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Dietary Intake Omega-3 Rich Fish Oil and Management of Diabetes

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Abstract

Diabetes mellitus is a multifactorial disorder and prolonged suffering from the diabetes leads to damage the several vital organs due to excessive oxidative stress. On the other hand, omega-3 polyunsaturated fatty acids prevent the oxidative stress as evidenced from the various literatures. Therefore, we hypothesized the dietary intake of omega-3 rich fish oil could be beneficial in the management of diabetes and thus protect the several organs from the oxidative damages. Diabetes was induced in Swiss albino mice, *Mus musculus*, by repeating the intra peritoneal injection of Alloxan (100mg / kg body weight). Half of the diabetic mice were fed ad libitum the pellet feed blended with 10% laboratory extracted fish oil from *Sardinella longiceps* for one month in the laboratory. Various biochemical parameters pertaining to oxidative stress were measured along with the histology of the various organs like heart, kidney, liver and pancreas and the expression of certain cytokines and other m RNAs was measured by one step reversed PCR. The results suggest the prophylactic effect of dietary intake of *Sardinella* oil in diabetic mice by regulating the expression of cytokines and other marinas along with the increase of ant oxidant molecules in various organs.

Keywords: Fish oil; Diabetes; Oxidative stress; Anti oxidant molecules

Introduction

The oxidative stress, which has been identified as the cause of several diseases and degenerative processes, plays an important role in the etiology of diabetes mellitus. The diabetes mellitus is a multifactorial disorder, triggered by different factors leading to rise in blood glucose level related to metabolism of carbohydrate, fat and protein resulting from a deficiency in insulin secretion, insulin action or both [1]. The recent report of the International Diabetes Federation attributed that worldwide 415 million peoples suffering from diabetes in 2015 and the figure might jump to 642 million by the year 2040. The hyperglycemia is assumed to be causal factor in vascular complication of diabetes. Several mechanisms like alteration in lipid metabolism, antioxidant defence mechanism and production of reactive oxygen species imbalance [2] changes in the inflammatory pathway [3] which play an important role in increased oxidative stress in diabetic patients. As insulin plays a central role in the regulation of lipid metabolism, in poorly controlled type 1-diabetes, ketoacidosis, hypertriglyceridemia and reduced HDL concentrations commonly occurs [4]. The dyslipidaemia associated with diabetes type 1 is likely a major risk factor for the accelerated macro-vascular diseases like atherosclerosis and coronary heart disease seen in diabetic patients [5]. Therefore, regulating the lipid metabolism through the dietary supplementation or drug might be helpful to enhance the insulin secretion and thus ameliorate the diabetes and its related complications.

Blood glucose homeostasis

The steadiness of blood glucose is achieved through well-balanced hepatic glucose release, transport and peripheral glucose disposal maintained by excellently tuned, synchronized network of metabolic, signalling, regulatory pathway. Within narrow physiological range, the complex balance of dietary intake helps to maintain blood glucose level, de novo glycogen storage, synthesis, release and insulin dependent and independent glucose acceptance of tissue [6]. The entrance of glucose into the circulation is influenced by the rate of assimilation of carbohydrates [7].

The glucose is used by the liver as fuel and also it has the capability to store it as glycogen and synthesize it from non-carbohydrate precursor. The glucose that is taken up by a cell in cytosol may be oxidized to pyruvate. The electrons produced for this course are transported to the mitochondria to form energy. In the mitochondria, the acetyl CoA produced by oxidizing pyruvate through the glycolytic pathway undergoes complete oxidation through the tricarboxylic acid cycle and inner membrane electron transport system generates nearly 36 moles high energy phosphate from each molecule of glucose [8].

The pancreas is one of the major organs of the body, beside with the liver. It has both endocrine and exocrine functions. It carries two functions, the production of enzymes in the digestive system in the exocrine tissue and creates hormones as part of the endocrine system. Several hormones regulate the carbohydrate metabolism, particularly which are produced by pancreatic cells of islets of Langerhans.

