Journal of Cytokine Biology

Debnath and Sarkar, J Cytokine Biol 2016, 1:1

Review Article Open Access

Obesity Induced Metaflammation: Pathophysiology and Mitigation

Monalisa Debnath* **and Sutripta Sarkar**

Department of Food and Nutrition, Barrackpore Rastraguru Surendranath College, Kolkata, West Bengal, India

***Coressponding author**: Monalisa Debnath, Department of Food and Nutrition, Barrackpore Rastraguru Surendranath College, Kolkata, West Bengal, India, Tel: 91-9674208448; E-mail: monalisadebnath1108@gmail.com

Received date: February 26, 2016; **Accepted date:** March 7, 2016; **Published date:** March 17, 2016

Abstract

Obesity is dramatically increasing worldwide and there exists a significant association of its prevalence with Type 2 Diabetes Mellitus, hypertension, cardiovascular diseases etc. The altered homeostasis of nutritionally overloaded metabolic cells marks the development of obesity induced inflammation. It is marked by elevated expression of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors-nuclear factor-kB, activator protein-1, nuclear factor of activated T cells and signal transducer and activator of transcription 3 and; execution of a macromolecular innate immune cell sensor- inflammasome to activate caspase-1 pathway resulting in photolytic maturation. In brief, there occurs an evidential increase in pro-inflammatory cytokines released from the M1 macrophages of white adipose tissue including TNF-α, IL-6, CRP, IL-1β, etc. on contrary an observable decrease in anti-inflammatory cytokines like IL-10, IL-Ra, adiponectin etc. released from M2 macrophages. Along with adipose tissue, immune cells, liver, brain, muscles and pancreas also suffers undergoes inflammatory damage. The inflammatory kinases like JNK and IKK apart from inhibiting insulin action and glucose uptake, also down-regulate transcriptional process resulting in increased expression of pro-inflammatory cytokines. The inflammatory process is initiated by Macrophage-like Kupffer cells following the transducer signals produced by the white adipose tissues further leading to necro-inflammation. Muscle fibre is said to suffer from decreased glycogen synthesis. Obesity also triggers the hypothalamic-pituitary adrenal axis. Pancreas modulating the insulin homeostasis and glucose tolerance is also exaggeratedly affected. Multi-dimensional interventions so as to check obesity induced metaflammation have been undertaken that includes therapeutic intervention and administration of synthetic drugs to target the actual inflammatory. Thus, by proper weight management and diet inflammatory responses in obesity can be controlled to a large extent.

Keywords Cytokines; Chemokines; Macrophage infiltration; Free fatty acid; White adipose tissue; Inflammatory cascade

Introduction

Obesity, being a grave problem and one of the profoundly discussed metabolic disorders is given immense of research concern to re-evaluate its pathophysiology [1]. It is one of the most escalating health hazard stretched all over the world population with a BMI >30 Kg/m^2 and; an approximate statistical prevalence of ~ 500 million people suffering with its synergistic morbidities [2-4]. Obesity aggravates broad spectrum of metabolic complications as all of these are inter-related through the vital bio-chemical pathways undertaken by the tissue system mainly adipose tissue, liver, pancreas, brain etc [5]. Metabolic homeostasis is hampered following excess nutrient intake during obesity that renders initiation of inflammatory phenomenon triggered by the specialized metabolic cells [6,7].

Obesity alters expression intracellular signalling molecules

The genes encoding for the inflammatory mediators like- cytokines, chemokines etc are up-regulated via activation of transcription factor-nuclear factor-kβ (NF-kβ), activator protein-1 (AP-1),nuclear factor of activated T cells (NFAT) and signal transducer and activator of transcription 3(STAT 3) [8,9]. Increasedsequestration of free fatty acid during obese condition signals inflammasome- a macromolecular innate immune cell sensor to activate caspase-1 pathway that results in proteolytic maturation and elevated secretion of pro-inflammatory cytokines [10-14]. Later to the up-regulated genes encoding for adipocytokines, there occurs fluctuation in the prominent intracellular factors like C-Junction N terminal Kinase (JNK), Inhibitors of K Kinase (IKK) and Protein Kinase R (PKR) that further induces inflammatory pathway in the metabolic tissues [15,16]. Researches on genetic analysis have rendered an inevitable association between obesity, its synergistic effects with varied phenotypes of metabolic complications and the gene induced inflammatory cascade [17-20].

