

Insulin Resistance Modulation with Lifestyle Modification- Proof-of-Concept Study in Rats

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ABSTRACT

Purpose: Fatigue, a physical and/or mental exhaustion is a common symptom of diabetes. Easy fatigability is not limited to uncontrolled diabetes however is comorbid with psychological, medical, metabolic, and chronic complications like insulin-resistance, glucose intolerance, and obesity. **Methods:** We analyzed the effect of lifestyle modification involving physical exercise and intake of omega 3 fatty acid-rich fish oil on insulin resistance and diabetic fatigue. For the same, diabetes was induced using single dose streptozocin injection in rats fed with a high-fat diet and were treated with fish oil alone and in combination with exercise training. Blood glucose levels, glucose tolerance, lipid profile, insulin levels, oxidative stress and glycogen content were monitored in rats exposed to swimming exercise and fatigue test. **Results:** Alone fish oil could improve symptoms of diabetic complications; however, the combination intervention of exercise and oral administration of fish oil significantly lowered the fasting blood glucose level and fatty acid profile in diabetic rats. Improvement in antioxidant profile was observed from the decreased levels of lipid peroxidation products and increased levels of antioxidants like superoxide dismutase and glutathione. Effective glucose disposal correlated with better insulin tolerance and improvement in lipid profile as indicated by a significant reduction in LDL, VLDL, free fatty acids, and leptin with an increase in HDL levels. Exercise-induced changes in the liver and skeletal tissue, enabling diabetic rats to restore their glycogen stores thus building the endurance required for prolonged exercise. **Conclusion:** Lifestyle modification with moderate exercise and consumption of antioxidant-rich fish oil is a novel and easy therapeutic intervention in the treatment of multifactorial syndrome of fatigue observed as a diabetic complication.

Key words: Insulin, Fatigue, Diabetes, Fish Oil, Exercise.

Submission Date: 15-09-2020;

Revision Date: 21-10-2020;

Accepted Date: 15-11-2020

DOI: 10.5530/ijper.54.4.173

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INTRODUCTION

Insulin resistance is approaching epidemic proportions globally due to a sedentary lifestyle accompanied by a diet with a high content of carbohydrate and transfat.¹ Fatigue is distinctly associated with diabetes mellitus and is directly correlated with the severity of the disease and complications.² The clinical symptoms of type 2 diabetes are increased blood glucose concentration, oxidative stress, insulin resistance,

hyperleptinemia, hypertension, and fatigue. Fatigue occurs very frequently in diabetic patients and it indicates the severity of hyperglycemic status and its complications.³⁻⁵ Oxidative stress and insulin resistance are directly correlated.⁶ Excess production of reactive free radicals is due to abnormal metabolism of lipids and glucose. High-fat consumption further adds a burden to the antioxidative system.⁷ The impairments in the endogenous antioxidative system lead to



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insulin resistance in peripheral metabolic tissues.⁸ High-fat diet consumption alters insulin secretion, glucose utilization, and glucose regulation in skeletal muscles.² Exercise augments insulin-assisted glucose uptake and attenuates hyperinsulinemia and insulin resistance in diabetic rats.^{9,10} Regular intake of saturated fat-rich diet (Western diet) and high intake of vegetable and animal fat leads to insulin resistance¹¹ whereas, a diet enriched with polyunsaturated fatty acids could overcome the insulin resistance.¹² Feeding fish oil to rats has reduced the occurrence of resistance towards insulin, especially in skeletal muscle.¹³ Therefore, dietary intervention and physical exercise are necessary to reduce the incidences of insulin resistance.¹⁴ Diabetes being a chronic disease requires long-term treatment and therefore, administration of fish oil by oral route will be convenient for the patient. We investigated the effect of lifestyle modification with exercise and fish oil consumption on the occurrence of insulin resistance and fatigue in diabetic rat model developed using combination of high-fat diet and intraperitoneal streptozocin.

MATERIALS AND METHODS

In vivo studies in animals

Rats (Sprague-Dawley, male, $n=50$, $n=2$ per cage) were housed in our institutional animal house (Vidya Institute, Bangalore and experiments were performed in accordance with the guidelines of the institutional ethics committee).

