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Nutrient-Adipokine Interaction in NAFLD: A Review

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Abstract Non-alcoholic fatty liver disease (NAFLD) is a non-communicable and a most common form of liver disease, and has strong ties with obesity epidemic. The pathophysiology of Non-alcoholic fatty liver disease (NAFLD) is complex and multifactorial, which makes the diagnosis difficult. On the basis of previous and recent published data, key characters could be proinflammatory cytokines and chemokines that are products of adipose tissue, namely inflammatory cells infiltrating the adipose tissue. In this review we will be discussing the role of adipokines in NAFLD and their interaction with the nutrients in the diet.

Keywords: *NAFLD, adipokines, N-3 PUFA, NASH*

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1. Introduction

NAFLD is characterized by excess fat accumulation in the liver with no history of alcohol abuse and in absence of other causes of secondary hepatic steatosis [1]. It is one of the most common chronic liver diseases. In the year 1981, NAFLD was firstly used as an umbrella term for a condition identified in pregnant women [2]. It describes a spectrum of diseases ranging from a simple benign fatty liver (hepatic steatosis) to nonalcoholic steatohepatitis (NASH), to progressive fibrosis and cirrhosis [3]. The pathogenesis of NAFLD is not fully understood and the earlier "two hit" theory involving two step process i.e. accumulation of triglycerides (first hit) and increased oxidative stress in hepatocytes (second hit) has now become obsolete and is not fully capable of explaining the metabolic and molecular changes taking place in the NAFLD. Therefore, the new multiple hit hypothesis involving multiple factors including role of insulin resistance, adipokines, nutritional factors, genetic and epigenetic factors leading to the more precise explanation of the NAFLD pathogenesis [4] has been recently introduced.

NAFLD was also found to have a strong tie with obesity epidemic, and its prevalence has been increasing in close relation to the increasing prevalence of obesity, diabetes and metabolic syndrome (MS) [5] with insulin resistance and visceral obesity as a central pathogenic factor. Visceral obesity is also marked by low grade systemic inflammation and exhibit increased production of inflammatory markers [6].

2. Relationship between Adipokine and NAFLD

Adipose tissue is considered to be the major and possibly the largest endocrine organ with a network of signaling pathways enabling the organism to adapt to a wide range of metabolic challenges, ability to synthesize variety of hormones, growth factors collectively called as cytokines with multi-potent effect on health and disease [7]. It releases adipokines which has local, peripheral and central effects and has a key role to play in energy balance of the body. Adipokines includes peptides, mainly but not exclusively, produced by adipocytes (e.g. Adiponectin and Leptin). Adipose tissue also produces other peptides, which are mainly but not exclusively produced by immune cells infiltrating adipose tissue [e.g. tumor necrosis factor (TNF)-α, interleukin (IL)-6] or endothelial cells of adipose tissue [8]. Adipose tissue releases numerous immune cells, including macrophages, B-cells, T-cells and neutrophils, obesity influences both the quantity and the nature of immune cell subtypes; when adipose tissue expands, it is infiltrated by more and different immune cells, which increase the burden of low-grade, but chronic inflammation of adipose tissue [9] Adipokines also have a pivotal role to play in the pathogenesis and severity of liver disease. In NAFLD, hypertrophied adipocytes release cytokines which stimulate pro-inflammatory and anti-inflammatory adipokines [10], which in turn modulate the steatosis, inflammation and fibrosis by interfering with the hepatic injury associated with the fatty infiltration [11]. In the current review we will be discussing the role of most prominent adipokines-adiponectin, leptin, resistin and visfatin and their interaction with diet in NAFLD.

2.1. Adiponectin

Adiponectin (named after adipose tissue) is secreted by adipose tissue and it is one of the most abundant adipokine, although apart from mature adipocytes, it can also be produced by other cells like hepatocytes in

response to hepatic injury, therefore it is considered to have an anti-inflammatory effect in NAFLD [12]. Adipocytes also have an anti steatotic effect as they increase energy consumption and free fatty acid oxidation in the hepatocytes by reducing hepatic triglyceride content, thereby improving the insulin sensitivity [13]. However, unlike other adipocytokines, adiponectin levels decrease in the diseased state causing hypoadiponectinemia. Low levels of adiponectin are found to be associated with visceral obesity, insulin resistance and dyslipidemia [14], which also suggests its possible association with the Metabolic Syndrome. Study done by Weyer et al, [15] also found decreased plasma concentrations of adiponectin in Japanese individuals with obesity, T2DM and CVD.