Insulin and glucagon produced by β cell and α cell respectively, have an important contribution on glucose metabolism. D cells and F and D1 cells produce hormone somatostanin and pancreatic polypeptides having a modulating effect on the secretion of insulin and glucagon. The large nutrient molecules were reduced by gastric juice in stomach by breaking down the large quantity of food and the nutrients released were absorbed into the bloodstream by the action of the intestine. The large nutrient molecules are cut down to smaller molecules by enzymes secreted by the pancreas, these molecules through the walls of the intestines can be absorbed into the bloodstream. Insulin is a protein chain or a peptide hormone consisting 51 amino acid molecules. Like the receptor for other protein hormones, the receptor for insulin is entrenched in the plasma membrane. The hydrolysis of dietary carbohydrates such as starch and sucrose within the small intestine liberate the glucose. Elevation of the concentration of glucose in the blood results in the release of insulin, which stimulate glucose uptake, use and storage (Figure 1). Depending upon the target tissue the effects of insulin on glucose metabolism vary [9].

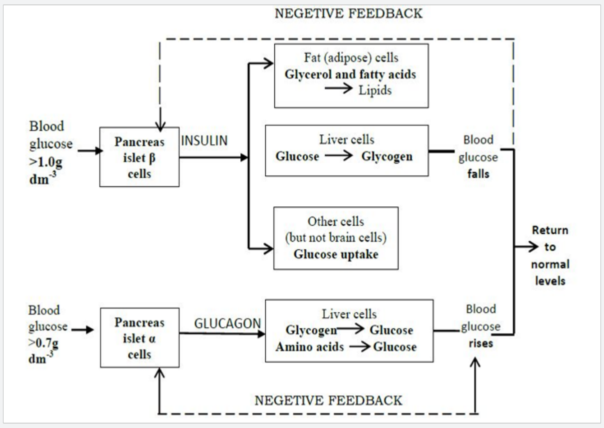

Figure 1: The homeostatic control of blood glucose level.

Oxidative stress, lipid peroxidation and diabetic complications

The complications associated with diabetes type 1 leads to increasing disability and shortened life expectancy and are main threat to the health and life of patients. Although the hyperglycemia is recognized as a risk factor for progression of diabetic complications, there is no agreement concerning the pathogenic relation among hyperglycemia and complications [10]. There are numbers of equally acceptable reasons for the origin of complications. Years of poorly controlled hyperglycemia lead to major types of diabetes related multiple, primarily microvascular (affect small vessels) and macrovascular (affect large vessels) complications or both and oxidative stress plays a pivotal role.

In diabetes over generation of reactive oxygen species (ROS) because of glucose auto-oxidation, metabolism and the progress of advanced glycosylation end products, stimulates toxic impacts. This leads to unsuccessful scavenging of ROS and disturbances in the regular redox state that damage all constituents of the cell, including proteins, lipids and DNA resulting in tissue impairment and damage [11]. Mainly the oxidative stress and years of inefficiently controlled hyperglycemia plays a vital part in the progress of diabetes complications that affect small vessels which damages tissues like eye, kidney (microvascular) and large vessels (macrovascular) causing cerebrovascular disease, coronary heart disease, peripheral arterial disease or both. Endogenous ROS in mitochondria, plasma membrane, endoplasmic reticulum and peroxisomes are produced through a variety of mechanisms, including oxidation of numerous compounds [12].

The two most pervasive ROS that can significantly influence the lipids are chiefly hydroxyl radical (HO·) and hydroperoxyl ($HO\cdot_2$). The prolonged production of superoxide causes the initiation of 5 noteworthy pathways [13] included in the pathogenesis of intricacies:

(A) polyol pathway flux,

(B) increased arrangement of AGEs (advanced glycation finished items),

(C) elevated articulation of the receptor for AGEs and its actuating legends,

(D) activation of protein kinase C isoforms and

(E) over activity of the hexosamine pathway.

A few lines of proof demonstrate that each of the 5 mechanisms triggered by upstream occlusion of ROS overproduction by mitochondria. A cell produces around 50 hydroxyl radicals every second, which can be neutralized or un-specie attack biomolecules [13] situated less than couple nanometers from its origin of generation which can cause oxidative damage and participate in cellular diseases such as neurodegeneration [14] cardiovascular disease [15] diabetes [16] and cancer [17].

