

REVIEW



The role of polyunsaturated fatty acids (n-3 PUFAs) on the pancreatic β -cells and insulin action

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ABSTRACT

Polyunsaturated Fatty acids have multiple effects in peripheral tissues and pancreatic beta cell function. The n-3 Polyunsaturated Fatty acids prevent and reverse high-fat-diet induced adipose tissue inflammation and insulin resistance. Insulin secretion is stimulated by glucose, amino acids, and glucagon-like peptide-1 in tissue containing high levels of n-3 Polyunsaturated Fatty acids than lower level of n-3 Polyunsaturated Fatty acids. Also, n-3 Polyunsaturated Fatty acids led to decreased production of prostaglandin, which in turn contributed to the elevation of insulin secretion. N-3 polyunsaturated fatty acids prevent cytokine-induced cell death in pancreatic islets. Supplementation of n-3 Polyunsaturated Fatty acids for human subjects prevent beta cell destruction and insulin resistance. It also enhances insulin secretion, reduction in lipid profiles and glucose concentration particularly in type II diabetes patients. Therefore there should be a focus on the treatment mechanism of insulin related obesity and diabetes by n-3 polyunsaturated fatty acids.

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Introduction

Fatty acids consist of a hydrocarbon chain (CH₂) or with an acid or carboxyl group (COOH) at one end and a methyl group at the other. They are classified as saturated or unsaturated, depending on the number of hydrogen atoms present. The group of polyunsaturated fatty acids (PUFAs) termed as omega-3 (ω 3 or n-3) distinguished by having the first double bond positioned on the third carbon atom from the methyl or N-terminal end of fatty acid chain [1]. The major varieties of PUFAs are n-3 such as Docosahexaenoic Acid (DHA), eicosapentaenoic acid (EPA) and n-6 PUFAs such as arachidonic acid (AA). N-3 PUFAs are synthesized from the modification of saturated fatty acid precursors by different desaturases and elongation enzymes. Mammals have neither the desaturase necessary to synthesize the precursors of other PUFAs, linoleic acid (LA, n-6), and α -linoleic acid (ALA, n-3), nor the n-3 FAs desaturase to convert n-6 PUFAs to n-3 PUFAs [2].

The normal role of insulin is increasing muscle cellular glucose uptake, glycogen synthesis, and cessation of hepatic glucose production [3]. An important factor associated with the pathogenesis of insulin resistance and pancreatic beta cell dysfunction is the glucolipotoxicity, which generates redox imbalance and oxidative stress. Palmitic acid induces production of reactive

oxygen species (ROS) and nitric oxide (NO) and impairs insulin secretion [4]. Pancreatic islets are considered as highly susceptible to oxidative stress presenting low activities [5].

Methods

This review was done using prospective and retrospective studies, cohort studies, systematic reviews, experimental studies and case-control studies that were done previously. Google, HINARI [www.who.int/hinari/], Medline (Pubmed), Google scholar, and Science Direct were used as search engines.

Therefore the main objective of this review is to update the current trend on “the role of n-3 PUFAs in the pancreatic β -cells and insulin action”. There have been many recent publications indicating Preventive and reverse effects of n-3 PUFAs on insulin resistance and sensitivity on human and animal studies.

Mechanism of β - cells dysfunction and n-3 PUFAs stimulation effect on islet survival and function

Beta cells are a specific cell types in the pancreatic islets of Langerhans, making up about 50%– 65% of the cells [6]. Pancreatic β cells produce insulin at an appropriate

rate to maintain blood glucose within a relatively narrow range [7]. Exposure to various factors may alter its structure and affect the normal function of the cells.

Several mechanisms have been proposed that could contribute to the dysfunction of the β - cells. Pighin et al. have demonstrated that the increased fat storage and decreased Pyruvate Dehydrogenase complex (PDHc) activity within the β - cells are possible mechanisms for mediating the altered insulin secretion. It undergoes with the stimulus effect of different secretagogues (e.g., glucose, palmitate, L-arginine) from dyslipemic insulin-resistant rats, fed a long-term sucrose-rich diet [8,9]. The inhibition of PDHc limits the conversion of pyruvate from glycolysis to acetyl-CoA and diminishes the oxidative glucose metabolism, which is a signal for insulin secretion and synthesis [8,9]. This finding is consistent with the reversion of these alterations after the administration of n-3 PUFAs. This completely normalized both fat storage and the PDHc activity within the β - cells as well as the insulin secretion patterns stimulated by glucose. This improved the hormone secretion under the stimulus of either palmitate or L-arginine [10].