2.1.1. Interaction with Lipids and Carbohydrates

There is a growing body of evidence suggesting the role of adiponectin in the regulation of both fat and carbohydrate metabolism in body [16]. The effects on carbohydrate and lipid metabolism are associated with elevated phosphorylation of 5'-AMP-activated protein kinase in liver and elevated expression of peroxisomal proliferator-activated receptor gamma2, caveolin-1, and mitochondrial markers in white adipose tissue [17].

Several other studies have examined the effect of fatty acids, dietary proteins, carbohydrate with low glycemic index and consumption of foods rich in fiber as well as high-fat diet on adiponectin concentration [18,19].

Several studies suggest that dietary composition in NAFLD should be such that it is targeted for the weight reduction as weight loss is safe for the liver and has a protective effect on cardio metabolic health of the liver patients [20,21]. Weight loss also has a positive association with concentration of adiponectin [22]. A cohort study conducted in 2008, indicated a strong direct relationship between adherence to heathy eating pattern and adiponectin levels [23]. Low levels of adiponectin are directly related to the small dense LDL, high apo B and triglyceride levels [14]. Adiponectin also has a close relation to insulin levels in the body. When insulin levels are marginal, adiponectin is critical for insulin signaling, endocytosis, and lipid uptake in subcutaneous white adipose tissue. In the absence of both insulin and adiponectin, severe lipoatrophy and hyperlipidemia worsens the condition [24]. A recent study conducted on mice indicates that acute loss of adiponectin is especially detrimental to lipid homeostasis, both under basal and insulinopenic conditions [25].

Therefore, studies suggest that long term treatment with adiponectin improves triglyceride content and insulin sensitivity of patients with NAFLD [16]. Similarly, in an animal model, a daily administration of very low dose of adipocytokine to the mice, consuming a high fat/sucrose diet caused profound and sustainable weight reduction without altering the food intake [26].

2.1.2. Interaction with N-3 PUFA

It is very well established that omega-3 PUFA may reduce plasma triglyceride (TG) level, arrhythmias, oxidative stress, inflammation, and improve endothelial dysfunction [27]. Variations in dietary lipid consumption have shown to impact obesity. Specifically, omega-3 fatty acids have been correlated with the prevention of obesity and subsequent development of chronic disease sequalae [28]. Accordingly, in a randomized controlled trial (RCT) conducted on 64 overweight and obese women, supplementation with Omega-3 fatty acids significantly increased serum levels of adiponectin and on the other hand significantly decreased glucose, insulin homeostatic model assessment for insulin resistance total cholesterol and low-density lipoprotein cholesterol compared with placebo [29]. Similar to this, a study conducted by Kondo et al [30], found that consumption of fish oil for 8 weeks improved serum adiponectin levels in young non-obese females. Experiments done in animal models also suggests that shifting the source of fat to fish oil not only improved plasma levels of adiponectin but also reversed insulin resistance and dyslipidemia without altering the gene expression [31].Similarly, meta-analysis of 14 placebo controlled RCTs also suggest that the fish oil moderately increases adiponectin levels but it does not support possible benefits of fish oil supplementation on insulin sensitivity and adipocyte function [32]. Mechanisms involved in the stimulatory action of n-3 PUFA on adiponectin involving the up-regulation of adiponectin secretion by fish oil in vivo, is mediated by a peroxisome-proliferator activated receptors (PPARg)-dependent and PPARa-independent manner in mice epididymal fat [33]. Activation of PPARγ results in increased insulin sensitivity in skeletal muscle and liver and improves the secretory profile of adipose tissue, thereby favoring release of adipokines which favors insulin secretion, such as adiponectin, and reducing inflammatory cytokines [34].