Obesity induced metaflammation

Adipose tissue: The adipose tissue acts as an endocrine gland initiating metabolic phenomenon of cytokine and chemokine secretion; hypoxia or cell death and infiltration of immune cells [21]. The distinctive M1 and M2 types of macrophages secreted from the white adipose tissue (WAT) are classically altered showing greater phenotypic coding of M1 macrophages as characterized by CD11+ surface marker and production of enzymes of nitric oxide synthase (iNOS) [22]. These further results in release of cytokines like TNF-α, CRP, IL-1β, complement C (C3) and IL-6 [23-26]. Contradictorily, the anti-inflammatory cytokines like IL-10, IL-1Ra and iNOS inhibited by arginase are found to be diminishingly produced by the macrophages [27,28]. These alterations later stimulate the hypothalamic—pituitary —adrenal axis [29-31]. Hence, such obesity related biomarkers may contribute vitally through regulating other metabolic complications like insulin sensitivity, diabetes, impaired glucose tolerance and altered lipid metabolism [26]. Aberrant lipid metabolism marked by fatty acyl CoA and diacyl glycerols production further results in altered insulin

signalling as a result of serine/threonine kinase cascade mediated phosphorylation of insulin receptor substrate (IRS)-1. Similar mechanism occurs in the liver where increased hepatocellular diacylglycerol activating protein kinase C hinders tyrosine phosphorylation of IRS-2 [32]. Downregulation of transcription factors including activator protein-1 (AP-1), NF-kB, interferon regulatory factor (IRF) and peroxisiome- proliferator-activated receptorγ (PPARγ) eventually renders decline in diponectin specified cytokines [33].

Immune cells: Alongwith macrophage levels which are mentioned to be elevated among obese mice as noted by researchers, an observable modulation of T cells, mast cells and natural killer cells (NK) are also noticed during obesity [34-37]. Obesity increases CD8+ to CD4+ T cell counts and decreases immunosuppressive T regulatory cell number that further promotes macrophage recruitment and aggravates kinase activity [38-42]. Adipose tissue over-expressing chemoattractant CCL2 leads to macrophage infiltration, insulin resistance and hepatosteatosis [43,44].

Liver: Macrophage like kupffer cells in the liver gets over-activated for inflammatory phenomenon among obese individuals as compared to controls [45,46]. Experimental studies on mice have shown liver specific activation of IKKβ resulting in reduced insulin sensitivity, glucose tolerance [46] and; increased cytokines like CRP, PAI-1 and serum amyloid A. A significant relation have been chalked out between WAT secreted products (leptin, adiponectin, TNF-α) and hepatic damage [47]. There is a reciprocal relationship between adiponectin and hepatic necro-inflammation [48,49]. The mechanisms underlying the deleterious association between accumulation of macrophages in WAT and liver pathology could involve increased free fatty acid (FFA) flux and/or delivery of proinflammatory factors to the liver through the portal circulation. Portal vein of obese subjects has marked increased IL-6 level that may end up in liver damage [50]. A significant worsening effect has been noted between omental WAT-secreted products (leptin, adiponectin,TNF-) and hepatic damage associated with necroinflammation [51-53].

Muscle: The inflammatory phenomenon in the muscle tissues and insulin sensitivity are said to be influenced by the inflammatory mediators like TNF-α, IL-6, CCL-2, retinol binding protein etc. Released from the liver and adipose tissue, although no such obesity induced macrophage infiltration is observed [54, 55]. Muscle wasting phenotype in the muscle tissues of mice via the activation of IKK/ NFkβ pathway have been revealed without any evidential cytokine mediated inflammation [56].

Brain: Convincing evidence submitted by Souza et al. revealed that obesity marks activation of inflammatory pathways in the hypothalamus that eventually modulates the expression of TNF-α, IL-1β and IL-6 resulting in hypothalamic apoptosis [57-59].