On the other hand, an experimental evidence on animal studies, by Su D et al. and Dong et al. showed that cytokine treatment for 48 hours led to a sharply elevated level of cell death in the wild-type islets (58 vs. 9% in the non-treated). However, the islets derived from the *mfat-1* transgenic mice (contain n-3 PUFAs) strongly resisted cytokine-induced cell death (13 vs. 8% in the non-treated islets). The result showed that n-3 PUFAs play important roles in the production of Ang-1 which has significant beneficial effect on islet survival and function [11,12]. A recent study done by Bi et al. proved that, therapeutic intervention in mice through nutritional supplementation or lentivirus-mediated expression of ω -3 fatty acid desaturase, *mfat-1*, insulin levels, prevented lymphocyte infiltration into regenerated islets, and sharply elevated the expression of the pancreatic β cell markers [13].

Another recent experimental study done on humans, on the overall effect of the FFAs on the profile of β -cells function. Treatment with the FFA mixture to obese adolescents with metabolic syndrome profile reduced the capacity to capture peroxynitrite compared to that of the control. Hence it supports for encouragement of the increase of ω -3-rich food consumption in order to reduce the likelihood of deterioration of β -cells [14].

Effects of n-3 PUFAs on insulin secretion

Insulin is an important hormone required for normal metabolism. In healthy subjects, insulin release is exquisitely exact to meet the metabolic demand. Specifically, β -cells sense changes in plasma glucose concentration

and respond by releasing corresponding amounts of insulin [15].

Currently, most evidence that supports promoting the effect of n-3 PUFAs on insulin secretion, has been obtained from in vitro or ex vivo studies. The Fat-1 transgenic mouse is a unique model for research into n-3 PUFAs, which is genetically modified to express the *Caenorhabditis elegans* Fat-1 gene. Fat-1 encodes n-3 fatty acid desaturase, which converts n-6 PUFA to n-3 PUFA [16].

Experimental evidence on animal model studies, done by Dong et al. showed that the transgenic islets contained much higher levels of n-3 PUFAs than the wild type; insulin secretion was significantly elevated in the transgenic islets. When challenged with tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and γ -interferon (IFN- γ), the transgenic islets completely resisted cytokine-induced cell death [17]. Another intervention done on non-obese diabetes (NOD) mice with ω -3 of an EPA/DHA-enriched diet showed significantly lower blood glucose concentrations. The improved glucose tolerance in the EPA/DHA-fed mice was primarily attributed to the elevated glucose-induced insulin secretion [13]. Cejudo et al. conducted an experimental research on human subjects that supported the findings of the above studies. According to the finding, n-3 PUFA supplementation for type II diabetes patients has an overall improvement in the lipid profile with a significant decrease in triacylglycerols which was correlated with enhancement of insulin secretion by n-3 PUFA. Insulin had greater improvement when it was combined with metformin that may warrant further investigation [18].

On the other side, Lalia et al. came up with contrasting findings in insulin-resistant humans. Dietary EPA+DHA supplementation didn't improve peripheral glucose disposal, insulin secretion, or skeletal muscle mitochondrial function in insulin-resistant nondiabetic humans. Even though there was a modest improvement in hepatic insulin sensitivity with EPA+DHA, but this was not associated with any improvements in clinically meaningful outcomes [19].

The expression of n-3 PUFAs (*mfat-1*) led to decreased production of PGE₂, which in turn contributed to the elevation of insulin secretion. Furthermore, that cytokine-induced activation of NF- κ B and extracellular signal-related kinase 1/2 (ERK1/2) was significantly attenuated and the expression of pancreatic duodenal homeobox-1 (PDX-1), glucokinase, and insulin-1 was increased as a result of n-3 PUFAs production. These data depict the enhanced insulin-secreting action of the β -cells that were pre-exposed to a high n-3 PUFAs environment (as a result of *mfat-1* expression) even long before birth. Also, acute elevation of n-3 PUFAs via *mfat*-

1 activity in the β -cells would also enhance insulin secretion [11]. Dangardt et al, showed that ω -3 PUFA supplementation was correlated with insulin action. After a relatively short intervention period with ω -3 PUFA supplementation, the fatty acid composition of skeletal muscle phospholipids and muscle triacylglycerol's improved in both obese boys and girls. This effect may correlate with insulin secretion and sensitivity which enhanced lipid metabolism and results reduction of lipid [20].