2.2. Leptin

Leptin is a non-glycosylated protein, mainly produced by adipocytes and plays a dual role as a hormone and cytokine [35]. As a hormone it influences multiple endocrine functions and bone metabolism, in addition to the key function of regulating energy homeostasis by thermoregulation, whereas as a cytokine it promotes inflammatory responses. Leptin plays a role in the regulation of food intake, energy expenditure, body fat storage and insulin signaling [14]. Leptin has a potential dual action on NAFLD experimental models, exerting a possible anti-steatotic, but also a proinflammatory and profibrogenic action. Leptin levels are found to be higher or similar between simple steatosis and nonalcoholic steatohepatitis [NASH] compared with controls [12].

With regard to the role of leptin in inflammation and immunity, the expression of leptin is increased in conditions that are associated with the release of pro-inflammatory cytokines, such as acute inflammatory conditions during sepsis [36]. In human adipose tissue, TNFa and IL-6 increases leptin mRNA only when added together with dexamethasone. It has been suggested that the increase in local cortisol and inflammatory cytokines in adipose tissue may contribute to higher leptin mRNA levels in obese subjects and to higher leptin levels observed after endotoxin administration [37].

2.2.1. Interaction with Carbohydrates

Leptin levels increases immediately after ingestion of meal, and post prandial levels are higher after intake of carbohydrate meal than an isoenergetic fat meal [38].

Similarly, another study shows that a carbohydrate free diet resulted in 19 percent decrease in overnight fasting leptin concentration and it decreased to 54 percent with total starvation. However, Koutsari et al [39] found that daily moderate intensity exercise suppresses fasting and post prandial leptin levels even after consumption of high carbohydrate diet, with insulin acting as an important modulator for leptinemia. It has been found that the quality of carbohydrates in the diet also holds an equal importance as diets rich in foods with high glycemic index are associated with high grade liver steatosis [40], increased hepatic fat and glycogen stores [41]. Similarly diets rich in sucrose have been shown to increase post prandial leptin levels [42], affecting leptin's ability to serve as an effective satiety signal. However, the diets restricted in energy, consumed during weight loss regimes may contribute to the strong propensity for weight regain as low levels of leptin during energy restriction is found to be associated with increased hunger sensation in humans [43].

2.2.2. Interaction with N-3 PUFA

Evidence suggests that marine PUFAs i.e fish oil, algal oil is likely to have a beneficial effect in the treatment of NAFLD [44] as intake of n-3 PUFAs have an effect on lowering serum triglycerides [45] and slightly lowering blood pressure [46]. N-3 PUFA has an ability to modulate leptin gene secretion and expression [47]. The underlying mechanism regulating the changes in leptin secretion was explained by Mueller et al, [48], and they reported that glucose transport and metabolism are important factors in the regulation of leptin expression and secretion and that the effect of insulin to increase adipocyte glucose utilization is likely to contribute to insulin-stimulated leptin secretion. Eicosapentaenoic acid (EPA), one of the n-3 PUFA has the ability to stimulate leptin m-RNA expression and secretion. Furthermore, insulin shifts glucose metabolism from anaerobic metabolism to lactate to mitochondrial oxidation, and this effect may contribute to insulin-mediated leptin production, since anaerobic glucose metabolism does not increase leptin secretion [49]. Like insulin, EPA also stimulates leptin production by increasing the non-anaerobic/oxidative metabolism of glucose [50]. A RCT by Ramel et al [51], studied the effects of n-3 PUFA on leptin levels in human subjects and have shown that the inclusion of either lean [150 g cod, three times per week] or fatty fish (150 g salmon, three times daily), or six fish oil capsules (approximately 3 g/d containing EPA + DHA) as part of an energy-restricted diet resulted in approximately 1 kg more weight loss, which was accompanied by a decrease in fasting insulin and leptin levels. Similar effect was seen in an animal model where dietary fish oil also positively regulated the plasma leptin levels in sucrose fed insulin-resistant rats [31].