Role of PUFA in health

Dietary lipid helps to keep up well-being and plays an essential role in physiological developments. Members of polyunsaturated fatty acid (PUFA) cluster are directly vital substances and these are accepted to be intricate in tissue lipid and are at current assuming increase prominence in biochemistry [18]. The alpha-linolenic acid, the precursor molecule of omega-3 PUFAs, and linoleic acid, the precursor of omega-6 PUFAs are the two essential fatty acids (EFAs) in human nutrition and PUFAs belong to omega-3 or omega-6 families cannot be interconverted. Both linoleic and alpha linolenic acid can be extended to various long chain (C-20, C-22) polyunsaturated fatty acids through elongation and desaturation processes. Therefore, humans must obtain these essential fatty acids from dietary sources [19].While the natural distribution of omega-6 fatty acids is cosmopolitan, the distribution of omega-3 fatty acids are restricted in terrestrial and freshwater ecosystems but abundant in the marine ecosystem.

These long chain omega-3 and omega-6 PUFAs produce distinct types of prostaglandins and thromboxanes through lipoxygenase and cyclooxygenase pathways, each of which has very different effects in the body and act in an antagonistic manner. These eicosanoids act as potent regulators of vital body functions and play role in the immune system and inflammatory responses [20]. The distinct types of prostaglandins and thromboxanes (collectively known as eicosanoids) were produced by arachidonic acid (AA, 20:4, ω-6), dihomo γ-linolenic acid (DGLA, 20:3, ω-6) and eicosapentaenoic acid (EPA, 20:5, ω-3) along with other long chain omega-3 and omega-6 fatty acids through lipoxygenase, cyclooxygenase and epoxygenase pathways (Figure 2). Each of these eicosanoids like hydroperoxides, prostaglandins, lipoxins, leukotrienes and epoxy fatty acids and other bio reactive molecules has very diverse effects on the body and act in an antagonistic way [19]. As a result enzymes involved in the production of these eicosanoids has become the target for the development of anti-inflammatory drugs [19]. Eicosanoids act as potent regulators of vital body functions and play role in the immune system and inflammatory responses [20].

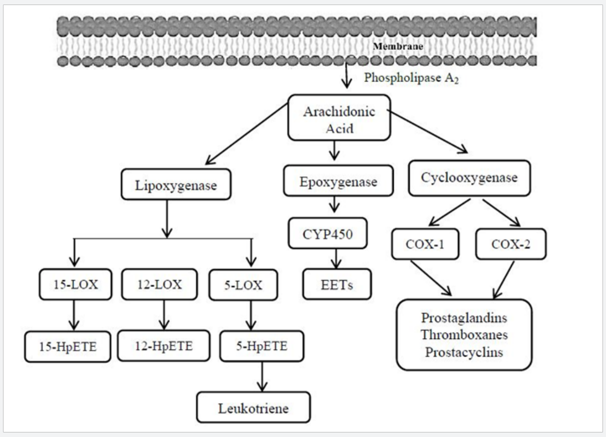

Figure 2: Overview of Oxygenation of Arachidonic Acid via COX, LOX and EPOX pathway Aparoy et al. [21]. COX- cyclooxygenase, LOX- lipoxygenase, EPOX- epoxygenase, HpETE- hydroperoxyeicosatetraenoic, CYP450- cytochrome 450, EETs- epoxyeicosatrienoic acids.

Over the past 10-15 years of research have demonstrated the health benefits associated with consumption of omega-3 PUFA rich fish oil and it has been in practice as most effective means of omega-3 supplementation [21,22]. Numerous studies have been also demonstrated the hypo-triglyceridemic effects of dietary fish oils [23]. The omega-3 enriched fish oils are associated with the prevention of several metabolic diseases [24], cancer [25] alcoholic liver disease [26], hepatitis [27], mental diseases such as dementia, depression, hyperactivity disorder etc. [28], to attenuate inflammation [29], oxidative stress [30] and useful for treatment of cardiovascular disease [31]. Goa being a coastal state, high intake of marine fish rich with omega-3 PUFA is common in the state, still diabetes on the rise in the state (according to report Times of India, 14 Nov 2013). However, often there are a controversy, conflicts and lacunae on consumption of which fish offers better protective effect. The effects of fish oil consumption are unclear in diabetes and there is no clear conclusion about the net benefits of administering omega-3 PUFA to diabetic patients [32]. Hence, the review paper was designed to test the hypothesis that the dietary fish oil rich with omega-3 polyunsaturated fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) might also help in reversing the metabolic changes and prevent the tissue damages due to prolonged diabetes.

