Mini Review

Lipid-induced cardiovascular diseases

Sumeet Manandhar¹, Sujin Ju¹, Dong-Hyun Choi² and Heesang Song¹,³*

¹Department of Biomedical Sciences, Chosun University, Gwangju 61452, Korea
²Department of Internal Medicine, Chosun University School of Medicine, Gwangju 61452, Korea
³Department of Biochemistry and Molecular Biology, Chosun University School of Medicine, Gwangju 61452, Korea

*Address for Correspondence: Heesang Song, PhD, Department of Biochemistry and Molecular biology, Chosun University School of Medicine, 309 Pilmundaero, Gwangju 501-759, Korea, Tel: +82 62 230 6290; Fax: +82 62 226 4165; Email: hsong@chosun.ac.kr

Submitted: 09 November 2017
Approved: 27 November 2017
Published: 28 November 2017

Copyright: © 2017 Song H, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Keywords: Lipotoxicity; Cardiovascular diseases; Pathogenesis

Abstract

Cardiovascular diseases are the leading cause of death worldwide. There are many evidences that the dysfunctioning lipotoxicity is the one of major factors of cardiovascular diseases such as, atherosclerosis, hypertension, and coronary heart disease. Obesity and diabetes increase circulating lipids that are likely with more generation of toxic intermediates, which leading to the complications associated with cardiovascular diseases. Indeed, lipotoxicity is a metabolic syndrome caused by abnormal lipid accumulation, which leads to cellular dysfunction and necrosis. Here we review the factors that induced pathogenesis of cardiovascular diseases by lipid accumulation and the mechanisms underlying the lipotoxicity.

Introduction

Lipids are the essential component to maintain the cellular structure and provide energy, and are involved in the various cell signaling [1]. However, an abnormal lipid accumulation is a metabolic syndrome, which causes cellular toxicity called lipotoxicity leading to cellular dysfunction and necrosis [2]. This metabolic syndrome has various risk factors like high triglycerides, hypertension, low HDL cholesterol concentrations and glucose intolerance [3,4], which is closely associated with other abnormalities like obesity and diabetes [5,6].

In fact, there are many evidences that lipotoxicity might be a cause of lot of pathogenesis. Infused lipid into skeletal muscle elevated the level of caspase 3, which later resulted in increased level of fatty acid that activates pro-apoptotic pathways [7]. In case of pancreatic cells, secretion of insulin is malfunctioned by the over accumulation of free fatty acids, lipotoxicity [8], which can also lead to apoptosis [9-11]. In addition, the destruction in cells were observed in lipid over-loaded pancreas [12]. Lipid accumulation results in oxidative and ER stress, cell death and inflammation in hepatocytes, and ultimately induced cirrhosis by the activation of fibrogenic response in hepatic cells [13]. According to an animal experiments, failure in gluconeogenesis is caused by an accumulated lipid [14]. In addition, there is a report that excess lipid result in renal dysfunctioning and injury [15]. And most of cardiovascular diseases (CVD) like atherosclerosis, hypertension and coronary heart disease are also well known to be caused by lipotoxicity [16]. In this paper, we review about the brief introduction about the lipid toxicity, various factors that induced pathogenesis heart diseases and also the various pathways causing lipotoxicity.

Lipotoxicity in pathogenesis of heart

Cardiovascular disease (CVD) account for approximately one third of all deaths globally [17]. Indeed, lipid accumulation in non-adipose tissues is the major factor for obesity, and diabetes mellitus and cardiovascular disease may be its co-morbidities [18]. People suffering from obesity are likely to be at higher risk of cardiac diseases.
compare to the average weight people [19]. Various results like cell death, mitochondrial dysfunction, endoplasmic reticulum (ER) stress etc. is cause to the excess lipid intake [20]. In addition, insulin resistance is also developed due to the accumulation of increases in fat in cardiomyocyte [21]. Recently there have been some report that in heart failure condition there is an impaired fatty acid oxidation in diabetes and obesity which are responsible for lipid overload in intramyocardial [22].

This shows a firm establishment of the relationship between cardiomyopathy and lipid abnormalities in diabetic and obese human [23]. This means that these obesity and diabetes relation to the cardiac complication will be the important goal for understanding for the treatment of lipotoxicity in myocytes. For the cardiomyocyte metabolism, fatty acid plays an important role however detrimental effect is induced due to the imbalance of cellular uptake and usage results in lipid accumulation [23,24]. Indeed, the main cause of lipotoxicity in heart is known due to ceramide metabolized from free fatty acid (FFA) [25]. In addition, high cholesterol increased the incidence of coronary heart disease compared to the polyunsaturated fatty acid [26-29]. Therefore, attention should be made by the people on their diet to prevent from these pathological conditions. Lipotoxicity leads to various pathogenesis of heart diseases and some of them are listed below.