2.3. Vistafin

Vistafin [term derived from visceral fat] was identified as an adipokine that was highly expressed in visceral fat of human subjects and rodents, whose plasma circulating levels were positively correlated with the size of visceral fat depots. Vistafin has also been shown to have intracellular enzymatic activity, as nicotinamide phosphoribosyl-transferase (NAMPT), catalyzing the rate limiting step in nicotinamide adenine dinucleotide (NAD) thereby regulating growth, apoptosis, angiogenesis and cellular energy metabolism [47]. Vistafin is produced by many tissues and has a wide range of involvement in many disorders like metabolic, inflammatory and immuno deficiency disorders [52]. It also plays a role in modulating glucose and lipid metabolism [53] and circulating vistafin levels were found to be positively associated with insulin resistance [54].

2.3.1. Interaction with N-3 PUFA

A study by Echarri et al, [55] shows that the oral supplementation of EPA ethyl ester (1 g/kg) during 35 days was able to prevent the decrease of vistafin gene expression observed in high fat diet-induced obese rats. Moreover, an inverse relationship with the homeostatic model assessment index was found, suggesting that the insulin-sensitizing effects of EPA could be related to its stimulatory action on vistafin gene expression in visceral fat. Other studies have reported the ability of dietary fatty acids to modulate vistafin gene expression. Wen et al, [53] reported that in contrast to EPA, palmitate and oleate (0.125-1Mm) down-regulated vistafin mRNA gene expression in 3T3-L1 adipocytes. Moreover, this down-regulation of vistafin was mentioned as a potential mechanism to directly induce insulin resistance by oleate and palmitate in vitro.

2.4. Resistin

Resistin (named after "resistance to insulin") an adipocyte-specific hormone, has been suggested to be an important link between obesity, insulin resistance and diabetes. Although its expression was initially defined in adipocytes, significant levels of resistin expression in humans are mainly found in mononuclear leukocytes, macrophages, spleen and bone marrow cells [56]. Study in rodents have shown the association of between resistin and IR, hepatic steatosis, inflammation and fibrosis, however the data remains inconclusive in humans. Study conducted by Bajaj et al, [57] in Type II diabetic patients reported that upon treating these patients with pioglitazone lead to significant decrease in plasma resistin levels, and this decrease in resistin levels were found to be positively corelated with the decrease in hepatic fat content & improvement in hepatic inulin sensitivity. Another study also reported that the over expression of hepatic resistin in NASH patients is found to be associated with the severity of liver inflammation and fibrosis, they also concluded that liver derived resistin has a key role to play in pathogenesis of human NASH [58]. On the contrary, a 7-year prospective study showed that resistin levels either at baseline or at the end of follow up was not at all associated with the NAFLD development [59].Despite the differences between rodents and humans regarding resistin and inconclusive evidence for circulating resistin in human NAFLD, existing data support that resistin may play a local hepatic role in inflammation and fibrosis. However, more studies are needed in this direction.

3. Conclusion

Adipokines plays a key role in the pathogenesis and severity of liver disease, as they have a substantial contribution to the inflammation of hepatocytes in NAFLD via dysregulated secretion of pro-inflammatory and anti-inflammatory cytokines such as adiponectin and leptin. Apart from leptin and adiponectin, the association between other adipokines and NAFLD is more obscure. Dietary changes, specifically changes in the macronutrient composition of the diet, are important for the regulation of adipokines in NAFLD. Shifting from simple to complex carbohydrates and inclusion of N-3 PUFA in our diets will provide a relief to hepatocytes.

List of Abbreviations

CVD: Cardiovascular diseases
EPA: Ecosapentaenoic acid
IL-6: Interleukin-6
LDL- Low density lipoprotein
MS: Metabolic Syndrome
NAD: Nicotinamide adenine dinucleotide
NAFLD: Non-alcoholic fatty liver disease
NASH: Non-alcoholic steatohepatitis
PUFA: Polyunsaturated fatty acid
RCT: Randomized control trial
T2DM: Type II diabetes mellitus
TG: Triglyceride
TNF- Tumor necrosis factor

References

[1] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012; 55[6]: 2005-23.

[2] Hassan K, Bhalla V, Ezz M, Regal E, Hesham H, Hassan A-KK, et al. Nonalcoholic fatty liver disease: A comprehensive review of a growing epidemic. World J Gastroenterol. 2014; 20[34]: 12082-101.