On another study ω -3 PUFA supplementation caused a significant improvement in the intervention group compared with the placebo. It resulted for the decrement of non-esterified free fatty acid concentrations which further improved insulin sensitivity in type 2 diabetic patients [21]. On the contrary a study by Spencer et al. examined the effects of fish oil (which are enriched with ω -3 PUFAs), on adipose tissue macrophages in obese humans with metabolic syndrome. Although there were no changes in insulin sensitivity, adipose tissue macrophages were decreased and adipose capillaries increased in the FO-treated subjects, along with a decrease in adipose [22].

Effects of n-3 PUFAs on insulin sensitivity

The n-3 PUFAs decreases the skeletal muscle triglyceride content and improves insulin action on glucose utilization and prevents the development of whole-body insulin resistance [23, 24]. Luo et al. demonstrated that insulin action was positively correlated with the fatty acid instauration index in membrane phospholipids of rat adipocytes [25]. Moreover, n-3 PUFAs prevented the decrease of insulin-stimulated glucose transport and the oxidation and incorporation into total lipids. Improved in vitro insulin-stimulated glucose incorporation into total lipids and glucose oxidation into CO₂ were also observed in adipocytes of neonatal diabetic rats fed a sucrose-rich diet to which 30% dietary n-3 PUFAs had been added [26].

Peyron-Caso et al. observed insulin stimulated glucose transport in adipocytes, associated with an increase of glucose transporter 4 (Glut 4) protein and mRNA levels in rats fed a sucrose-rich diet supplemented with n-3 PUFAs [27]. In another recent study by Albert et al. demonstrated that higher n-3 PUFA supplementation were associated with improved insulin sensitivity. Insulin sensitivity was 43% higher in those who took high ω -3 than in low ω -3 men. This was associated with a more favorable metabolic profile in middle-aged overweight men [28].

However an experimental study conducted on animal model by Sebokova et al. showed that a raised dietary intake of n-3 PUFAs in hereditary hypertriglyceridemia rats didn't alter the number of Glut 4 protein levels in

muscle [29]. But similar study by Mori et al. in fatty rats, (a model of spontaneous type 2 DM with obesity), demonstrated that the long-term administration of n-3 PUFAs for 17 to 18 weeks enhances insulin secretion. When n-3 PUFAs replaced the vegetable oil present in the rats' diet, it prevented the onset of dyslipidemia, insulin insensitivity in main target tissues (liver, skeletal muscle, adipose tissue) and whole-body insulin resistance in high sucrose or fructose-fed rodents [30].

Mechanism involving the action of n-3 PUFAs through GPR 120 and GPR40 on insulin

A great advance in the field was achieved in 2009 when Oh and co-workers described a completely new anti-inflammatory mechanism involving the action of n-3 PUFAs through GPR120. Upon ligand binding, GPR120 recruits β -arrestin-2, leading to the internalization of the receptor/regulatory protein complex. The internalized β -arrestin-2 binds to TAB1 and inhibits its binding to TAK1, which results in the inhibition of its activity. TAK1 is a point of convergence for TNF- α and TLR4 signal transduction, and its inhibition impairs the progression of the signal toward JNK and IKK activation, which results in the inhibition of inflammation [31]. N-3 PUFAs also directly affect β -cell function via alterations in lipid raft function, or by binding to PPARs, GPR40 and GPR120.

A recent study, reported the beneficial metabolic effects of a small molecule that acts as a specific agonist for GPR120 [32]. Obese mice treated with this molecule exhibit improved glucose tolerance and decreased hepatic steatosis accompanied by a reduction of the metabolic inflammation phenotype. This indicates, GPR120 is an attractive potential target for the treatment of obesity-associated metabolic disorders [31]. Oh et al. also proved that ω -3 FAs supplementation for mice cause GPR120-mediated anti-inflammatory and insulin sensitizing effects *in vivo*. Taken together, GPR120 emerges as an important control point in the integration of anti-inflammatory and insulin sensitizing responses, which may prove useful in the future development of new therapeutic approaches for the treatment of insulin resistant diseases [33].

