrates potentially involved in insulin resistance.

The most important substrate described is the insulin receptor substrate 1 (IRS-1) which is phosphorylated at Ser 1101, inactivating the receptor and impairing insulin signaling. These observations are confirmed in muscle biopsies of patients with insulin resistance and type 2 diabetes.

Lipotoxicity and dyslipidemia

Lipotoxicity is clinically observed as a part of the metabolic syndrome. Hepatic dysfunction with non-alcoholic hepatic steatosis (NAFLD), is associated with insulin resistance lead to de novo lipogenesis.
and triglyceride esterification and secretion as VLDL\textsuperscript{26-27}. This secretion is responsible, at least partially, for the triglyceridemia observed in those patients. Strong associations have been reported between amount of liver fat and features of the cardiometabolic risk profile predicting both risk of type 2 diabetes and cardiovascular disease\textsuperscript{13}.

Thus, the relation between circulating NEFA and hypertriglyceridemia is reciprocal as lipotoxicity leads to triglyceride secretion and sustained hypertriglyceridemia leads to adipose dysfunction\textsuperscript{1}. Also, increased liver fat and visceral adipose tissue are both associated with augmented cardiometabolic risk\textsuperscript{19}.

\section*{LIPOTOXICITY AND THE KIDNEY}

\subsection*{Lipid metabolism in the kidney}

In the last decade, research in pathology has shown that CKD may constitute a state of acquired lipodystrophy, which leads to ectopic lipid deposition. For decades, CKD has been described as a cause of dyslipidemia with increased plasma triglycerides\textsuperscript{28}. Recent studies show that adipose tissue distribution may be altered in CKD, resulting in a loss of white adipose tissue and accumulation of lipids in ectopic sites\textsuperscript{29}. The body mass index does not reflect the amount of atherogenic visceral and ectopic adipose tissue, particularly in CKD patients\textsuperscript{18}.

Experimental evidence showed that CKD is associated with reduction of fat deposit sizes and ectopic lipid distribution\textsuperscript{28,29}. This is also common in aging and lipodystrophic syndromes\textsuperscript{30}. Since adipocyte size and number are related to insulin sensitivity, glucose and fatty acid uptake as well as cytokine release, changes in function and cellular composition of white adipose tissue may lead to changes in metabolic state and subsequent complications\textsuperscript{31}. The main function of the white adipose tissue is to store the energy surplus in the form of lipids, by converting circulating cytotoxic NEFA into triglycerides\textsuperscript{1}.

Also in renal disease, profiles of adipokines are altered\textsuperscript{32}. The incubation of adipocytes from visceral adipose tissue in uraemic plasma increases the secretion of leptin\textsuperscript{33}. Also, there seems to exist a crosstalk between white adipose tissue and the kidney through adiponectin. Plasma adiponectin concentration is lower in obese patients, probably due to suppression of its production by macrophages infiltrating adipose tissue in these individuals. Adiponectin has beneficial cardiovascular effects and improves insulin sensitivity. Sharma \textit{et al.}\textsuperscript{34} showed that adiponectin null-mice exhibit proteinuria with foot process disappearance and that treatment with adiponectin normalizes proteinuria through stimulation of AMPK and suppression of an isoform of NADPH-oxidase.

Lipotoxicity in CKD seems to be partly related to adipose tissue dysfunction\textsuperscript{1}. Incubation of human adipocytes in uraemic sera results in an increase in baseline lipolysis and a decreased expression of the messenger RNA that codes perilipin\textsuperscript{35}. The decline in fat mass and ability to store lipids seen in CKD seems to contribute to fat redistribution into other tissues\textsuperscript{31}.