Pancreas: Increased macrophage infiltration results in steep increase of inflammatory cytokines and recruitment of neutrophils, monocytes, and lymphocytes to the pancreas during obesity thus paving way to glucose intolerance [60-63]. Activation of NF-kβ pathways is influenced by IL-1β and IFN ϒ that can be downregulated by using non-degradable inhibitor for NF-kβ which signals IKBα thus resulting in curing of islets from NO2 production and IL-1β induced apoptosis [64]. Obesity and pancreatitis together creates more proneness to higher circulating inflammatory cytokines among patients [65,66].

Mitigation of inflammatory responses in obesity: Multidimensional approaches including targeted inflammatory molecule or therapeutic interventions are being undertaken so as to check obesity induced metainflammation with an objective of hindering inflammatory response by neutralizing the cytokines, chemokines, adhesion molecules/ other mediators [67-71]. Available research evidence has revealed improved insulin action in animal models by blocking specific inflammatory kinases pathway [72,73]. Checking the plasma concentration of TNF-α using its antagonist have shown to down regulate blood glucose level and elevate adiponectin levels [74]. Recombinant IL-1 receptor antagonist, synthetic/peptide JNK inhibitors and interfering RNAs have shown to result in insulin sensitivity and glucose tolerance [75-79]. Significant reduction in cholesterol level, diminished proneness towards CVD and depressed cell adhesion/ migration associated with metainflammatory phenomenon have been achieved by statin therapy which henceforth checks TNF-α and IL-6 concentration [80-86]. Statin therapy has shown to act via different immune-mechanism in obesity induced inflammatory cascade [86-90]. Cell-based immunotherapy have proved beneficial thus by eliminating T cell and mast cell population, CD11+ cells [91-93]. Introduction to chemical chaperons, thiazolidenes exhibit positive effects as the former reduces ER stress and the later possess agonistic properties to PARPϒ which altogether enhances insulin sensitivity and glucose tolerance [94-98]. Recombinant protein has shown to curtail TNF-α production, blood sugar and fatty liver synthesis [99-101]. Diet restricted with excess fat and empty calories can prove beneficial. Omega-3 and omega-6fatty acid; linolenic fatty acid and PUFA constituting of metabolites-EPA and DHA renders anti-inflammatory function can prevent CVD, atherosclerosis along with depressing cytokine expression and macrophage infiltration [102-106]. Dietary consumption of Mediterranean foods, use of mustard oil/soya bean oil, increased intake of fruits, vegetables, nuts and whole gram can curb the complication [107,108]. Coffee, cocoa, vitamin E and green tea also help in the mitigation of inflammatory responses in obesity [109-111]. Regular physical activity also deliver better and positive results with mitigated inflammation among obese patients [112,113]; also improvement in endothelial function, liver and tissue angiogenesis [114,115]. Thus, by proper weight management and diet inflammatory responses in obesity can be controlled to a large extent [116].

References

1. Debnath M, Agrawal S, Agrawal A, Dubey GP (2015) Metaflammatory responses during obesity: Pathomechanism and treatment. Obes Res Clin Pract .
2. Yach D, Stuckler D, Brownell KD (2006) Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med 12: 62-66.
3. World Health Organisation (2014) Global Health Observatory.
4. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, et al. (2003) Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. JAMA 290: 2271-2276.
5. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ (2008) Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 9: 474-488.
6. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, et al. (2005) Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 11: 183-190.
7. Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, et al. (2007) Increased number of islet-associated macrophages in type 2 diabetes. Diabetes 56: 2356-2370.
8. Smale ST (2010) Selective transcription in response to an inflammatory stimulus. Cell 140: 833-844.