**Atherosclerosis**

Coronary artery disease (CAD) can be defined as development of athermanous plaques in the vessel of heart and block the flow of blood to the myocardium. And where lipotoxicity works as an elevating ectopic fat aggregation which cause worsen the condition local fat depots of CAD [30,31]. Indeed, the incidence of atherosclerosis is found to be elevated in patient showing insulin resistance with suffering from diabetes mellitus [32], lipotoxicity is the major factor for insulin resistance [21].

Studies in both animal and human showed that non-esterified fatty acids (NEFA) increased by lipid infusion also elevated diacylglycerol which has an inhibitory effect in insulin secretion [33]. The insulin resistance has a close bonding with the people with type 2 diabetic mellitus and obese which are elevated by increased in ceramide level in both muscle and plasma. In addition except, this circulating NEFA has inflammatory effect which activates toll-like receptor 4. Normally, the elevation of NEFA in people with normal glucose resistance increases the connective tissue growth factor which has a characteristic feature of atherogenesis plaque deposition [21]. In addition, overexpression of platelet-derived growth factor receptor (PDGFR) and malfunctioning activation of PDGFR signaling was seen due to the inactivation of lipoprotein receptor-related protein 1 (LRP1) in vascular smooth muscle cells (VSMCs) of mice which resulted in the deterioration of elastic layer and pointed sensitivity to cholesterol induced atherosclerosis [34].

Hyperlipidemia and hypertension, both causes oxidative stress and oxygen free radical production by the arterial wall. In the presence of hyperlipidemia, there is the occurrence of atherosclerosis and formation of foam cell. These both hyperlipidemia and hypertension have synergistic effects on the artherosclerosis [35].

**Pathogenesis in hypertension**

There is a positive correlation of patient with heritable pulmonary arterial hypertension (PAH) and lipotoxicity. A rodent model with expression of mutation of bone morphogenic protein receptor 2 (BMPR2), a gene that cause the heritable PAH, showed the lipid over-deposition in right ventricle [36]. Studies have shown that there is the alteration of lipid metabolism with high intake of fat diet, sequentially leading to lipid accumulation in renal, elevation in oxidative stress and renal injury, including glomerulosclerosis, interstitial fibrosis and albuminuria. In addition, filtered albumin bound to FFA leads to tubule-interstitial damage later causing pro-inflammatory phenotype, then can lead to the hypertension [37].
Lipid-induced cardiovascular diseases

Pathogenesis of ventricular dysfunction and cardiac hypertrophy

Malfunctioning in the lipid storage in the cardiac in systemic metabolism leads to cardiomyopathy. Mitochondrial fatty acid oxidation, caused by cardiac lipid overload is linked with the heart failure and sudden death [38]. This aggregation of lipid also has shown the triggering effect of arrhythmias in the cardiomyocyte from mice. In addition, the progression of increase of serum FFA and triglycerides has been revealed due to the functional loss of leptin receptor, which also showed that deposition of fat induced death and deprivation in systolic function in cardiomyocytes [39]. In this model, the lipid accumulation shows the various cardiac myopathy with initial effect with hypertrophic condition in heart, subsequently malfunctioning of left-ventricular and premature death, which was coincided with another report that lipid accumulation showed cardiac hypertrophy, contractility function impaired and increased mortality [24]. These reports demonstrated that lipid accumulation leads to cardiac hypertrophy and systemic ventricular dysfunction.

Lipid signaling pathways

Accumulation of the lipid in the cardiomyocyte due to the deterioration of lipid metabolism is caused by fatty acids and fatty acyl coA, acylcar nitine, unesterified cholesterol, lysolecithin, diacylglycerol and ceramide [40]. Apoptosis, inflammation, mitochondrial dysfunction, and/or defective intracellular signaling plays an important role of these toxic lipids. The various signaling pathways that lead to lipid accumulation are explained below and the associated mechanisms in circulatory systems are also shown in table 1.

Apoptotic pathways

Obesity and diabetes is associated with cardiac lipid overload and this is induced by apoptotic cascade. Some reports have shown that palmitic acid causes cardiolipin loss cytochrome c release, mitochondrial swelling, and DNA laddering with the change in mitochondrial swelling in isolated neonatal rat myocytes [41,42]. In addition, ceramide can participate in a variety of cellular signaling, including the regulating differentiation, proliferation, and apoptosis of cells. Several studies have shown that ceramide accumulation followed by the treatment of apoptotic agents including ionizing radiation [43], UV light [44], TNF-alpha [45], and chemotherapeutic agents, resulting to cellular apoptosis via mitochondrial dysfunction [46,47]. Ceramide is synthesized by two ways. In the first, serine palmitoyltransferase catalyzes patmitoyl-coA serine, generating 3 ketosphingonine which later produce ceramide [48-50]. And sphingomyelinase hydrolyzes sphingomyelin and ceramide is released in other pathway [51]. Thus, obesity increases intracellular lipid leading to diabetes.