Another recent study by Dragano et al. reported that TUG1197 the GPR120 agonist, predominantly reducing hypothalamic inflammation. TUG905, the GPR40 agonist, predominantly reducing body mass and increasing the expression of the anorexigenic precursor. The use of a compound that acts simultaneously on GPR120 and GPR40, GW9508, results in the best metabolic outcomes, reducing body mass, improving glucose tolerance and reducing hypothalamic inflammation [34].

Different studies have also shown the beneficial metabolic effects of GPR40 activation by n-3 PUFAs [35,36]. This receptor is highly expressed in pancreatic β -cells and, upon activation by PUFAs, which increases glucose-induced insulin secretion [35].

Mechanisms of n-3 PUFA for prevention of insulin resistance

Insulin resistance (IR) is an early metabolic abnormality in the course of obesity, metabolic Syndrome, and type 2 diabetes. Although the molecular mechanism is not fully understood, at the cellular level the strength of insulin signaling from its receptor to its final action is attenuated. In conditions of insulin resistance, these actions are impaired leading to a vicious cycle of fasting or post-prandial hyperglycemia, elevated free fatty acids, hyperinsulinemia, and pancreatic β -cell dysfunction [37]. There are different mechanisms by which insulin resistance may present. N-3 PUFA may reduce insulin resistance through a number of different mechanisms. Dose-dependent effect on increasing the expression of genes related to hepatic lipid oxidation and decreasing the expression of genes related to hepatic de novo lipogenesis (SREBP-1c, ChREBP). This indicates enhancement of insulin action in the liver and a protective effect of n-3 PUFA in the course of development of insulin resistance.

There are findings that support the beneficial effect of n-3 PUFA in insulin resistance. Ramel et al. conducted an experiment on human young overweight or obese individuals. These groups were enhanced to consume fish oil during an 8 week energy restricted diet. After exposure it exerted positive effects on fasting insulin and on a measure of insulin resistance. The present randomized dietary intervention trial supports previous epidemiological evidence, and demonstrates the importance of Long chain (LC) n-3 PUFA consumption for improvement of insulin resistance and possibly for the prevention of type 2 diabetes [38].

It is now accepted that increased inflammation is one of the major factors that leads to the development of insulin resistance. Toll like receptors (TLR) on the cell surface when stimulated by bacterial cell wall lipopolysaccharides activate the NF- κ B pathway for the production of inflammatory cytokines. N-3 PUFA inhibit TLR-2 and TLR-4 [39]. Among the n-3 PUFA, DHA is the most potent inhibitor of this pathway. EPA reduces the production of inflammatory eicosanoids from arachidonic acid by competing for the cyclooxygenase and lipooxygenase enzymes. Both DHA and EPA decrease the release of arachidonic acid by inhibiting phospholipase-2 [40]. Oxygenated metabolites of EPA and DHA formed by COX-2 in the presence of aspirin are called resolvins

E and D, respectively; both these series of resolvins oppose the effects of inflammatory prostaglandins [41].

The circulating levels of a number of hormones (adiponectin, leptin, resistin, Vaspin and visfatin) and adipocytokines produced by the adipose tissue also contribute to the development of insulin resistance. Leptin and adiponectin both exert insulin-sensitizing effects. A number of studies examined the effects of n-3 PUFA on the secretion of these two hormones. Addition of EPA to cultured rat adipocytes increased both the expression and secretion of leptin [42]. Derosa et al. did an experiment of the association of insulin resistance with adiponectin, visfatin, and vaspin on human subjects. After treatment with LC n-3 PUFA, it resulted in a greater improvement of lipid profile and adiponectin compared to placebo in a baseline condition, and an improvement of all insulin resistance parameters after an oral fat load. And there was a decrement in the mean values of visfatin and vaspin even though there was no significant variations [43].

N-3 PUFA regulate the expression of a number of genes involved in carbohydrate and lipid metabolism by modulating the activity or expression of a number of transcription factors. Peroxisome proliferator activated receptors (PPAR), sterol regulatory element binding protein-1c (SREBP-1c), hepatic nuclear factors (HNF), retinoid X receptors (RXR) and liver X receptor (LXR) regulated by n-3 PUFA [44]. Thus, n-3 PUFA increase glucose clearance, and fatty acid oxidation, and inhibit fatty acid synthesis. In addition to the mechanisms discussed earlier n-3 PUFA decrease insulin resistance through effects of decrease in circulating triglycerides and small dense LDL particles, membrane fluidity, signal transduction, and others.