9. Baumgart S, Ellenrieder V, Fernandez-Zapico ME (2013) Oncogenic transcription factors: cornerstones of inflammation-linked pancreatic carcinogenesis. Gut 62: 310-316.
10. Strowig T, Henao-Mejia J, Elinav E, Flavell R (2012) Inflammasomes in health and disease. Nature 481: 278-286.
11. Stienstra R, Tack CJ, Kanneganti TD, Joosten LA, Netea MG (2012) The inflammasome puts obesity in the danger zone. Cell Metab 15: 10-18.
12. Lamkanfi M, Kanneganti TD (2012) The inflammasome: a remote control for metabolic syndrome. Cell Res 22: 1095-1098.
13. Church LD, Cook GP, McDermott MF (2008) Primer: inflammasomes and interleukin 1beta in inflammatory disorders. Nat Clin Pract Rheumatol 4: 34-42.
14. Dagenais M, Dupaul-Chicoine J, Saleh M (2010) Function of NOD-like receptors in immunity and disease. Curr Opin Investig Drugs 11: 1246-1255.
15. Solinas G, Karin M (2010) JNK and IKKbeta: molecular links between obesity and metabolic dysfunction. FASEB J 24: 2596-2611.
16. Nakamura T, Furuhashi M, Li P, Cao H, Tuncman G, et al. (2010) Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. Cell 140: 338-348.
17. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, et al. (2002) High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 51: 455-461.
18. Festa A, D'Agostino R, Tracy RP, Haffner SM (2002) Insulin Resistance Atherosclerosis Study Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes 51: 1131-1137.
19. Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, et al. (2008) Genetics of gene expression and its effect on disease. Nature 452: 423-428.
20. Chen Y, Zhu J, Lum PY, Yang X, Pinto S, et al. (2008) Variations in DNA elucidate molecular networks that cause disease. Nature 452: 429-435.
21. Osborn O, Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 18: 363-374.
22. Sartipy P, Loskutoff DJ (2003) Monocyte chemoattractant protein 1 in obesity and insulin resistance. Proc Natl Acad Sci USA 100: 7265-7270.
23. Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA (2013) Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. Int J Endocrinol 2013: 678159.
24. Fuentes E, Fuentes F, Vilahur G, Badimon L, Palomo I (2013) Mechanisms of chronic state of inflammation as mediators that link obese adipose tissue and metabolic syndrome. Mediators Inflamm 2013: 136584.
25. Leal Vde O, Mafra D (2013) Adipokines in obesity. Clin Chim Acta 419: 87-94.
26. Balistreri CR, Caruso C, Candore G (2010) The role of adipose tissue and adipokines in obesity-related inflammatory diseases. Mediators Inflamm 2010: 802078.
27. Osborn O, Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 18: 363-374.
28. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, et al. (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17: 4-12.
29. Van Dyken SJ, Locksley RM (2013) Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease. Annu Rev Immunol 31: 317-343.
30. Tateya S, Kim F, Tamori Y (2013) Recent advances in obesity-induced inflammation and insulin resistance. Front Endocrinol (Lausanne) 4: 93.
31. Valle M, Martos R, Gascón F, Cañete R, Zafra MA, et al. (2005) Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. Diabetes Metab 31: 55-62.
32. Morino K, Petersen KF, Shulman GI (2006) Molecular mechanisms of insulin resistance. Diabet Med 22: 674-682
33. Trujillo ME, Scherer PE (2005) Adiponectin--journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med 257: 167-175.
34. Song MJ, Kim KH, Yoon JM, Kim JB (2006) Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. Biochem Biophys Res Commun 346: 739-745.
35. Xu H, Barnes GT, Yang Q, Tan G, Yang D, et al. (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112: 1821-1830.
36. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796-1808.
37. Olefsky JM, Glass CK (2010) Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 72: 219-246.
38. Johnson AR, Milner JJ, Makowski L (2012) The inflammation highway: metabolism accelerates inflammatory traffic in obesity. Immunol Rev 249: 218-238.
39. Liu J, Divoux A, Sun J, Zhang J, Clément K, et al. (2009) Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat Med 15: 940-945.
40. Ohmura K, Ishimori N, Ohmura Y, Tokuhara S, Nozawa A, et al. (2010) Natural killer T cells are involved in adipose tissues inflammation and glucose intolerance in diet-induced obese mice. Arterioscler Thromb Vasc Biol 30: 193-199.
41. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM (1995) Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 95: 2409-2415.
42. Harman-Boehm I, Blüher M, Redel H, Sion-Vardy N, Ovadia S, et al. (2007) Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity. J Clin Endocrinol Metab 92: 2240-2247.
43. Kamei N, Tobe K, Suzuki R, Ohsugi M, Watanabe T, et al. (2006) Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. J Biol Chem 281: 26602-26614.
44. Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, et al. (2006) MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 116: 1494-1505.
45. Baffy G (2009) Kupffer cells in non-alcoholic fatty liver disease: the emerging view. J Hepatol 51: 212-223.
46. Sidiropoulos PI, Karvounaris SA, Boumpas DT (2008) Metabolicsyndrome in rheumatic diseases. Arthritis Res Ther 10: 207.
47. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, et al. (2005) IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 11: 191-198.
48. Cai D, Frantz JD, Tawa NE Jr, Melendez PA, Oh BC, et al. (2004) IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell 119: 285-298.
49. Ito A, Suganami T, Yamauchi A, Degawa-Yamauchi M, Tanaka M, et al. (2008) Role of CC chemokine receptor 2 in bone marrow cells in the recruitment of macrophages into obese adipose tissue. J Biol Chem 283: 35715-35723.
50. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S (2007) Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 56: 1010-1013.
51. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, et al. (2004) Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 40: 46-54.
52. Marra F, Aleffi S, Bertolani C, Petrai I, Vizzutti F (2005) Adipokines and liver fibrosis. Eur Rev Med Pharmacol Sci 9: 279-284.
53. Musso G, Gambino R, Biroli G, Carello M, Fagà E, et al. (2005) Hypoadiponectinemia predicts the severity of hepatic fibrosis and