High fat dieting, diabetes induction, and glucose monitoring

The experimental protocol was approved by the Institutional ethics committee and experiments were performed following the guidance from committee members. Sprague Dawley rats ($n=50$) were equally divided into five groups with 10 animals in each group. Normal control group rats ($n=10$) were given a regular diet. The rest of the 4 groups ($n=40$) were on high fat diet for two weeks. Streptozotocin (35mg/kg, ip, single dose) was given to these four groups to induce diabetes mellitus.¹⁵ The glucose level in blood sampled from the tail vein was quantified using AccuCheck (a glucose diagnostic kit – Ser.No.GB 14561388). Rats were designated as diabetic if non-fasting blood sugars were ≥ 250 mg/dl. Before the start of the treatment glucose tolerance test (GTT) was performed. Post 10 weeks of streptozotocin administration (end of the treatment), serum was derived from blood samples, frozen, and analyzed later for biochemical data. Serum glucose concentration was derived using the kits that

were available locally (Crest Biosystems, India) via the glucose oxidase peroxidase (GOD-POD) method¹⁶. Rats with diabetes were divided into four groups as follows: type 2 diabetic control (DC group), diabetic rats with exercise training (DE), diabetic rats with oral dose of fish oil (DF group), diabetic rats with oral dose of fish oil and exercise training (DFE). Fish oil (Marincap capsules 500mg with -3 fatty acids (35%), EPA, 18%, and DHA, 12%. 0.4 g/kg was administered (to group DF and DFE). The lifestyle modification regimen involved for the swimming exercise was 40 min/day and 5 days/week for groups DE and DFE and oral supplementation of fish oil for group DF and DFE.

Swimming exercise and fatigue test

The rats from groups DE and DFE were trained to exercise as per the procedure of Rahman *et al.*¹⁷ The swimming chamber was made up of glass (H - 80cm, L – 100cm, W – 80 cm) and filled till a height of 60 cm with warm water ($36 \pm 1^\circ\text{C}$). The temperature of the water was maintained using a thermostat and air bubbles were produced by using an air pump system. Rats were forced to swim for 40 minutes. The rats from the other groups, NC, DC, and DF were trained alternate days, 10 mins/session, in the last two weeks of the treatment protocol. Three fatigue tests were conducted. The increase in swimming endurance capacity is when the rats were able to keep their nose and head above the water surface. The rats were forced to swim until exhaustion (signs of fatigue), a point wherein the nose of rats stayed below the surface for 10 sec, and swimming time was recorded until exhaustion.¹⁸

Blood analyses

Fasting blood glucose (FBG) level, Insulin and Insulin Resistance

The fasting blood glucose (FBG) levels were determined every 14 days with a blood glucose meter. GTT was performed by administering a glucose solution (30%. 0.2 g/100 gm body weight)¹⁹ was injected intraperitoneally. ELISA test kits (ALPCO Diagnostics) were used Insulin resistance = [glucose (mmol/l) x Insulin (IU/L)]/22.5.

Lipid profile

Blood from 12-hr-fasted rats was collected from the caudal vena cava immediately following sacrifice. The serum levels of total cholesterol (TC), triglyceride (TG), HDL, LDL, and free fatty acid (FAA) were determined. The Friedewald formula was used to estimate VLDL. $\text{VLDL} = \text{TG}/5$.²⁰ ELISA kits were used to measure the plasma leptin levels.

Detection of Oxidative Stress

Thiobarbituric acid reactive substances (TBARS) levels in plasma

The plasma TBARS level was determined based on the reaction with thiobarbituric acid (TBA) at 90–100°C in acidic condition pH 2-3.²¹ Lipid oxidation materials react with TBA react together and result in the formation of a pink-colored complex which is analyzed spectrophotometrically at 532 nm.