Future perspective on n-3 PUFAs as preventive mechanism for insulin resistance

Supplementation of n-3 PUFAs

The need for sustainable, alternative n-3 -PUFA sources has stimulated research in several fields. Cellular and molecular methodologies exist that allow the introduction or increased expression of genes for the enzymatic machinery involved in desaturation and elongation of shorter chain fatty acids into LC-PUFA. The potential of plants and animals to biosynthesize these nutrients through genetic manipulation, with the aim to increase the amount of desired fatty acids in their lipid profiles, is currently under investigation with the production of transgenic oilseed crops and animals [45,46]. While important advances have been made on the production of oils from transgenic plants. The commercial use of

genetically manipulated products of food is the focus of much scientific and social debate.

On the other hand, functional foods enriched with *n*-3 PUFA from either fish or microbial origin, are generally perceived as interesting by consumers [47]. As their belief on the effectiveness of these products to deliver important health benefits has increased in recent years [48]. Hence, the *n*-3 LC-PUFA supplemented food sector-including cereals, beverages, cheeses, yogurts, eggs, milk, margarines, spreads and dressings has been one of the fastest growing food categories in Europe and North America [48].

At present, alternatively to fish oils, some *n*-3 LC-PUFA-rich single cell oils, mostly of micro algal origin, are used in marketed fortified foods. Recently, the health risks and side effects posed by *n*-3 LC-PUFA consumption from various sources were reviewed [49]. Fish oil supplementation was investigated using several delivery methods (capsules, fish-containing meals, fortified foods, or parenteral administration). Results from two studies advised caution when supplying high dietary *n*-3 LC-PUFA levels in both type 2 diabetes mellitus patients and individuals with impaired glucose tolerance, due to risks of increased glycaemia. Algal oils appeared to be well tolerated and no major negative effects have been reported [50].

Challenges of *n*-3 PUFAs to use for the health perspective

The production of very high purity *n*-3 PUFAs represented a considerable challenge. This may be due to the complexity of the lipids in the biomass, the nature of the biomass, and the degree to which the *n*-3 PUFA needed to be purified. Also, the whole suite of technologies with regard to processing costs, product yield and product quality are another challenges to use it [47].

Conclusions

Polyunsaturated FAs (*n*-3 PUFAs) increased intracellular insulin content, antioxidant enzymatic defense capacity and decreased pro-oxidant generating activities. Those are associated with maintenance of pancreatic beta cell redox state in response to *n*-3 PUFA in most animal and human studies. Continuous *n*-3 PUFAs supplementation can enhance insulin secretion and confers strong resistance to cytokine-induced β -cell destruction. Results from a number of studies on human and animal studies suggest that *n*-3 PUFA can prevent and reverse insulin resistance and increase its sensitivity. However, there is some controversy results from the studies, therefore there should be large scale experimental studies to ensure the overall effect of *n*-3 PUFA on human subjects and to

develop guidelines on the mechanism of *n*-3 PUFA supplementation. Particularly *n*-3 PUFA Supplementation in some studies for type II diabetes patients show an improvement in the lipid profile and glucose concentration which may seek to look forward.

What is already known on this topic

Different authors had published the result of *n*-3 PUFAs on insulin, so based on their finding

- results from a number of studies suggest that *n*-3 PUFA can prevent and reverse insulin resistance

Stable cellular production of *n*-3 PUFAs can enhance insulin secretion.

What this study adds

- *N*-3 PUFAs affects transcription factors will undoubtedly contribute to human health and disease
- Recent studies that focus on human subjects come up with positive results in
 - Prevention and treatment of type II diabetes
 - Reduction in insulin resistance and increase in insulin secretion & action
 - Prevent in beta cell destruction
 - May open a forum *n*-3 PUFA that targets obesity & diabetes
- Functional foods enriched with *n*-3 PUFA from either fish or microbial origin, are targets for insulin therapy in recent years

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No potential conflicts of interest were disclosed.

Authors' contributions

All the authors contribute equally in development of the review
HWB, SM: were responsible for commencement of the idea and drafting of the concept

SA, HWB: were responsible in designing the study, searching for data

SM, SA, HWB: were responsible in write up of the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- [1] Nettleton, JA. *Omega-3 fatty Acids and Health*. New York: Chapman and Hall; Vol. 354. 1995.