pancreatic Beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis. Am J Gastroenterol 100: 2438-2446.

54. Olefsky JM, Glass CK (2010) Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 72: 219-246.
55. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, et al. (2005) Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436: 356-362.
56. Saghizadeh M, Ong JM, Garvey WT, Henry RR, Kern PA (1996) The expression of TNF alpha by human muscle. Relationship to insulin resistance. J Clin Invest 97: 1111-1116.
57. Obici S, Zhang BB, Karkanias G, Rossetti L (2002) Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med 8: 1376-1382.
58. Moraes JC, Coope A, Morari J, Cintra DE, Roman EA, et al. (2009) High-fat diet induces apoptosis of hypothalamic neurons. PLoS One 4: e5045.
59. Zhang X, Zhang G, Zhang H, Karin M, Bai H, et al. (2008) Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135: 61-73.
60. Saeki K, Kanai T, Nakano M, Nakamura Y, Miyata N, et al. (2012) CCL2-induced migration and SOCS3-mediated activation of macrophages are involved in cerulein-induced pancreatitis in mice. Gastroenterology 142: 1010-1020.
61. Perides G, Weiss ER, Michael ES, Laukkarinen JM, Duffield JS, et al. (2011) TNF-alpha-dependent regulation of acute pancreatitis severity by Ly-6C(hi) monocytes in mice. J Biol Chem 286: 13327-13335.
62. Bedrosian AS, Nguyen AH, Hackman M, Connolly MK, Malhotra A, et al. (2011) Dendritic cells promote pancreatic viability in mice with acute pancreatitis. Gastroenterology 141: 1915-1926.
63. Hoque R, Sohail M, Malik A, Sarwar S, Luo Y, et al. (2011) TLR9 and the NLRP3 inflammasome link acinar cell death with inflammation in acute pancreatitis. Gastroenterology 141: 358-369.
64. Giannoukakis N, Rudert WA, Trucco M, Robbins PD (2000) Protection of human islets from the effects of interleukin-1beta by adenoviral gene transfer of an Ikappa B repressor. J Biol Chem 275: 36509-36513.
65. Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. J Clin Invest 115: 1111-1119.
66. Leser HG, Gross V, Scheibenbogen C, Heinisch A, Salm R, et al. (1991) Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. Gastroenterology 101: 782-785.
67. Hartman H, Abdulla A, Awla D, Lindkvist B, Jeppsson B, et al. (2012) P-selectin mediates neutrophil rolling and recruitment in acute pancreatitis. Br J Surg 99: 246-255.
68. Gukovskaya AS, Vaquero E, Zaninovic V, Gorelick FS, Lusis AJ, et al. (2002) Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. Gastroenterology 122: 974-984.
69. Abdulla A, Awla D, Thorlacius H, Regnér S (2011) Role of neutrophils in the activation of trypsinogen in severe acute pancreatitis. J Leukoc Biol 90: 975-982.
70. Hartwig W, Klafs M, Kirschfink M, Hackert T, Schneider L, et al. (2006) Interaction of complement and leukocytes in severe acute pancreatitis: potential for therapeutic intervention. Am J Physiol Gastrointest Liver Physiol 291: G844-850.
71. Werner J, Hartwig W, Hackert T, Kaiser H, Schmidt J, et al. (2012) Multidrug strategies are effective in the treatment of severe experimental pancreatitis. Surgery 151: 372-381.
72. Kaneto H, Nakatani Y, Miyatsuka T, Kawamori D, Matsuoka TA, et al. (2004) Possible novel therapy for diabetes with cell-permeable JNK-inhibitory peptide. Nat Med 10: 1128-1132.
73. Liu G, Rondinone CM (2005) JNK: bridging the insulin signaling and inflammatory pathway. Curr Opin Investig Drugs 6: 979-987.
74. Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, et al. (2011) TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab 96: E146-150.
75. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, et al. (2007) Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 356: 1517-1526.
76. Kaneto H, Nakatani Y, Miyatsuka T, Kawamori D, Matsuoka TA, et al. (2004) Possible novel therapy for diabetes with cell-permeable JNK-inhibitory peptide. Nat Med 10: 1128-1132.
77. Nakatani Y, Kaneto H, Kawamori D, Hatazaki M, Miyatsuka T, et al. (2004) Modulation of the JNK pathway in liver affects insulin resistance status. J Biol Chem 279: 45803-45809.
78. Wilcox DM, Yang R, Morgan SJ, Nguyen PT, Voorbach MJ, et al. (2006) Delivery of RNAi reagents in murine models of obesity and diabetes.J RNAi Gene Silencing 3: 225-236.
79. Siddiqui MA, Reddy PA (2010) Small molecule JNK (c-Jun N-terminal kinase) inhibitors. J Med Chem 53: 3005-3012.
80. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, et al. (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. below N Engl J Med 359: 2195-2207.
81. Ridker PM, Danielson E, Fonseca FA. (2009) Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 373:1175—1182.
82. Waehre T, Yndestad A, Smith C, Haug T, Tunheim SH, et al. (2004) Increased expression of interleukin-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. Circulation 109: 1966-1972.
83. Cambuli VM1, Musiu MC, Incani M, Paderi M, Serpe R, et al. (2008) Assessment of adiponectin and leptin as biomarkers of positive metabolic outcomes after lifestyle intervention in overweight and obese children. J Clin Endocrinol Metab 93: 3051-3057.
84. Henriksbo BD, Schertzer JD (2015) Is immunity a mechanism contributing to statin-induced diabetes? Adipocyte 4: 232-238.
85. Ando H, Takamura T, Ota T, Nagai Y, Kobayashi K (2000) Cerivastatin improves survival of mice with lipopolysaccharide-induced sepsis. J Pharmacol Exp Ther 294: 1043-1046.
86. Rosenson RS, Tangney CC, Casey LC (1999) Inhibition of proinflammatory cytokine production by pravastatin. Lancet 353: 983-984.
87. Park OY, Kim SH, Ahn YK(2008) Statin reduces C-reactive protein and interleukin-6 in normocholesterolemic patients with acute coronary syndrome. Chonnam Med J 44:13 16.
88. Rysz J, Ray KK, Abdollahi M (2013) The effects of statins on blood pressure in normotensive or hypertensive Intl J.Cardio. 168: 2816-2824
89. Banach M, Nikfar S, Rahimi R, Bielecka-Dabrowa A, Pencina MJ, et al. (2013) The effects of statins on blood pressure in normotensive or hypertensive subjects--a meta-analysis of randomized controlled trials. Int J Cardiol 168: 2816-2824.
90. Stępień M, Stępień A, Wlazeł RN, Paradowski M, Banach M, et al. (2013) Obesity indices and adipokines in non-diabetic obese patients with early stages of chronic kidney disease. Med Sci Monit 19: 1063-1072.
91. Barylski M, Malyszko J, Rysz J, Mysliwiec M, Banach M (2011) Lipids, blood pressure, kidney - what was new in 2011? Arch Med Sci 7: 1055-1066.
92. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, et al. (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15: 930-939.
93. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, et al. (2009) CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med 15: 914-920.
94. Winer S, Chan Y, Paltser G, Truong D, Tsui H, et al. (2009) Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med 15: 921-929.