[3] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005 Jun; 41[6]: 1313-21.

[4] Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease [NAFLD]. Metabolism. 2016;65[8]:1038-48.

[5] Alisi A, Cianfarani S, Manco M, Agostoni C, Nobili V. Non-alcoholic fatty liver disease and metabolic syndrome in adolescents: pathogenetic role of genetic background and intrauterine environment. Ann Med. 2012 Feb; 44[1]: 29-40.

[6] Sun X, Zemel MB. Calcium and 1,25-dihydroxyvitamin D3 regulation of adipokine expression. Obesity [Silver Spring]. 2007 Feb; 15[2]: 340-8.

[7] Polyzos SA, Kountouras J, Mantzoros CS. Leptin in nonalcoholic fatty liver disease: a narrative review. Metabolism. 2015 Jan; 64[1]: 60-78.

[8] Fasshauer M, Blüher M. Adipokines in health and disease. Trends Pharmacol Sci. 2015 Jul; 36[7]: 461-70.

[9] Grant RW, Dixit VD. Adipose tissue as an immunological organ. Obesity [Silver Spring]. 2015 Mar; 23[3]: 512-8.

[10] Braunersreuther V, Viviani GL, Mach F, Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. World J Gastroenterol. 2012 Feb 28; 18[8]: 727-35.

[11] Marra F, Bertolani C. Adipokines in Liver Diseases. Hepatology. 2009 Sep; 50[3]: 957-69.

[12] Polyzos SA, Kountouras J, Mantzoros CS. Adipokines in nonalcoholic fatty liver disease. Metabolism. 2016; 65[8]: 1062-79.

[13] Wang Z, Nakayama T. Inflammation, a Link between Obesity and Cardiovascular Disease. Mediators Inflamm. 2010; 2010: 17.

[14] Havel PJ. Update on Adipocyte Hormones. Diabetes. 2004; 53[Suppl 1]: 143-51.

[15] Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001 May;86[5]:1930-5.

[16] Karbowska J, Kochan Z. Role of adiponectin in the regulation of carbohydrate and lipid metabolism. J Physiol Pharmacol. 2006 Nov;57 Suppl 6: 103-13.

[17] Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, et al. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. Endocrinology. 2004 Jan; 145[1]: 367-83.

[18] Havel PJ, Callahan HS, Swarbrick MM, Weigle DS, Matthys CC, Kratz M. Effect of dietary n–3 polyunsaturated fatty acids on plasma total and high-molecular-weight adiponectin concentrations in overweight to moderately obese men and women. Am J Clin Nutr. 2008; 87[2]: 347-53.

[19] Kovacova Z, Vitkova M, Kovacikova M, Klimcakova E, Bajzova M, Hnevkovska Z, et al. Secretion of adiponectin multimeric complexes from adipose tissue explants is not modified by very low-calorie diet. 2009 Apr; 160[4]: 585-92.

[20] G M, Cassader M RF, R G. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease [NAFLD]: A systematic review and meta-analysis of randomised trials. Diabetologia. 2012; 55[4]: 885-904.

[21] Elias MC, Parise ER, de Carvalho L, Szejnfeld D, Netto JP. Effect of 6-month nutritional intervention on non-alcoholic fatty liver disease. Nutrition. 26[11-12]: 1094-9.

[22] Izadi V, Azadbakht L. Specific dietary patterns and concentrations of adiponectin. J Res Med Sci. 2015 Feb; 20[2]: 178-84.

[23] Fargnoli JL, Fung TT, Olenczuk DM, Chamberland JP, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. Am J Clin Nutr. 2008 Nov; 88[5]: 1213-24.

[24] Ye R, Holland WL, Gordillo R, Wang M, Wang QA, Shao M, et al. Adiponectin is essential for lipid homeostasis and survival under insulin deficiency and promotes β-cell regeneration. Elife. 2014; 23[3].

[25] Xia JY, Sun K, Hepler C, Ghaben AL, Gupta RK, An YA, et al. Acute loss of adipose tissue-derived adiponectin triggers immediate metabolic deterioration in mice HHS Public Access. Diabetologia. 2017; 61[4]: 932-41.