| Table 1: Lipid-associated mechanisms in circulatory systems |
|-----------------------------|-------------------------------|-----------------|
| Mechanism                  | Observation                     | References    |
| AMPK                       | Activation protects against FA-induced cell death | [77,78]         |
| Autophagy                  | Enhanced by FA-induced activation of PKC | [79]           |
|                            | Enhanced by WD via O-GlcNAcylation of autophagy proteins | [80]           |
|                            | Inhibition protects against FA-induced cell death in endothelium | [81]           |
| Ceramide                   | Enhances PP2A-eNOS mediated endothelial dysfunction | [82]           |
|                            | Inhibition protects against FA-induced cell death | [25,83]       |
| ER stress                  | Enhanced by FA-induced activation of Ca"<sup>2+</sup>-mediated activation of BCL-2, BAX, and BAK | [22]           |
| Leptin                     | Treatment protects against cardiac dysfunction by reducing lipid accumulation and restoring PPAR signaling | [84]           |
| Lipid (TG) storage         | Feeding unsaturated FA, protects against saturated FA-induced cell death by sequestering lipids in intracellular droplets | [85,86]       |
|                            | Perilpins regulate FA-storage to regulate and maintain normal oxidative balance | [87,88]       |
| MicroRNA                   | FA-induced changes in miR regulation results in insulin resistance | [89]           |
| Mitochondrial function     | FA-induced mitochondrial fragmentation and increased reactive oxygen species (ROS) | [90]           |

* FA: fatty acid; TAG: triacylglycerol; WD: western diet.
To show the effect of ceramide on lipotoxicity in heart, blocking of ceramide formation by myriocin, inhibitor of serine palmitoyltransferase (SPT), or deletion of long chain base biosynthesis protein 1 (LCB1), a part of SPT, showed the increased survival rate [48]. In addition, declining of fatty acid and elevation of glucose oxidation in lipoprotein lipase (LpL)-overexpressed heart by blocking of SPT reduced the cardiac sphingomyelin and ceramide and then finally improved systolic function and survival was prolonged [25]. Therefore, reduction of the ceramide might be the selective target of the drug for the treatment of lipid-induced heart disease in obese and diabetic patients.

**AMP activated protein kinase**

AMP activated protein kinase (AMPK) has an important role in the energy homeostasis in cellular level. ATP activates AMPK which has been correlated to FA transport and oxidation [52]. The effect of palmitate on myocyte is blocked by the activation of AMPK with a cell permeable AMPK activator, AICAR. That causes to reduce malonyl-coA level which results in the decrease of FA transportation and oxidation in mitochondria and ultimately decreases the toxicity in cells. In addition, AMPK is also an activator for expression of fatty acid transport proteins, FAT/CD36 and plasma membrane fatty acid-binding protein (FABPpm), in a time dependent and dose dependent, which were not overexpressed when the AMPK phosphorylation was blocked [41,53,54]. Thus, AMPK is an essential 'master regulator' of the metabolism of sugar and FA for the normal functioning of heart. Therefore AMPK signaling pathway will be an important target in the treatment of cardiovascular disease induced by lipid accumulation.

**Peroxisome proliferator-activated receptors**

Peroxisome proliferator-activated receptors (PPARs) are known as nuclear receptors, all three members PPARα, PPARδ, and PPARγ. PPARα has been directly related to elevate the oxidation of fatty acid in heart [55]. In addition, PPARα is a ligand activating transcription of mitochondrion fatty acid oxidation enzymes involved in cellular fatty acid intake [56]. Indeed, there was an increase in fatty acid metabolism and expression of genes of lipid uptake in myocardium by the overexpression of PPAR [55]. And the decreased PPARα gene expression causes to decrease the metabolic rate of fatty acid in both in cardiac hypertrophy and infracted myocardium [57-59], which was likely due to the hypoxic condition by some evidences. In fact, PPARα expression level in human heart was decreased by 54% in patient with hypertrophy and also in MI rat heart. Furthermore, PPARs generates the peroxisomal and mitochondrial enzymes such as acyl CoA oxidase (AOX) and carnitine palmitoyltransferase which controls the fatty acid metabolism in hearts [60,61]. In addition, PPAR has the capability to decrease the plasma triglyceride and elevate HDL cholesterol level, which was effective in the treatment of abnormal in lipid level [62]. Decreasing the levels of circulating triglycerides responsible for triglycerides inducing adipose cell hypertrophy and hyperplasia is reduced by PPARα activators [63]. In conclusion, PPARs has important role in the maintenance of lipid level which has direct relationship with the atherosclerosis, inflammation, and the reduced foam cell formation.

**Protein kinase C**

Protein kinase C (PKC) is an enzyme which regulates function of protein through phosphorylation of amino acids and performs various cellular activities. These are widely expressed in myocardium and have function for the regulating some pathways in heart. There are evidences that PKCβ has an effect to cause myocardial necrosis and to thicken ventricular walls [64]. Furthermore, lipotoxicity is increased in heart during the activation of PKCβ2 by the high intake of fat diet, resulting into cardiac hypertrophy [65].