- [2] Simopoulos AP. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. *World Rev Nutr Diet.* 2003;92:1–22. doi:10.1159/000073788
- [3] Petersen KF, Shulman GI. Pathogenesis of skeletal muscle insulin resistance in Type 2 Diabetes Mellitus. *Am J Cardiol.* 2002;90(5):11–18. doi:10.1016/S0002-9149(02)02554-7
- [4] Michalska M, Wolf G, Walther R, et al. Effects of pharmacological inhibition of NADPH oxidase or iNOS on pro-inflammatory cytokine, palmitic acid or H₂O₂-induced mouse islet or clonal pancreatic beta-cell dysfunction. *Biosci Rep.* 2010;30(6):445–53. doi:10.1042/BSR20090138
- [5] Grankvist K, Marklund SL, Taljedal IB. CuZn superoxide dismutase, Mn-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. *Biochem J.* 1981;199(2):393–8. doi:10.1042/bj1990393
- [6] McDaniel ML, Kwon G, Hill JR, et al. Cytokines and nitric oxide in islet inflammation and diabetes. *Proc Soc Exp Biol Med.* 1996;211(1):24–32. doi:10.3181/00379727-211-43950D
- [7] Henquin JC. Triggering and amplifying pathways of regulation of insulin secretion by glucose. *Diabetes.* 2000;49(11):1751–1760. doi:10.2337/diabetes.49.11.1751
- [8] Pighin D, Karabatas L, Rossi A, et al. Fish oil affects pancreatic fat storage, pyruvate dehydrogenase complex activity and insulin secretion in rats fed a sucrose-rich diet. *J Nutr.* 2003;133(12):4095–101. doi:10.1093/jn/133.12.4095
- [9] Lewis GF, Carpentier A, Khosrow A, et al. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev.* 2002;23(2):201–29. doi:10.1210/edrv.23.2.0461
- [10] Oguzhan B, Zhang Y, Louchami K, et al. Pancreatic islet function in omega3 fatty acid-depleted rats: glucose metabolism and nutrient-stimulated insulin release. *Endocrine.* 2006;29(3):457–66. doi:10.1385/ENDO:29:3:457
- [11] Wei D, Li J, Shen M, et al. Cellular production of n-3 PUFAs and reduction of n-6-to-n-3 ratios in the pancreatic beta-cells and islets enhance insulin secretion and confer protection against cytokine-induced cell death. *Diabetes.* 2010;59(2):471–8. doi:10.2337/db09-0284
- [12] Su D, Zhang N, He J, et al. Angiotensin-1 production in islets improves islet engraftment and protects islets from cytokine-induced apoptosis. *Diabetes.* 2007;56(9):2274–83. doi:10.2337/db07-0371
- [13] Bi X, Li F, Liu S, et al. ω -3 polyunsaturated fatty acids ameliorate type 1 diabetes and autoimmunity. *J Clin Invest.* 2017;127(5):1757–1771. doi:10.1172/JCI87388
- [14] Velasquez C, Vasquez JS, Balcazar N. *In Vitro* Effect of Fatty Acids Identified in the Plasma of Obese Adolescents on the Function of Pancreatic β -Cells. *Diabetes Metab J.* 2017;41(4):303–315. doi:10.4093/dmj.2017.41.4.303
- [15] Schmitz O, Rungby J, Edge L, et al. On high-frequency insulin oscillations. *Ageing Res Rev.* 2008;7(4):301–5. doi:10.1016/j.arr.2008.04.002
- [16] Kang JX, Wang J, Wu L, et al. Transgenic mice: Fat-1 mice convert n-6 to n-3 fatty acids. *Nature.* 2004;427(6976):–698.
- [17] Clarke SD. The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. *Curr Opin Lipidol.* 2004;15(1):13–8. doi:10.1097/00041433-200402000-00004