[26] Fruebis J, Javorschi S, Ebbets-Reed D, Erickson MRS, Yen FT, Bihain BE, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A. 2001; 98[4]: 2005-10.

[27] Mostowik M, Gajos G, Zalewski J, Nessler J, Undas A. Omega-3 polyunsaturated fatty acids increase plasma adiponectin to leptin ratio in stable coronary artery disease. Cardiovasc Drugs Ther. 2013; 27[4]: 289-95.

[28] Gray B, Steyn F, Davies PSW, Vitetta L. Omega-3 fatty acids: a review of the effects on adiponectin and leptin and potential implications for obesity management. Eur J Clin Nutr. 2013 Dec; 67[12]: 1234-42.

[29] E. M, M. R, L. F, M. A-J, S. S. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. Asia Pac J Clin Nutr. 2012; 21[4]: 511-8.

[30] Kondo K, Morino K, Nishio Y, Kondo M, Fuke T, Ugi S, et al. Effects of a fish-based diet on the serum adiponectin concentration in young, non-obese, healthy Japanese subjects. J Atheroscler Thromb. 2010 Jun 30; 17[6]: 628-37.

[31] Rossi AS, Lombardo YB, Lacorte J-M, Chicco AG, Rouault C, Slama G, et al. Dietary fish oil positively regulates plasma leptin and adiponectin levels in sucrose-fed, insulin-resistant rats. Am J Physiol Regul Integr Comp Physiol. 2005 Aug; 289[2]: R486-94.

[32] Wu JHY, Cahill LE, Mozaffarian D. Effect of fish oil on circulating adiponectin: A systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Endocrinology and Metabolism. 2013. p. 98[6]: 2451-9.

[33] Neschen S, Morino K, Rg J, Rossbacher C, Pongratz RL, Cline GW, et al. Fish Oil Regulates Adiponectin Secretion by a Peroxisome Proliferator-Activated Receptor-Dependent Mechanism in Mice. 2006; 55[4]: 924-8.

[34] Astapova O, Leff T. Adiponectin and PPARγ: Cooperative and Interdependent Actions of Two Key Regulators of Metabolism. In: Vitamins and Hormones. Academic Press Inc.; 2012. p. 143-62.

[35] La Cava A. Leptin in inflammation and autoimmunity. Cytokine. 2017; 98: 51-8.

[36] Sarraf P, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet Iii DJ, et al. Multiple Cytokines and Acute Inflammation Raise Mouse Leptin Levels: Potential Role in Inflammatory Anorexia. J Exp Med •. 1997; 185[1]: 171-5.

[37] Lee M-J, Fried SK. Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. Am J Physiol Metab. 2009; 296[6]: E1230-8.

[38] Romon M, Lebel P, Velly C, Marecaux N, Fruchart JC, Dallongeville J. Leptin response to carbohydrate or fat meal and association with subsequent satiety and energy intake. Am J Physiol Metab. 1999; 277[5]: E855-61.

[39] Koutsari C, Karpe F, Humphreys SM, Frayn KN, Hardman AE. Plasma leptin is influenced by diet composition and exercise. Int J Obes Relat Metab Disord. 2003 Aug; 27[8]: 901-6.

[40] Valtueña S, Pellegrini N, Ardigò D, Del Rio D, Numeroso F, Scazzina F, et al. Dietary glycemic index and liver steatosis. Am J Clin Nutr. 2006 Jul; 84[1]: 136-42; quiz 268-9.

[41] Bawden S, Stephenson M, Falcone Y, Lingaya M, Ciampi E, Hunter K, et al. Increased liver fat and glycogen stores after consumption of high versus low glycaemic index food: A randomized crossover study. Diabetes Obes Metab. 2017; 19[1]: 70-7.

[42] Raben A, Astrup A. Leptin is influenced both by predisposition to obesity and diet composition. Int J Obes Relat Metab Disord. 2000 Apr; 24[4]: 450–9.

[43] Havel PJ. Role of adipose tissue in body-weight regulation: mechanisms regulating leptin production and energy balance. Proc Nutr Soc. 2000 Aug; 59[3]: 359-71.