**Low-density lipoprotein receptors**

Low-density lipoprotein receptor-related protein 1 (LPR1) has a function over the storage of lipid in the liver through canonical Wnt5a signaling pathway [34].
study showed that there was pathological accumulation of lipid in the liver during the silencing of LRP1 gene in animal experiment. In this condition, there was an indirect accumulation of lipid in liver via white adipocytes. In addition, wnt5a corrected the malfunctioning of the cholesterol and cholesteryl ester accumulation during silencing of LRP1 in mouse embryonic fibroblasts (MEFs) [34]. Low-density lipoprotein receptor-related protein 5 (LRP5) have been also shown as an important part for maintaining the level of cholesterol, and there was a downfall in the hepatic clearance of chylomicron in LRP5 deficient mice fed with high fat diet [66]. CD36, also known as platelet glycoprotein 4, fatty acid translocase (FAT), is a multifunctional membrane protein found on the surfaces of various cell types including cardiomyocytes. Kim, et al have reported that the saturated fatty acid, palmitate, significantly induced lipotoxic cell death in RAW264.7 macrophages, which was antagonized by the monounsaturated fatty acid, oleate, through the down-regulation of CD36 expression [67]. In addition, the treatment of high density lipoprotein (HDL) reversed palmitic acid-induced lipotoxicity and energy metabolism imbalance in H9c2 cardiomyoblast cells and in neonatal rat cardiomyocytes [68].

**Lipid-induced defective insulin signaling**

Insulin signaling mediated by activation of eNOS in hearts such as increasing the carbohydrate oxidation during ischemia and direct activation of AKT have shown anti-apoptotic function and cardiac protecting effect [69]. Insulin resistance is caused due to the improper metabolism of lipid in heart which leads to the improper management of insulin and decreases cardiac efficiency in cardiomyocytes [30,70-73]. Further, insulin has effects on maintaining of the intracellular Ca²⁺ and survival of cardiomyocytes. In fact, deficiency of insulin signaling caused to exacerbate cardio-lipotoxicity [69,70], which are caused by ceramide and diacyl glycerol (DAG).

**MAPK**

Mitogen activated protein kinases (MAPKs) represent an essential group of kinases which is involved in cell signaling and regulation pathways. Erk1, Erk2, JNK1, JNK2, and P38 are members of MAPK which involves in oxidative stress in cardiomyocytes and are identified to regulate insulin signaling [74,75]. Treatment of Erk and JNK antagonist showed the blocking of dilation of left ventricular end systole and elevation of fraction and the decrease of myocardial fibrosis [76]. Addition, JNK has shown an apoptotic effect on rat cardiomyocytes induced by oleate combined with palmitate. From these reports, MAPKs might be a mediator for protection of lipid mediated apoptosis.

**Conclusion**

As from various studies, it has shown that alteration in the lipid metabolism has concomitant effect in the normal functioning of the heart with development of various cardiovascular diseases and similarly affecting other organs too. And there are various signaling pathways for the accumulation of lipid and eventually causing lipotoxicity. Therefore, main focus for the research should be taken on the signaling pathways of lipid accumulation and the development of therapeutic drugs for the adjustment of lipid level. In addition, the earlier prediction of lipotoxicity should be needed to prevent the late complication of lipotoxicity.

**Acknowledgements**

This was supported by grants from the Chosun University, 2015

**References**

1. Mattes RD. Fat taste and lipid metabolism in humans. Physiol Behav. 2005; 86: 691-697. [Ref: https://goo.gl/nN6YSn]

2. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol. 2003; 14: 281-287. [Ref: https://goo.gl/ScoErq]
3. Alshehri AM. Metabolic syndrome and cardiovascular risk. J Family Community Med. 2010; 17: 73-78. Ref: https://goo.gl/d8mLvy

4. Chavez JA, Summers SA. Lipid oversupply, selective insulin resistance, and lipotoxicity: molecular mechanisms. Biochim Biophys Acta. 2010; 1801: 252-265. Ref: https://goo.gl/YB4P7f

5. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001; 24: 683-689. Ref: https://goo.gl/KRIxB2

6. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002; 156: 1070-1077. Ref: https://goo.gl/5mcBBn

7. Turpin SM, Ryall JG, Southgate R, Darby I, Hevener AL, et al. Examination of ‘lipotoxicity’ in skeletal muscle of high-fat fed and ob/ob mice. J Physiol. 2009; 587: 1593-1605. Ref: https://goo.gl/wpCrgA

8. Winzell MS, Svensson H, Enerback S, Ravnskjaer K, Mandrup S, et al. Pancreatic beta-cell lipotoxicity induced by overexpression of hormone-sensitive lipase. Diabetes. 2003; 52: 2057-2065. Ref: https://goo.gl/bnLzvh