Ameliorative effect of supplementation of fish oil on diabetic mice

The diabetes was induced in the swissalbino mice, *Mus musculus* by repeated interpaeritoneal injection of alloxan at a dose of 100mg /kg mice at every 5 days interval. The diabetic mice were divided into 2 groups; one group was fed with the pellet diet supplemented with 10% laboratory extracted oil from *Sardinella longiceps* ad libitum and another group of mice were fed with regular pellet diet. Beside, control group of mice was also maintained with regular diet. Both the diabetic and control mice were maintained in hygienic condition for one month with the approval of the Institutional Animal Ethics Committee. The fatty acid analysis of the fish oil (*Sardinella longiceps*) revealed that it contained 46% saturated fatty acids and 54% unsaturated fatty acids. Among the unsaturated fatty acid most predominated fatty acids are eicosapentaenoic and docosahexaenoic acids contributing around 32% of the total fatty acids.

Prolongedalloxan administration to the mice architecturally distorted liver, kidney, heart and pancreas. Diabetic mice showed liver with the accumulation of lipid in hepatocytes, kidney with deformation, glomerular expansion, heart with degeneration, inflammation and deformation of the pancreas with the presence of the lymphocytic infiltrates in islets [33]. This could be ascribed to impaired metabolism of fatty acids resulting in increased quantities of fat within liver cells [34] and successive effects of hyperglycemia, which persuades degenerative changes in tissues may be due to the augmented ROS generation [35] and diminished defense of antioxidant system [36]. It was also noted that induction of diabetes mice by alloxan (Table 1) lead to destruction of insulin producing beta cell of pancreatic islet,

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with about 7.5 fold augmentation in the level of free sugar in the blood and increased concentration of glycosylated hemoglobin by 5 fold, which might be due to deprived regulation of glucose metabolism or which might be due to gluconeogenesis and glycogenolysis [33].

Table 1: Effect of dietary supplementation of *Sardinella* oil in alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

	Serum Insulin Concentration (Ng /Dl)	Concentration of Glycated Haemoglobin (%)	Concentration of Blood Sugar (Mg / Dl)
Control group of mice(C)	82.00 ± 1.10	4.28 ± 0.34	76.38 ± 11.35
Diabetic mice (D)	41.80 ± 1.00	21.1 ± 0.52	566.1 ± 13.8
Diabetic mice ± fish oil (DF)	64.30 ± 1.20	11.6 ± 0.54	64.01 ±1.09

The diabetes also resulted in alterations in the lipid peroxidation and antioxidant status. Superoxide dismutase (SOD) and catalase, which are free radical scavenging enzymes and reduced glutathione (GSH), which counterbalance free radical facilitated damage and acts as an endogenous antioxidant [37]. Induction of diabetes with alloxan injection the concentrations of vitamin E, vitamin C, antioxidants decreased by 25-65%, with about 2 to 6 fold augmented levels of thiobarbituric acid reactive substances (TBARS) in all the tissues of diabetic mice (Tables 2&3). The reason for this change is might be excessive lipid peroxidation and the generation of free radicals. Oxidative stress triggered by extreme production of superoxide and an inequity in antioxidant enzymes or increased consumption might be the reason for a reduction in the level of biomolecules and enzymatic antioxidant status in tissues of diabetic mice [38]. Supplementation with PUFAs rich fish oils to alloxan-induced diabetic mice helped to recover the architectural tissue damage, which was also reflected in biochemical composition and enzyme activity of these tissues. Fish oil supplementation in diabetic mice ensued significant reduction of glycosylated hemoglobin and free sugar along with elevation in the level of insulin by 50% (Table 1) confirmed the role of fish oil in increasing insulin action and in regulating glucose metabolism [39]. This is may be due to mechanism based on substituting of fuel with increased glucose utilization and reduced fatty acid accessibility and enhancing the effect of insulin, the cycle involved with glucose-fatty acid could also be the reason [40].