\subsection*{Ectopic lipid deposition on the kidney}

Lipid accumulation occurs, not only in adipose tissue, but also in non-adipose tissues (e.g., ectopic fat deposition and lipotoxicity in kidney – Figure 2)\textsuperscript{36}. When the energy intake exceeds the storage capacity of subcutaneous white adipose tissue, lipid accumulation is induced in ectopic sites\textsuperscript{37}. Triglycerides are not considered toxic \textit{per se}. On the contrary, they are safe storage forms. The principal determinant of lipotoxicity seems to be excessive intracellular free fatty acid content which leads to the accumulation of potentially toxic metabolites such as fatty acyl-CoA, diacilglycerols and ceramides\textsuperscript{38}. These metabolites may lead to mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis and eventually to dysfunction and injury. The contribution of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors to the improvement of proteinuria and the preservation of renal function seems to confirm the role of lipids in renal damage\textsuperscript{37,39}. In the last decades, lipid ectopic accumulation has started to be considered a relevant factor in metabolic disease\textsuperscript{60}. The first and most relevant pathological condition caused by ectopic lipid accumulation is non-alcoholic fatty liver disease, the most common chronic liver disease in the world, which is associated with insulin-resistance\textsuperscript{37}. Nowadays, a high intramyocellular fat level is considered a sign of insulin resistance\textsuperscript{37}, and this process is closely related to visceral fat accumulation\textsuperscript{38}. 
Lipid accumulation in ectopic sites is also a characteristic feature of lipodystrophy, a metabolic disorder in which adipose tissue loses its ability to buffer the post-prandial influx of fatty acids\(^\text{28,27}\). As ectopic fat accumulation damages insulin response, it may lead to impaired insulin synthesis and secretion by pancreatic beta cells\(^\text{8,9}\). Hence, diabetes may occur, and both lipogenesis and adipogenesis may become

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**Figure 2**
Assessment of ectopic lipid deposition. A. Mass spectrometry imaging of lipids (Linoleic and Palmitic acid, Cholesterol and a triglyceride) and total phosphate distribution (cell membrane) on a sagittal kidney section obtained by TOF-SIMS (S Mas); B. Quantitation of diet-induced lipid accumulation on wild-type and ApoE knockout mice. C. Oil-Red-O staining in murine proximal tubular cells (MCT) showing increased lipid accumulation after 24 h incubation with ox-LDL (25 μg/mL). (From Sastre et al. PLoS One. 2013 Dec 30;8(12):e83713.).
stationary while lipolysis is activated. The resultant increase in circulating non-esterified fatty acids contributes to the increased reliance on fat oxidation to provide energy and the generation of fat oxidation by-products suppresses glucose oxidation. Additionally, lipid accumulation in ectopic sites contributes to impaired mitochondrial function. Evidence suggests that mitochondrial dysfunction, which can accelerate fat accumulation, can be a consequence of insulin resistance rather than a primary defect. Lipotoxic cellular dysfunctions and injuries occur through several mechanisms, including the generation of reactive oxygen species (ROS); multiple organellar damages and disruption of intracellular signalling pathways; the release of proinflammatory and profibrotic factors; and lipid-induced apoptosis.

In mice fed with a high-fat diet, the accumulation of lipids in the glomerular and tubulointerstitial cells (Figure 2) with increased expression of sterol regulatory element binding protein (SREBP-1), a transcription factor which plays a key role in lipogenesis and its related genes (ACC, acetyl-coA carboxylase, FAS, fatty acid synthase). These changes lead to significant glomerulosclerosis and proteinuria. These data were supported by finding a protection from these effects in mice lacking SREBP-1, when submitted to a high-fat diet.

Excessive lipid droplets can be found in different renal cell types including podocytes. Recent data showed that cholesterol accumulation in podocytes plays a critical role in diabetic nephropathy and contributes to lipotoxicity. Oxidized lipids initiate and modulate the inflammatory cellular events with the formation of macrophages foam cells. Evidence has reported that ox-LDL induces loss of nephrin expression in cultured podocytes.