Superoxide dismutase (SOD) and Glutathione-peroxidase activity in Plasma SOD

Total SOD activity was determined according to the method of Sun *et al.*²² The test was performed on the ethanolic fraction of plasma after mixing with ethanol /chloroform mixture (5:3). Plasma GSH-Px (EC 1.6.4.2) activity was measured by an enzymatic reaction leading to a color change, that was monitored spectrophotometrically at 340 nm (U/ml).²³

Glycogen content

The tissue sample of about 1g of animal tissue was taken in a centrifuge tube containing 3ml of KOH (30%) solution. The glycogen was precipitated with the addition of saturated sodium sulfate and ethanol (95%). The precipitated glycogen was purified and hydrolyzed by adding 0.6 N HCl and neutralized the acid by adding sodium hydroxide. Finally, the glucose in the hydrolyzate was determined as reducing sugar.²⁴

Statistical analysis

The Prism 8.0.2 software (GraphPad Software Inc., San Diego, CA, USA) was used for the statistical analysis of the data. All the data were expressed as mean \pm standard error of the mean (SEM). The student's *t*-test was used as appropriate for discrimination. The data were first tested for normality and homogeneity and analyzed using a one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test for the within-group analysis, given the 5% significance level.

RESULTS

Effect of high fat diet and diabetes induction on body-weight

The initial weight of rats was 220.8 ± 12 g and after 2 weeks of treatment with a high-fat diet, the rats gained weight up to 340 ± 15 g showing a weight gain of 54.5%. This was significantly higher than the rats fed with a normal diet (227.1 ± 10 g $p < 0.001$).

Glucose tolerance test GTT

The GTT was performed at the end of the 2nd week to analyze the state of glucose intolerance/insulin resistance of the rats. The GTT showed an increase in glycemia in diabetic control compared to normal control (Figure 1). Post two weeks of the high-fat diet, a single sub-diabetogenic dose of STZ (35mg/kg) induced clinical diabetes with hyperglycemia (< 400 mg/dl). Rats with blood glucose levels >250 and <350 mg/dl were used in the study.

Impact of exercise, consumption of fish oil and dual combination intervention on exercise performance (Endurance capacity)

The NC and DC groups showed a swimming time of 111 ± 6 and 53 ± 3 min respectively. When the DC group swimming time was decreased by 52 % indicative of a decline in endurance capacity in diabetic rats. The diabetic rats were significantly exhausted at a much quicker. However, this fatigue was alleviated significantly in diabetic rats that were subjected to supplementation of fish oil and exercise.

The swimming time in DE, DF, and DFE groups was 96 ± 5 , 75 ± 6 , and 105 ± 5 min respectively. When compared with the DC group, there was a significant increase in the swimming time in DE (81.1%), DF (41.5%), and DFE (98.1%) groups (Figure 2A).

The swimming time also increased by 40% in the DFE group compared to the DF group. Diabetic rats supplemented with fish oil and subjected to exercise training (DFE group) exhibited an increase in endurance capacity than their counterpart groups such as DE ($p < 0.001$) and DF ($p < 0.001$) rats. On the other hand, diabetic rats treated with fish oil alone did not seem to be benefitted from the early recovery from fatigue. However, a noteworthy 49.44% increase in the endurance time in the DFE group compared to DE rats, indicates a higher endurance capacity when fish oil was added to exercise training (Figure 2B).

Impact of exercise, consumption of fish oil, and dual combination intervention on FBG levels and insulin related parameters

Consumption of a high-fat diet for 2 weeks significantly increased the FBG level. When the same animals were injected with STZ, we observed a drastic surge in FBG levels in DC, DF, DE, and DFE. These levels increased gradually until the end of the treatment period and displayed a 2.55 fold increase than the control group but there was a gradual decrease in glucose levels in the groups subjected to exercise and fish oil

supplementation. The glucose levels lowered significantly in DE (20%), DF (47%), and DFE (56%) groups when compared to untreated diabetic rats (Figure 3).

Insulin levels were altered significantly when compared to the NC group. The combined action of fish oil and exercise in the DFE group has ameliorated this significantly altered insulin level towards normal value (Table 1).