Table 2: Effect of dietary supplementation of *Sardinella* oil on the concentration of Vitamin C and Vitamin E in alloxan induced diabetic mice. Data represented the mean of six values and their standard error. *The value for serum represented per unit of dl.

Tissue	Concentration of Vitamin C(mg/100mg)			Concentration of Vitamin E(µmol/100mg)		
	C	D	DF	C	D	DF
Serum*	144.7±2.11	66.2 ± 2.0	123.2 ± 1.82	6.30 ± 0.012	3.33 ± 0.011	5.22 ± 0.007
Liver	1.8 ± 0.25	0.708 ± 0.05	2.12 ± 0.28	0.062 ± 0.001	0.047 ± 0.001	0.056 ± 0.001
Heart	1.37 ± 0.14	0.625 ± 0.05	1.165 ± 0.18	0.055 ± 0.001	0.042 ± 0.001	0.049 ± 0.001
Kidney	1.47 ± 0.20	0.653 ± 0.07	1.402 ± 0.20	0.060 ± 0.001	0.044 ± 0.001	0.053 ± 0.001
Pancreas	1.30 ± 0.09	0.541 ± 0.06	1.28 ± 0.05	0.050 ± 0.001	0.004 ± 0.001	0.047 ± 0.001

Table 3: Effect of dietary supplementation of *Sardinella* oil on the concentration of reduced glutathione and TBARS in alloxan induced diabetic mice. Data represented the mean of six values and their standard error*. The value for serum represented per unit of dl.

Tissue	Concentration of Reduced Glutathione			Concentration of TBARS E(µmol/100mg) (µ mol / 100 mg))		
	C	D	DF	C	D	DF
Serum*	2247.6±80.4	1310.5±112	1950.3±50.6	0.262±0.004	1.75±0.005	0.505±0.002
Liver	0.473±0.031	0.217±0.006	0.388±0.022	0.268±0.018	0.581±0.048	0.353±0.012
Heart	0.444±0.012	0.215±0.011	0.250±0.014	0.247±0.007	0.581±0.016	0.347±0.014
Kidney	0.496±0.022	0.207±0.013	0.275±0.032	0.222±0.01	0.526±0.026	0.362±0.018
Pancreas	0.333±0.016	0.202±0.009	0.430±0.034	0.237±0.012	0.450±0.012	0.430±0.034

Kamat & Roy [33] reported an improved antioxidant status in fish oil supplemented diabetic mice. The concentration of antioxidants like GSH, Vitamin E and Vitamin C (Table 2&3) and activity of antioxidant enzymes SOD, catalase (Table 4) were elevated by 25-60% and the level of TBARS (Table 3) was decreased by 30-75%. Similarly, the activity of GGT, lipid peroxidation variables was increased significantly approximately by 25 -70% along with a sharp decreased of about 50% of the

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activities of lactate dehydrogenase (Table 5) in all the tissues of the diabetic mice upon supplementation of 10% fish oil. This indicates that omega-3 PUFAs rich fish oils are having a useful effect on attenuation of oxidative stress and antioxidant potential which is in support with previous results, which had authenticated that omega3 PUFAs present in edible oils shows anti-inflammatory effect signifying their use in the treatment of diabetes or hyperglycemia [41].