9. Shimabukuro M, Zhou YT, Levi M, Unger RH. Fatty acid-induced beta cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci USA. 1998; 95: 2498-2502. Ref: https://goo.gl/djrqfD

10. Prentki M, Joly E, El-Assaad W, Roduit R, Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in beta-cell adaptation and failure in the etiology of diabetes. Diabetes. 2002; 51: 405-413. Ref: https://goo.gl/obLxVH

11. Lupi R, Dotta F, Marselli L, Del Guerra S, Masini M, et al. Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that beta-cell death is caspase mediated, partially dependent on ceramide pathway, and Bcl-2 regulated. Diabetes. 2002; 51: 1437-1442. Ref: https://goo.gl/BgdR6t

12. Robertson RP, Harmon J, Tran PO, Poitout V. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes. 2004; 53: 119-124. Ref: https://goo.gl/Xif2YQ

13. Trauner M, Arrese M, Wagner M, Fatty liver and lipotoxicity. Biochim Biophys Acta. 2010; 1801: 299-310. Ref: https://goo.gl/8x9B9d

14. Ibdah JA, Paul H, Zhao Y, Binford S, Salleng K, et al. Lack of mitochondrial trifunctional protein in mice causes neonatal hypoglycemia and sudden death. J Clin Invest. 2001; 107: 1403-1409. Ref: https://goo.gl/WvQCb8

15. Bobulescu IA, Renal lipid metabolism and lipotoxicity. Curr Opin Nephrol Hypertens. 2010; 19: 393-402. Ref: https://goo.gl/CpBSf2

16. Kim JA, Montagnani M, Chandrasekran S, Quon MJ. Role of lipotoxicity in endothelial dysfunction. Heart Fail Clin. 2012; 8: 589-607. Ref: https://goo.gl/SbMja6

17. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014; 2950-2959. Ref: https://doi.org/10.3389/funct.2014.00182

18. Abel ED, Litwin SE, Sweeney G, Cardiac remodeling in obesity. Physiol Rev. 2008; 88: 389-419. Ref: https://goo.gl/jh2U9f

19. Kenchahia S, Evans JC, Levy D, Wilson PW, Benjamin EJ, et al. Obesity and the risk of heart failure. N Engl J Med. 2002; 347: 305-313. Ref: https://goo.gl/AazmFW

20. Dyntar D, Epenner-Eberhardt M, Maedler K, Pruschy M, Epenner-Ham HM, et al. Glucose and palmitic acid induce degeneration of myofibrils and modulate apoptosis in rat adult cardiomyocytes. Diabetes. 2001; 50: 2105-2113. Ref: https://doi.org/10.2337/diabetes.50.5.2105

21. DeFronzo RA, Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia. 2010; 53: 1270-1287. Ref: https://doi.org/10.1007/s00125-010-1750-1

22. Wende AR, Abel ED, Lipotoxicity in the heart. Biochim Biophys Acta. 2010; 1801: 311-319. Ref: https://doi.org/10.1016/j.bbac.2010.07.020

23. Goldberg IJ, Trent CM, Schulze PC, Lipid metabolism and toxicity in the heart. Cell Metab. 2012; 15: 805-812. Ref: https://doi.org/10.1016/j.cmet.2012.02.018

24. Yagyu H, Chen G, Yokoyama M, Hirata K, Augustus A, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. J Clin Invest. 2003; 111: 419-426. Ref: https://doi.org/10.1128/JCM.111.3.419-426.2003
25. Park TS, Hu Y, Noh HL, Drosatos K, Okajima K, et al. Ceramide is a cardiotoxin in lipotoxic cardiomyopathy. J Lipid Res. 2008; 49: 2101-2112. Ref: https://goo.gl/raLwnF

26. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med. 2006; 355: 1991-2002. Ref: https://goo.gl/NvdZ6S

27. Hu FB, Willett WC, Optimal diets for prevention of coronary heart disease. JAMA. 2002; 288: 2569-2578. Ref: https://goo.gl/q9qXqY

28. Lavie CJ, Milani RV, Mehra MR, Ventura HO, Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol. 2009; 54: 585-594. Ref: https://goo.gl/QNpSwq

29. Mozaffarian D, Wu JH, Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011; 58: 2047-2067. Ref: https://goo.gl/16Eeq

30. Young ME, Guthrie PH, Razeghi P, Leighton B, Abbasi S, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. Diabetes. 2002; 51: 2587-2595. Ref: https://goo.gl/aj1MRb

31. Sharma S, Adrogue JV, Golfman L, Uray I, Lemm J, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. Faseb J. 2004; 1892-1700. Ref: https://goo.gl/dPWB1w

32. Watson KE, Peters Harmel AL, Matson G. Atherosclerosis in type 2 diabetes mellitus: the role of insulin resistance. J Cardiovasc Pharmacol Ther. 2003; 253-260. Ref: https://goo.gl/gPizLV