Microalbuminuria, a major feature of diabetic nephropathy, is normally considered a consequence of hyperglycaemia and associated glomerular hyperfiltration. However, it also occurs in non-diabetic insulin-resistant patients, and studies have shown that lipid accumulation in the kidney may be the cause of renal injury associated with the metabolic syndrome. Renal glucose output is markedly increased in type 2 diabetes, resulting in an increased net renal glucose uptake. It has been proposed that this glucose overload may contribute to the glycogen deposit, which is not associated with an evident fat intrarenal accumulation. In diabetic patients, renal glucose uptake is inversely correlated with FFA uptake, suggesting the existence of a renal glucose-FFA cycle.

In renal, as well as in the overall systemic vascular bed, the generation of oxidized lipids can modulate the formation of macrophage foam cells. An imbalance between the synthesis of ROS and antioxidants is described as oxidative stress and also as inflammatory state. NADPH oxidase is the enzyme responsible for ROS production and the inhibition of this enzyme weakens the focal adhesion of macrophages within the intimal plaque, restoring their mobility. In inflammatory states, lipids are deposited in tissues and become oxidized. Inflammatory cytokines and growth factors may enhance lipid synthesis, leading to significant intracellular lipid accumulation and foam cell formation both at the systemic and renal levels.

Additionally, ectopic kidney fat deposits have been associated with hypertension. Thus, renal sinus fat is associated with stage II hypertension. In the Framingham heart study, individuals with “fatty kidneys” (high perinephric fat levels) had a higher risk of hypertension (OR 2.12), which persisted after adjustment for body mass index (BMI) and visceral fat.

Lipotoxicity and podocytes

Podocytes are the cells that modulate the glomerular size-selectivity barrier to proteins in the nephrons. Different slit diaphragm-associated proteins, such as nephrin, CD2-associated protein, podocin and alfa actin, contribute to maintain glomerular size-selective permeability.

Gutwein et al. showed that chemokine CXCL-16 is the main scavenger receptor for ox-LDL in human podocytes, and is related with the production of another chemokine, CXCL12, which further impairs nephrin expression.

Bussolati et al. showed that ox-LDL induces loss of nephrin expression in cultured podocytes. It seems that nephrin, when phosphorylated, causes the remodeling of the actin cytoskeleton and an increase in albumin diffusion across podocytes.
Sun et al.\textsuperscript{43} showed, in animal models of type 1 diabetes, that sterol regulatory element binding proteins (SREBP) are increased in the kidney cortex, resulting in upregulation of the enzymes responsible for FFA synthesis. Even with a normal serum lipid level, animals with SREBP-1 overexpression have elevated renal triglyceride levels, increased mesangial matrix expansion, proteinuria and glomerulosclerosis. These findings indicate that increased triglyceride accumulation in the intracelular mesangium may play a central role in the development of diabetic nephropathy.

\textbf{Lipotoxicity and tubular cells}

Oxidative processes are pivotal events in the injury of renal tubular epithelial cells exposed to ox-LDL (Figure 2c). CD36 are the main receptors for the uptake of ox-LDL in tubular renal cells\textsuperscript{36,39,41}. Heme oxygenase, a redox-sensitive enzyme in proteinuric renal disease, is induced in epithelial cells following an exposure to ox-LDL and is accompanied by cytotoxicity, \textit{in vitro}. In fact, protection of cells with antioxidants resulted in a significant attenuation of cytotoxicity. A similarity was observed between the behaviour of endothelial cells and renal tubular epithelial cells after exposure to ox-LDL, concerning oxidant-mediated toxicity and expression of heme oxygenase. These findings suggest that the paradigm regarding the role of ox-LDL in atherogenesis may apply to tubulointerstitial fibrosis, also via atherosclerotic processes, which in turn lead to tubulointerstitial ischaemia\textsuperscript{7,9,23}.

The mechanisms that explain the oxidation of LDL in proteinuric renal disease are not completely understood. There are two hypotheses: (1) LDL is vulnerable to oxidative attack in the urinary space, from where LDL may be endocytosed by tubular cells or (2) LDL may be oxidized within tubular cells and in the microvascular bed which surrounds the tubulointerstitial tissue\textsuperscript{7,9,23}.