95. Patsouris D, Li PP, Thapar D, Chapman J, Olefsky JM, et al. (2008) Ablation of CD11c-positive cells normalizes insulin sensitivity in obese insulin resistant animals. Cell Metab 8: 301-309.

96. Kars M, Yang L, Gregor MF, Mohammed BS, Pietka TA, et al. (2010) Tauroursodeoxycholic Acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. Diabetes 59: 1899-1905.

97. Ruan H, Pownall HJ, Lodish HF (2003) Troglitazone antagonizes tumor necrosis factor-alpha-induced reprogramming of adipocyte gene expression by inhibiting the transcriptional regulatory functions of NF-kappaB. J Biol Chem 278: 28181-28192.

98. Kolak M, Yki-Järvinen H, Kannisto K, Tiikkainen M, Hamsten A, et al. (2007) Effects of chronic rosiglitazone therapy on gene expression in human adipose tissue in vivo in patients with type 2 diabetes. J Clin Endocrinol Metab 92: 720-724.

99. Peraldi P, Xu M, Spiegelman BM (1997) Thiazolidinediones block tumor necrosis factor-alpha-induced inhibition of insulin signaling. J Clin Invest 100: 1863-1869.

100. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, et al. (2002) Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 106: 2767-2770.

101. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, et al. (2003) Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 278: 2461-2468.

102. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, et al. (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7: 941-946.

103. Wall R, Ross RP, Fitzgerald GF, Stanton C (2010) Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev 68: 280-289.

104. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE (2003) Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. Circulation 107: 1852-1857.

105. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, et al. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell 142: 687-698.

106. Todoric J, Löffler M, Huber J, Bilban M, Reimers M, et al. (2006) Adipose tissue inflammation induced by high-fat diet in obese diabetic mice is prevented by n-3 polyunsaturated fatty acids. Diabetologia 49: 2109-2119.

107. Kesavulu MM, Kameswararao B, Apparao Ch, Kumar EG, Harinarayan CV (2002) Effect of omega-3 fatty acids on lipid peroxidation and antioxidant enzyme status in type 2 diabetic patients. Diabetes Metab 28: 20-26.

108. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, et al. (1999) Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 99: 779-785.

109. Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, et al. (2002) Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet 360: 1455-1461.

110. Jia H, Aw W, Egashira K, Takahashi S, Aoyama S, et al. (2014) Coffee intake mitigated inflammation and obesity-induced insulin resistance in skeletal muscle of high-fat diet-induced obese mice. Genes Nutr 9: 389.

111. Gu Y, Yu S, Lambert JD (2014) Dietary cocoa ameliorates obesity-related inflammation in high fat-fed mice. Eur J Nur 25: 439 - 445.

112. Min-Yu C (2011) Hepatoprotection of vitamin E and green tea on oxidative stress and inflammatory responses in animal models of obesity-triggered non-alcoholic fatty liver Disease. University of Connecticut, USA.

113. Schmidt FM, Lichtblau N, Minkwitz J, Chittka T, Thormann J, et al. (2014) Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. J Psychiatr Res 55: 29-34.

114. Ertek S, Cicero A (2012) Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci 8: 794-804.

115. Shephard RJ, Johnson N (2015) Effects of physical activity upon the liver. Eur J Appl Physiol 115: 1-46.

116. You T, Arsenis NC, Disanzo BL, Lamonte MJ (2013) Effects of exercise training on chronic inflammation in obesity : current evidence and potential mechanisms. Sports Med 43: 243-256.