33. Kelley DE. Skeletal muscle fat oxidation: timing and flexibility are everything. J Clin Invest. 2005; 1699-1702. Ref: https://goo.gl/Rcohyl

34. Terrand J, Bruban V, Zhou L, Gong W, El Asmar Z, et al. LRP1 controls intracellular cholesterol storage and fatty acid synthesis through modulation of Wnt signaling. J Biol Chem. 2009; 381-388. Ref: https://goo.gl/CCydTp

35. Alexander RW. Theodore Cooper Memorial Lecture. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. Hypertension. 1995; 155-161. Ref: https://goo.gl/9Rd8uc

36. Hennes AR, Brittain EL, Trammell AW, Fessel JP, Austin ED, et al. Evidence for right ventricular lipotoxicity in heritable pulmonary arterial hypertension. Am J Respir Crit Care Med. 2014; 325-334. Ref: https://goo.gl/b6Ua5j

37. Zhao X. Prevention of local lipotoxicity: a new renoprotective mechanism of peroxisome proliferator-activated receptor-alpha activation in hypertension and obesity? Hypertens Res. 2009; 821-823. Ref: https://goo.gl/T7CDlJ

38. Kelly DP, Hales DE, Rutledge SL, Ogden ML, Whelan AJ, et al. Molecular basis of inherited medium-chain acyl-CoA dehydrogenase deficiency causing sudden child death. J Inherit Metab Dis. 1992; 171-180. Ref: https://goo.gl/FPmU8b

39. Kurtz DM, Rinaldo P, Rhead WJ, Tian L, Millington DS, et al. Targeted disruption of mouse long-chain acyl-CoA dehydrogenase gene reveals crucial roles for fatty acid oxidation. Proc Natl Acad Sci USA. 1998; 15592-15597. Ref: https://goo.gl/DqxeyC

40. Drosatos K, Schulze PC. Cardiac lipotoxicity: molecular pathways and therapeutic implications. Curr Heart Fail Rep. 2013; 109-121. Ref: https://goo.gl/qyGyci

41. Hickson-Bick DL, Buja LM, McMillin JB. Palmitate-mediated alterations in the fatty acid metabolism of rat neonatal cardiac myocytes. J Mol Cell Cardiol. 2000; 511-519. Ref: https://goo.gl/1se7ws

42. Sparagna GC, Hickson-Bick DL, Buja LM, McMillin JB. A metabolic role for mitochondria in palmitate-induced cardiac myocyte apoptosis. Am J Physiol Heart Circ Physiol. 2000; H2124-2132. Ref: https://goo.gl/rUwtZx

43. Dbaibo GS, Pushkareva MY, Rachid RA, Alter N, Smyth MJ, et al. p53-dependent ceramide response to genotoxic stress. J Clin Invest. 1998; 102: 329-339. Ref: https://goo.gl/mBJUv5

44. Rotolo JA, Zhang J, Donepudi M, Lee H, Fuks Z, et al. Caspase-dependent and -independent activation of acid sphingomyelinase signaling. J Biol Chem. 2005; 26425-26434. Ref: https://goo.gl/WaVFu

45. Dbaibo GS, El-Assaad W, Krikorian A, Liu B, Diab K, et al. Ceramide generation by two distinct pathways in tumor necrosis factor alpha-induced cell death. FEBS Lett. 2001; 7-12. Ref: https://goo.gl/JYXgjj
46. Quillet-Mary A, Jaffrezou JP, Mansat V, Bordier C, Naval J, et al. Implication of mitochondrial hydrogen peroxide generation in ceramide-induced apoptosis. J Biol Chem. 1997; 21388-21395. Ref: https://goo.gl/TnhYZ4

47. Siskind LJ. Mitochondrial ceramide and the induction of apoptosis. J Bioenerg Biomembr. 2005; 143-153. Ref: https://goo.gl/1RMjof

48. Weiss B, Stoffel W. Human and murine serine-palmitoyl-CoA transferase–cloning, expression and characterization of the key enzyme in sphingolipid synthesis. Eur J Biochem. 1997; 239-247. Ref: https://goo.gl/HBTYc7

49. Shimabukuro M, Higa M, Zhou YT, Wang MY, Newgard CB, et al. Lipoapoptosis in beta-cells of obese prediabetic fa/fa rats. Role of serine palmitoyltransferase overexpression. J Biol Chem. 1998; 32487-32490. Ref: https://goo.gl/o9DBkr

50. Merrill AH, Jr. De novo sphingolipid biosynthesis: a necessary, but dangerous, pathway. J Biol Chem. 2002; 25843-25846. Ref: https://goo.gl/xy7cMM

51. Haimovitz-Friedman A, Kan CC, Ehleiter D, Persaud RS, McLoughlin M, et al. Ionizing radiation acts on cellular membranes to generate ceramide and initiate apoptosis. J Exp Med. 1994; 525-535. Ref: https://goo.gl/ahzCL7