Table 4: Effect of dietary supplementation of *Sardinella* oil on the activities of reduced Superoxide dismutase and Catalase in alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

Tissue	Activities of Superoxide dismutase (IU/mg protein)			Activities of Catalase (μmol H_2O_2/min/mg protein)		
	C	D	DF	C	D	DF
Serum	11.97± 0.23	8.23 ±0.12	10.25±0.22	165.12±10.26	140.23±12.23	225.14±21.12
Liver	14.18 ± 0.18	9.37 ±0.21	13.02 ±0.15	161.32±15.18	138.12±21.43	210.32±17.34
Heart	13.5 ±0.16	7.26 ±0.15	11.53 ±0.20	150.14±18.21	122.14±16.24	185.54±21.26
Kidney	12.15 ±0.21	6.15 ±0.11	9.67 ±0.18	201.12±20.42	142.24±18.67	175.25±19.09
Pancreas	12.05 ±0.22	6.25 ±0.21	10.05 ±0.15	145.25±16.56	140.45±21.12	171.45±18.37

Table 5: Effect of dietary supplementation of *Sardinella* oil on the activities of reduced Gamma glutamyl transpeptidase and Lactate dehydrogenase in alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

Tissue	Gamma Glutamyl Transpeptidase (IU/mg Protein)			Activities of LDH (IU/mg Protein)		
	C	D	DF	C	D	DF
Serum	11.97±0.13	8.23±0.10	10.25±0.14	105.12±10.12	200.23±15.43	125.14±10.24
Liver	14.18±0.24	9.37±0.12	13.02±0.25	101.32±9.32	208.12±10.12	110.32±11.12
Heart	13.5±0.11	7.26±0.15	11.53±0.19	100.14±10.17	222.14±13.24	105.54±9.96
Kidney	12.15±0.16	6.15±0.09	9.67±0.11	150.12±15.43	242.24±9.45	155.25±15.25
Pancreas	12.05±0.21	6.25±0.11	10.05±0.21	105.25±9.25	190.45±12.23	101.45±13.26

Dietary supplementation of fish oils on gene expression in diabetic mice

Table 6: Effect of dietary supplementation of *Sardinella* oil on the relative expression of IL 1 α and TNF α in alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

Tissue	IL 1 α			TNF α		
	C	D	DF	C	D	DF
Liver	0.82±0.005	1.18±0.010	0.71±0.002	1.08±0.008	1.72±0.021	0.62±0.008
Heart	0.72±0.004	1.08±0.008	0.70±0.001	1.05±0.010	1.85±0.018	0.68±0.010
Kidney	0.85±0.003	1.21±0.006	0.62±0.004	1.01±0.012	1.70±0.017	0.59±0.008

Traditionally, diabetes was not believed to be a disease related to the immune system, however, there is increasing evidence supporting a role for inflammation in diabetes. In the pathogenesis of diabetes through increased inflammation and fibrosis affecting vascular system the inflammatory cells, cytokines, and profibrotic growth factors, including TGF-β, TNF-α, connective tissue growth factor (CTGF), monocyte chemo attractant protein-1 (MCP-1), interleukins-(IL-1, IL-6, IL-18) and cell adhesion molecules (CAMs) have been involved [42,43]. TNF-α and IL-1 are beneficial when produced appropriate quantities, but the overproduction of these may result in inflammation [44]. In the present study, about 40-60% increase in the expression of inflammatory cytokines like TNFα and IL1α was observed in liver, kidney and heart tissues (Table 6) of alloxan induced diabetic mice. The activation of NFκB or the initiation of caspases activation is promoted by the binding of TNF-α to TNF-R1 which has a major role in the implementation of programmed cell death or apoptosis [45]. NFκB stimulates the expression of genes encoding cytokines like TNF-α, Inteleukins, INF-γ, CM-CSF and CAMs, chemokine receptors and inducible enzymes (e.g., COX- 2, iNOS). The early event which contributes to the disease process in the liver during inflammation is an increase in TNF- α in type 1 diabetes [43]. Animal and human studies have shown that production of cytokines can be reduced by n-3 fatty acids [46]. In our study the expression of IL1α, TNFα and TGF β in the dietary fish oil supplemented groups lowered by 35-60% ($P<0.001$) in spite of alloxan induced diabetes. It is specified by the studies that omega-3 PUFA and their explicit lipid mediators can diminish the process of activation of inflammation and also supplementation of fish oil reduces the production of TNF-α and IL-1 in mononuclear cells [27,47,48].