- [18] Cejudo MGJ, Ramos RV, López ALG, et al. Effect of n-3 Polyunsaturated Fatty Acid Supplementation on Metabolic and Inflammatory Biomarkers in Type 2 Diabetes Mellitus Patients. *Nutrients.* 2017;9(5):573. doi:10.3390/nu9060573
- [19] Lalia AZ, Johnson ML, Jensen MD, et al. Effects of Dietary n-3 Fatty Acids on Hepatic and Peripheral Insulin Sensitivity in Insulin-Resistant Humans. *Diabetes Care.* 2015;38(7):1228–1237. doi:10.2337/dc14-3101
- [20] Dangardt F, Chen Y, Gronowitz E, et al. High Physiological Omega-3 Fatty Acid Supplementation Affects Muscle Fatty Acid Composition and Glucose and Insulin Homeostasis in Obese Adolescents. *Journal of Nutrition and Metabolism.* 2012; 2012(2012), Article ID 395757, 9 pages. doi:10.1155/2012/395757
- [21] Farsi1 PF, Djazayeri A, Eshraghian MR, Ian H, et al. Effects of supplementation with omega-3 on insulin sensitivity and non-esterified free fatty acid (NEFA) in type 2 diabetic patients. *Arq Bras Endocrinol Metab.* 2014;58(4):335–40. doi:10.1590/0004-2730000002861
- [22] Spencer M, Finlin BS, Unal R, et al. Omega-3 Fatty Acids Reduce Adipose Tissue Macrophages in Human Subjects With Insulin Resistance. *Diabetes.* 2013;62:1709–1717. <http://diabetes.diabetesjournals>.
- [23] Podolin DA, Gayles EC, Wei Y, et al. Menhaden oil prevents but does not reverse sucrose-induced insulin resistance in rats. *Am J Physiol.* 1998;274(43):840–8. <http://ajpregu.physiology.org/>
- [24] JS, Howard BV. Dietary Fats, Insulin Resistance, and Diabetes. 1994;1(1):31–37. Available at; <https://doi.org/10.1177/174182679400100106>
- [25] Luo J, Rizkalla SW, Boillot J, et al. Dietary (n-3) polyunsaturated fatty acids improve adipocyte insulin action and glucose metabolism in insulin-resistant rats: relation to membrane fatty acids. *J Nutr.* 1996;126(8):1951–8.
- [26] Soria A., Chicco A., Alessandr MED., et al. Dietary fish oil reverse epididymal tissue adiposity, cell hypertrophy and insulin resistance in dyslipemic sucrose fed rat model. *The journal of nutritional biochemistry.* 2002;13(4):209–218. doi:10.1016/S0955-2863(01)00214-5
- [27] E Caso P, S Nadler F, Kabir M, et al. Regulation of glucose transport and transporter 4 (Glut-4) in muscle and adipocytes of sucrose-fed rats: effects of n-3 poly- and monounsaturated fatty acids. *Horm Metab Res.* 2002;34(7):362–6.
- [28] Albert BB, Derraik JGB, Brennan CM, et al. Higher omega-3 index is associated with increased insulin sensitivity and more favorable metabolic profile in middle-aged overweight men. *Sci Rep.* 2014;4:6697. doi:10.1038/srep06697
- [29] Ide T. Interaction of Fish Oil and Conjugated Linoleic Acid in Affecting Hepatic Activity of Lipogenic Enzymes and Gene Expression in Liver and Adipose Tissue. *Diabetes.* 2005;54(2):412–23. doi:10.2337/diabetes.54.2.412
- [30] Figueras M, Olivan M, Busquets S, et al. Effects of eicosapentaenoic acid (EPA) treatment on insulin sensitivity in an animal model of diabetes: improvement of the inflammatory status. *Obesity (Silver Spring).* 2011;19(2):362–9. doi:10.1038/oby.2010.194
- [31] uceyar H, Ozutemiz O, Huseyinov A, et al. Is administration of n-3 fatty acids by mucosal enema protective