52. Hardie DG, Carling D,Carlson M. The AMP-activated/SNF1 protein kinase subfamily: metabolic sensors of the eukaryotic cell? Annu Rev Biochem. 1998; 821-855. Ref: https://goo.gl/fP4hp3

53. Chabowski A, Momken I, Coort SL, Calles-Escandon J, Tandon NN, et al. Prolonged AMPK activation increases the expression of fatty acid transporters in cardiac myocytes and perfused hearts. Mol Cell Biochem. 2006; 201-212. Ref: https://goo.gl/E4DPKj

54. Habets DD, Coumans WA, Voshol PJ, den Boer MA, Febbraio M, et al. AMPK-mediated increase in myocardial long-chain fatty acid uptake critically depends on sarcosommal CD36. Biochem Biophys Res Commun. 2007; 204-210. Ref: https://goo.gl/Qo1fFp

55. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest. 2002; 121-130. Ref: https://goo.gl/Tgo6Jk

56. Vega RB, Huss JM, Kelly DP. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Mol Cell Biol, 2000; 1868-1876. Ref: https://goo.gl/1XuSzq

57. Karbowska J, Kochan Z, Smolenski RT. Peroxisome proliferator-activated receptor alpha is downregulated in the failing human heart. Cell Mol Biol Lett. 2003; 49-53. Ref: https://goo.gl/zfFVAu

58. Masamura K, Tanaka N, Yoshida M, Kato M, Kawai Y, et al. Myocardial metabolic regulation through peroxisome proliferator-activated receptor alpha after myocardial infarction. Exp Clin Cardiol. 2003; 61-66. Ref: https://goo.gl/LPRDH7

59. Narravula S,Colgan SP. Hypoxia-inducible factor 1-mediated inhibition of peroxisome proliferator-activated receptor alpha expression during hypoxia. J Immunol. 2001; 7543-7548. Ref: https://goo.gl/pvsQDV

60. Aoyama T, Peters JM, Iritani N, Nakajima T, Furihata K, et al. Altered constitutive expression of fatty acid-metabolizing enzymes in mice lacking the peroxisome proliferator-activated receptor alpha (PPARalpha). J Biol Chem. 1998; 5678-5684. Ref: https://goo.gl/6N7BKG

61. Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, et al. Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Mol Cell Biol. 1995; 3012-3022. Ref: https://goo.gl/EVF3d

62. Kersten S. Peroxisome proliferator activated receptors and lipoprotein metabolism. PPAR Res. 2008; 132960. Ref: https://goo.gl/vxmLo

63. Yoon M. PPARalpha in Obesity: Sex Difference and Estrogen Involvement. PPAR Res. 2010. Ref: https://goo.gl/dFMJ2x

64. Inoguchi T, Battan R, Handler E, Sportsman JR, Heath W, et al. Preferential elevation of protein kinase C isofrom beta II and diacylglycerol levels in the aorta and heart of diabetic rats: differential reversibility to glycemic control by islet cell transplantation. Proc Natl Acad Sci U S A. 1992; 11059-11063. Ref: https://goo.gl/49QxVc

65. Jalili T, Manning J,Kim S. Increased translocation of cardiac protein kinase C beta2 accompanies mild cardiac hypertrophy in rats fed saturated fat. J Nutr. 2003; 358-361. Ref: https://goo.gl/E9WeXu
66. Fujino T, Asaba H, Kang MJ, Ikeda Y, Sone H, et al. Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. Proc Natl Acad Sci U S A. 2003; 229-234. Ref: https://goo.gl/TzbGv6

67. Kim DH, Cho YM, Lee KH, Jeong SW, Kwon OJ. Oleate protects macrophages from palmitate-induced apoptosis through the downregulation of CD36 expression. Biochem Biophys Res Commun. 2017; 477-482. Ref: https://goo.gl/RVFm9

68. Wen SY, Velmurugan BK, Day CH, Shen CY, Chun LC, et al. High density lipoprotein (HDL) reverses palmitic acid induced energy metabolism imbalance by switching CD36 and GLUT4 signaling pathways in cardiomyocyte. J Cell Physiol. 2017; 3020-3029. Ref: https://goo.gl/oph6mT

69. Park SY, Cho YR, Kim HJ, Higashimori T, Danton C, et al. Unraveling the temporal pattern of diet-induced insulin resistance in individual organs and cardiac dysfunction in C57BL/6 mice. Diabetes. 2005; 3530-3540. Ref: https://goo.gl/LtGceU

70. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, et al. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. Diabetes. 2002; 3020-3024. Ref: https://goo.gl/nEBTVo

71. Mazumder PK, O'Neill BT, Roberts MW, Buchanan J, Yun UJ, et al. Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts. Diabetes. 2004; 2366-2374. Ref: https://goo.gl/oE4W2