[44] de Castro GS, Calder PC. Non-alcoholic fatty liver disease and its treatment with n-3 polyunsaturated fatty acids. Clin Nutr. 2018; 37[1]: 37-55.

[45] Salem N. Introduction to polyunsaturated fatty acids. Backgrounder. 1999; 3[1]: 1-8.

[46] Kris-Etherton PM, Harris WS, Appel LJ. Omega-3 Fatty Acids and Cardiovascular Disease New Recommendations From the American Heart Association. 2003; 23[2]: 151-2.

[47] Moreno-Aliaga M, Alfredo M. Sesion 3: Fatty acids and the immune system. Regulation of adipokine secretion by n-3 fatty acids Portion size estimation View project EVASYON View project. 2010; 69[3]: 324-32.

[48] Mueller WM, Gregoire FM, Stanhope KL, Mobbs C V, Mizuno TM, Warden CH, et al. Evidence That Glucose Metabolism Regulates Leptin Secretion from Cultured Rat Adipocytes*. 1998; 139[2]: 551-8.

[49] Mueller WM, Stanhope KL, Gregoire F, Evans JL, Havel PJ. Effects of metformin and vanadium on leptin secretion from cultured rat adipocytes. Obes Res. 2000; 8[7]: 530-9.

[50] Pérez-Matute P, Marti A, Martínez JA, Fernández-Otero MP, Stanhope KL, Havel PJ, et al. Eicosapentaenoic fatty acid increases leptin secretion from primary cultured rat adipocytes: role of glucose metabolism. Am J Physiol Regul Integr Comp Physiol. 2005 Jun; 288[6]: R1682-8.

[51] Ramel A, Martinez JA, Kiely M, Bandarra NM, Thorsdottir I. Effects of weight loss and seafood consumption on inflammation parameters in young, overweight and obese European men and women during 8 weeks of energy restriction. Eur J Clin Nutr. 2010 Sep; 64[9]: 987-93.

[52] Dahl TB, Holm S, Aukrust P, Halvorsen B. Visfatin/NAMPT: a multifaceted molecule with diverse roles in physiology and pathophysiology. Annu Rev Nutr. 2012 Aug 21; 32[1]: 229-43.

[53] WEN Y, WANG H, WU J, LU H, HU X, Katherine C. Effects of fatty acid regulation on visfatin gene expression in adipocytes. Chin Med J [Engl]. 2006 Oct; 119[20]: 1701-8.

[54] Chang Y-C, Chang T-J, Lee W-J, Chuang L-M. The relationship of visfatin/pre-B-cell colony-enhancing factor/nicotinamide phosphoribosyltransferase in adipose tissue with inflammation, insulin resistance, and plasma lipids. Metabolism. 2010 Jan; 59[1]: 93-9.

[55] Pérez-Echarri N, Pérez-Matute P, Marcos-Gómez B, Martínez JA, Moreno-Aliaga MJ. Effects of eicosapentaenoic acid ethyl ester on visfatin and apelin in lean and overweight [cafeteria diet-fed] rats. Br J Nutr. 2009 Apr; 101[7]: 1059-67.

[56] Jamaluddin MS, Weakley SM, Yao Q, Chen C, DeBakey ME. Themed Section: Fat and Vascular Responsiveness Resistin: functional roles and therapeutic considerations for cardiovascular disease Correspondence. 2011; 165[3]: 622-32.

[57] Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA. Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated type II diabetic patients. Int J Obes Relat Metab Disord. 2004 Jun; 28[6]: 783-9.

[58] Shen C, Zhao C-YY, Wang W, Wang Y-DD, Sun H, Cao W, et al. The relationship between hepatic resistin overexpression and inflammation in patients with nonalcoholic steatohepatitis. BMC Gastroenterology 2014 p. 1-9.

[59] Musso G, Bo S, Cassader M, De Michieli F, Gambino R. Impact of sterol regulatory element-binding factor-1c polymorphism on incidence of nonalcoholic fatty liver disease and on the severity of liver disease and of glucose and lipid dysmetabolism. Am J Clin Nutr. 2013; 98[4]: 895-906.