- against trinitrobenzene-induced colitis in rats? Prostaglandins Leukot. Essent Fatty Acids. **1999**;61(6):339–45. doi:10.1054/plef.1999.0111
- [32] Marion-Letellier R, Butler M, Dechelotte P, et al. Comparison of cytokine modulation by natural peroxisome proliferator-activated receptor gamma ligands with synthetic ligands in intestinal-like Caco-2 cells and human dendritic cells—potential for dietary modulation of peroxisome proliferator-activated receptor gamma in intestinal inflammation. *Am J Clin Nutr.* **2008**;87(4):939–48. doi:10.1093/ajcn/87.4.939
- [33] Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an Omega-3 Fatty Acid Receptor Mediating Potent Anti-Inflammatory and Insulin Sensitizing Effects. *Cell.* **2010**;142(5):687–698. doi:10.1016/j.cell.2010.07.041
- [34] Dragano NRV, Solon C, Ramalho AF, et al. Polyunsaturated fatty acid receptors, GPR40 and GPR120, are expressed in the hypothalamus and control energy homeostasis and inflammation. *Journal of Neuro inflammation.* **2017**;14:91.
- [35] Cabre E, Manosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases – a systematic review. *Br J Nutr.* **2012**;107(2):240–52. doi:10.1017/S0007114512001626
- [36] Tanaka T, Yano T, Adachi T, et al. Cloning and characterization of the rat free fatty acid receptor GPR120: in vivo effect of the natural ligand on GLP-1 secretion and proliferation of pancreatic beta cells. *Naunyn Schmiedebergs Arch Pharmacol.* **2008**;377(4-6):515–22. doi:10.1007/s00210-007-0250-y
- [37] Reaven, G.M. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* **1988**;37(12):1595–1607. doi:10.2337/diab.37.12.1595
- [38] Ramel A, Martínéz A, Kiely M, et al. Beneficial effects of long-chain *n*-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. *Diabetologia.* **2008**;51(7):1261–1268. doi:10.1007/s00125-008-1035-7
- [39] Lee JY, Zhao L, Youn HS, et al. Saturated fatty acid activates but polyunsaturated fatty acid inhibits Toll-like receptor 2 dimerized with Toll-like receptor 6 or 1. *J Biol Chem.* **2004**;279(17):16971–9. doi:10.1074/jbc.M312990200
- [40] Martin RE. Docosahexaenoic acid decreases phospholipase A2 activity in the neurites/nerve growth cones of PC12 cells. *J Neurosci Res.* **1998**;54(6):805–13. doi:10.1002/(SICI)1097-4547(19981215)54:6<805::AID-JNR8>3.0.CO;2-4
- [41] Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual antiinflammatory and pro-resolution lipid mediators. *Nat Rev Immunol.* **2008**;8(5):349–61. doi:10.1038/nri2294
- [42] P Matute P, N Echarri P, Martinez JA, et al. Eicosapentaenoic acid actions on adiposity and insulin resistance in control and high-fat-fed rats: role of apoptosis, adiponectin and tumour necrosis factor-alpha. *Br J Nutr.* **2007**;97(2):389–98. doi:10.1017/S0007114507207627
- [43] Derosa G, Cicero AFG, Fogari E, et al. Effects of *n*-3 PUFA on insulin resistance after an oral fat load. *Eur J Lipid Sci Technol.* **2011**;113:950–960. doi:10.1002/ejlt.201000504
- [44] Jump DB, Tripath S, Depner CM. Fatty Acid-Regulated Transcription Factors in the Liver. *Annu Rev Nutr.* **2013**;33:249–269. doi:10.1146/annurev-nutr-071812-161139
- [45] Wu X, Ouyang H, Duan B, et al. Production of cloned transgenic cow expressing omega-3 fatty acids. *Transgenic Res.* **2012**;21(3):537–43. doi:10.1007/s11248-011-9554-2
- [46] Zhang P, Zhang Y, Dou H, et al. Handmade cloned transgenic piglets expressing the nematode fat-1 gene. *Cell Reprogram.* **2012**;14(3):258–66.
- [47] Martins DA, Custódio L, Barreira L, et al. Alternative Sources of *n*-3 Long-Chain Polyunsaturated Fatty Acids in Marine Microalgae. *Mar Drugs.* **2013**;11(7):2259–2281. doi:10.3390/md11072259
- [48] Bigliardi B, Galati F. Innovation trends in the food industry: Trends in Food Science and Technology. **2013**;31(2):118–129
- [49] Tur J.A, Bibiloni M, Sureda A, et al. Dietary sources of omega 3 fatty acids: Public health risks and benefits. *Br J Nutr.* **2012**;107(2):23–52. doi:10.1017/S0007114512001456
- [50] Bermudez SPC, Hernandez IA, Chavez DLC, et al. Extraction and purification of high-value metabolites from microalgae: essential lipids, astaxanthin and phycobiliproteins. *Microb Biotechnol.* **2015**;8(2):190–209. doi:10.1111/1751-7915.12167