Table 7: Effect of dietary supplementation of *Sardinella* oil on the relative expression of Ins1, Ins 2 and Gcg in the pancreas of alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

Gene	C	D	DF
Ins1	1.031±0.005	0.419±0.006	0.870±0.004
Ins2	1.027±0.003	0.446±0.007	0.667±0.010
Gcg	0.419±0.006	0.667±0.010	0.569±0.004

The expression of Ins1 and Ins2 decreased by 55-60% in the pancreas tissue (Table 7) of diabetes induced mice, which might be due to inflammation of the pancreatic islet, resulting in the preferential destruction of insulin producing β-cells to varying degrees by the rigorous action of auto reactive T-cells and monocytic cells [49].The functional impairment evolves to β-cell death after prolonged exposure to IL-1β + Interferon-γ and/or tumor necrosis factor (TNF) -α, but not to either cytokine alone [50]. This also results in failure to suppress glucagon secretion and intra-islet paracrine mechanisms results in the hyper secretion of glucagon. The supplementation of 10% fish oil to the diabetic mice elevated the decreased expression of Ins1 and Ins2 by 55-100% in the pancreas, which was also reflected in serum insulin concentration, with nearly 10-15% decrease in expression of glycogen. Substantial evidence showed that the dietary fat subtypes played major role in insulin action. Saturated fatty acid intake is strongly linked to the development of obesity and insulin resistance due to poor oxidization and mobilization by lipolytic stimuli, which in return impairs membrane function by increasing the gene expression associated with adipocyte proliferation, while PUFAs shows contrasting action [51]. The action of omega-3 PUFA is based on metabolizing of incretin, hormone that stimulates insulin secretion in response to meals, glucagon-like peptide-1 which increases endogenous insulin secretion [52].

In our study, we found that the expression of the GLUT2 minimally decreased by about 25% along with about 35 % decrease in GLUT4 expression in the liver of alloxan induced diabetic mice, which show the existence of a β cell-specific control of expression, an observation consistent with previous reports. The β-cell glucose unresponsiveness and insulin inadequacy is associated with loss of GLUT2 and GLUT4 expression. The supplementation of 10% fish oil helped to slightly increase the expression of glucose transporters in the liver (Table 8). This observation suggests that a diet rich with PUFA induces changes in lipid composition of the membrane and enhances the membrane fluidity [53] which might increase the glucose transporter inherent activity. The increase in expression of COX-2 and not much changes in expression of COX-1 genes was observed in the liver of diabetic mice. COX-1, sub serve housekeeping functions, expressed constitutively in most cells, is the main source of prostanoids. The up regulation of COX-2 in diabetes, is may be due to inflammatory stimuli, hormones and growth factors [20]. The supplement of fish oils contains EPA, which acts as the natural COX inhibitor, inhibits both COX-1 and COX-2 activity. EPA inhibits AA metabolism and acts as alternate substrate for COX. Prostaglandin PGH2 which is produced by conversion of AA by COX is replaced by EPA, which gets converted to n-3 homolog PGH3 [54,55]. The changes in the level of various prostaglandins of 2 and 3 series in the diabetic mice need to be confirmed.

Table 8: Effect of dietary supplementation of *Sardinella* oil on the relative expression of GLUT2, GLUT4, Cox 1 and CoX 2 in the liver of alloxan induced diabetic mice. Data represented the mean of six values and their standard error.

Gene	C	D	DF
GLUT2	0.806±0.037	0.576±0.024	0.626±0.023
GLUT4	0.821±0.024	0.536±0.011	0.604±0.009
COX 1	1.023±0.035	1.131±0.039	0.970±0.010
COX 2	0.678±0.010	1.151±0.046	0.770±0.017

Conclusion

Finally, it can be concluded that 10% supplementation of fish oil with long chain fatty acids helps to maintain health of Mus musculus in an improved way. Our study showed that dietary supplementation of Sardinella oils rich with long chain polyunsaturated fatty acids, namely eicosapentaenoic and docosahexaenoic acids, significantly alleviates the alloxan induced diabetes, which was reflected in the composition of biochemical molecules, the activity of enzymes, histological study of tissues along with the expression of cytokines, glucose transporter, insulin, and prostaglandin synthesis genes. Overall results support the concept that dietary fish oils rich in omega-3 PUFA may be of therapeutic benefit in patients with diabetes.

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