72. How OJ, Aasum E, Severson DL, Chani FY, Essop MF, et al. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. Diabetes. 2006; 466-473. Ref: https://goo.gl/2mXJ4A

73. Belke DD, Larsen TS, Gibbs EM, Severson DL. Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am J Physiol Endocrinol Metab. 2000; 1104-1113. Ref: https://goo.gl/DkGsHp

74. Kolter T, Uphues J, Eckel J. Molecular analysis of insulin resistance in isolated ventricular cardiomyocytes of obese Zucker rats. Am J Physiol. 1997; 59-67. Ref: https://goo.gl/GcveR7

75. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science, 2004; 457-461. Ref: https://goo.gl/bRDo8T

76. Wu W, Muchir A, Shan J, Bonne G, Worman HJ. Mitogen-activated protein kinase inhibitors improve heart function and prevent fibrosis in cardiomyopathy caused by mutation in lamin A/C gene. Circulation. 2011; 55-61. Ref: https://goo.gl/Qa4PS9

77. Turdi S, Kandadi MR, Zhao J, Huff AF, Du M, et al. Deficiency in AMP-activated protein kinase exaggerates high fat diet-induced cardiac hypertrophy and contractile dysfunction. J Mol Cell Cardiol. 2011; 712-722. Ref: https://goo.gl/iV3gp

78. Li YJ, Wang PH, Chen C, Zou MH, Wang DW. Improvement of mechanical heart function by trimetazidine in db/db mice. Acta Pharmacol Sin. 2010; 560-569. Ref: https://goo.gl/RV6C6P

79. Tan SH, Shui G, Zhou J, Li JJ, Bay BH, et al. Induction of autophagy by palmitic acid via protein kinase C-mediated signaling pathway independent of mTOR (mammalian target of rapamycin). J Biol Chem. 2012; 14364-14376. Ref: https://goo.gl/MBKrB

80. Marsh SA, Powell PC, Dell'Italia LJ, Chatham JC. Cardiac O-GlcNAcylation blunts autophagic signaling in the diabetic heart. Life Sci. 2013; 648-656. Ref: https://goo.gl/JkXcdK

81. Khan MJ, Rizwan Alam M, Waldeck-Weiermair M, Karsten F, Groschner L, et al. Inhibition of autophagy rescues palmitic acid-induced necroptosis of endothelial cells. J Biol Chem. 2012; 21110-21120. Ref: https://goo.gl/Bfj3K

82. Zhang QJ, Holland WL, Wilson L, Tanner JM, Kearns D, et al. Ceramide mediates vascular dysfunction in diet-induced obesity by PP2A-mediated dephosphorylation of the eNOS-Akt complex. Diabetes. 2012; 21110-21120. Ref: https://goo.gl/2K6CyX

83. Ussher JR, Holmes CD, Keung W, Fillmore N, Jaswal JS, et al. Inhibition of autophagy increases ceramide levels and reduces lipid accumulation following diet-induced insulin resistance. PLoS One. 2012; e37703. Ref: https://goo.gl/HeE3o4

84. Rame JE, Barouch LA, Sack MN, Lynn EG, Abu-Asab M, et al. Caloric restriction in leptin deficiency does not correct myocardial steatosis: failure to normalize PPAR(α)/PGC1(α) and thermogenic glycerolipid/fatty acid cycling. Physiol Genomics. 2011; 726-738. Ref: https://goo.gl/c2ZM47

85. Gordon GB. Saturation of fatty acid toxicity. II. Lipid accumulation, ultrastructural alterations, and toxicity in mammalian cells in culture. Exp Mol Pathol. 1977; 262-276. Ref: https://goo.gl/dj9TM7
86. Greenberg AS, Coleman RA, Kraemer FB, McManaman JL, Obin MS, et al. The role of lipid droplets in metabolic disease in rodents and humans. J Clin Invest. 2011; 2102-2110. Ref: https://goo.gl/res3cF

87. Wang H, Sreenivasan U, Hu H, Saladino A, Polster BM, et al. Perilipin 5, a lipid droplet-associated protein, provides physical and metabolic linkage to mitochondria. J Lipid Res. 2011; 2159-2168. Ref: https://goo.gl/ZfCy7H

88. Kuramoto K, Okamura T, Yamaguchi T, Nakamura TY, Wakabayashi S, et al. Perilipin 5, a lipid droplet-binding protein, protects heart from oxidative burden by sequestering fatty acid from excessive oxidation. J Biol Chem. 2012; 23852-23863. Ref: https://goo.gl/6QDxYr

89. Jordan SD, Kruger M, Willmes DM, Redemann N, Wunderlich FT, et al. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. Nat Cell Biol. 2011; 434-446. Ref: https://goo.gl/W5wpR7

90. Jheng HF, Tsai PJ, Guo SM, Kuo LH, Chang CS, et al. Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol Cell Biol. 2012; 309-319. Ref: https://goo.gl/LyUoeT