\textbf{THERAPEUTICS FOR LIPOTOXICITY}

\textbf{Statins}

Statins lower cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase and may have additional benefits on vascular function beyond their lipid lowering effect.

Statins also reduce AER and urinary loss of podocytes, a marker of severity of glomerular injury\textsuperscript{47}. Bussolati et al.\textsuperscript{46} showed, \textit{in vitro}, that ox-LDL induced apoptosis in human podocytes and that this effect could be prevented by statins. Tonolo et al.\textsuperscript{48} showed that treatment with simvastatin maintains steady patterns of GFR, AER and nephrin expression.

\textbf{Fenofibrate (potent PPAR-\alpha agonist)}

Hong et al.\textsuperscript{49} demonstrated, in animal models, the renoprotective effect of fenofibrate by ameliorating lipotoxicity in the kidney. It was already known that in diabetic nephropathy there is an increase in renal lipid accumulation, apoptotic renal injury and oxidative stress. The authors were able to relate these events to a decreased level of PPAR\alpha expression in diabetic mice which lead to the inactivation of AMPK-PGC-1a-ERR-1a, subsequently resulting in an increase in oxidative stress in the kidney.

Fenofibrate, by activation of AMPK-PGC-1a-ERR-1a signalling, reverses renal lipid accumulation and ameliorates diabetic nephropathy.

The PPAR\alpha activation leads to an increase in fatty acid catabolism and ATP production as well as a decrease in the levels of cytotoxic fatty acid peroxidation products, and promotes cell viability by inhibiting renal epithelium cell death. Furthermore, the authors demonstrated that fenofibrate directly activates AMPK by activation of PPAR\alpha, which prevents renal lipid accumulation and renal cell injury both in diabetic mice and in cultured mesangial cells treated with high glucose media\textsuperscript{49}.

Tanaka et al.\textsuperscript{50} have also shown a protective effect of fenofibrate. It reduces glomerular lipid (mainly triglycerides) accumulation and oxidative stress associated with decreased albuminuria and glomerulosclerosis, on mice under a high-fat diet.

These results suggest that fenofibrate can be a potential therapeutic modality to treat type 2 diabetic nephropathy.

\textbf{Polyphenols and flavonoids}

Naturally occurring molecules, such as polyphenols and flavonoids, present in food and plant extracts,
lipotoxicity. Be beneficial in the prevention and treatment of cytokines released by activated immune cells and creas to cause insulin resistance. Pro-inflammatory organs such as the liver, skeletal muscle and the pan-inflammatory disease, which may spread to remote cate with every organ in the body.

Adipose tisse is an important endocrine organ high mortality mainly because of cardiovascular dis-susceptibility to chronic kidney disease and the impact of dyslipidemia on the progression of chronic kidney disease. The supplementation with grape seed and skin extract (GSSE) results in a reduction of triglyceride deposition, copper depletion and kidney disfunction. The authors believe that GSSE acted indirectly on the kidney, and not directly as previously thought, by interfering with the process of weight and fat loss. Histological data also supported that GSSE is protective against proteinuria induced by a high-fat diet.

The specific polyphenols implicated in such pro-tection have not yet been identified. Resveratrol, quercetin or catechins as well as unsaturated fatty acids found in grape seed oil are potential candidates, although a synergism between these compounds is the most likely option.

In conclusion, the use of an antioxidant could be beneficial in the prevention and treatment of lipotoxicity.

CONCLUSIONS

There is an epidemic of obesity and the metabolic syndrome across the world. Both are associated with high mortality mainly because of cardiovascular diseases. Adipose tisse is an important endocrine organ and secretes different molecules that can communicate with every organ in the body.

Obesity is currently seen as a chronic low-grade inflammatory disease, which may spread to remote organs such as the liver, skeletal muscle and the pancreas to cause insulin resistance. Excess intracellular non-esterified fatty acids and their metabolites (FA-CoA, DAG, and ceramides) promote insulin resistance and exert deleterious effects on various organs.

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References