Impact of exercise, consumption of fish oil and dual combination intervention on plasma lipid profile and leptin levels

The untreated diabetic rats (DC) had shown a remarkable abnormal lipid profile in terms of increased total cholesterol (Figure 4A), triglycerides (Figure 4B), LDL (Figure 4D) and VLDL (Figure 4E), free fatty acid (Figure 4F), leptin (Figure 4G), and decreased HDL (Figure 4C) in comparison with the normal control (NC) group. However, the diabetic rats treated with the combination of fish oil with exercise (DFE) had set back these abnormal values toward normalcy (Figure 4). The effects observed in the DFE group were significantly different than the individual treatment groups, namely, exercise-trained DE or fish oil-fed, DF.

Impact of exercise, consumption of fish oil, and dual combination intervention on antioxidant activity

There was a significant difference in antioxidant levels when compared to the control group. However, the exercise impact on fish oil supplementation in rats with diabetes had brought back the levels of antioxidants towards normalcy (Table 2).

Impact of exercise, consumption of fish oil, and dual combination intervention on glycogen content

The increase in insulin sensitivity in tissues, especially skeletal muscle indicates their capacity to store glucose as glycogen. The glycogen content in skeletal muscle and liver was analyzed. An increase in glycogen content in all treated groups but the DE group did not show a significant effect when compared to disease control (Table 3).

DISCUSSION

Westernized fat-rich diet with high consumption of soft drinks containing fructose), contributes to the development of metabolic complications.²⁵ The

Table 1: Effect of exercise and fish oil supplementation on insulin and insulin resistance in type-2 diabetes mellitus rats.

| Group | NC | DC | DE | DF | DFE |
|--------------------|------------|---------------|---------------|---------------|---------------|
| Insulin (IU/L) | 12.57±1.15 | 19.91±3.24*** | 15.42±2.14*** | 16.23±2.06*** | 10.56±1.61*** |
| Insulin Resistance | 3.69±0.09 | 14.93±0.1*** | 6.16±0.1*** | 9.13±0.1*** | 3.52±0.1*** |

NC: normal control; DC: diabetes control group; DE: diabetic rat with exercise group; DF: diabetic rat with fish oil supplementation; DFE: diabetic rat with exercise and fish oil supplementation. The data is reported as the mean ± SEM (n = 10). *p < 0.05 versus the NC group. **p < 0.01 and ***p < 0.001 versus the DC group.

Table 2: Impact of exercise and fish oil consumption on antioxidant activity.

| Parameters | Groups | | | | |
|--------------|-----------|--------------|----------------|-----------------|----------------------|
| | NC | DC | DE | DF | DFE |
| MDA (mmol/L) | 0.95±0.02 | 2.42±0.12*** | 2.06±0.03***.# | 2.12±0.06***.# | 1.24±0.03***.###.@@@ |
| SOD (IU/L) | 164.2±2.2 | 78.6±8.6*** | 98.4±3.4***.# | 104.6 ±1.2***.# | 128.2±4.2***.###.@@@ |
| GSH (ng/mL) | 2.02±0.22 | 0.48±0.12*** | 1.32±0.16** | 1.25±0.19** | 1.98 ±0.18###.\$.@ |

The data is reported as the mean ± SEM (n = 10). *p < 0.05, **p < 0.01, ***p < 0.001 versus the NC group. #p < 0.05, ##p < 0.01 and ###p < 0.001 versus the DC group. \$\$\$p < 0.01 and \$\$\$p < 0.001 versus the DE group, @p < 0.05 and @@p < 0.01, @@@p < 0.001 versus DF group.

Table 3. Impact of exercise and fish oil consumption on glycogen content.

| Glycogen (mg/gm) | Groups | | | | |
|------------------|-------------|----------------|--------------|---------------|----------------|
| | NC | DC | DE | DF | DFE |
| Skeletal | 9.13± 1.18 | 3.36 ± 1.24** | 4.92 ± 1.08 | 7.12 ± 1.16# | 7.86 ± 1.61# |
| Liver | 54.22± 4.66 | 28.36± 5.32*** | 38.35 ± 2.54 | 42.14 ± 3.45# | 49.12 ± 2.18## |

The data is reported as the mean ± SEM (n = 10). *p < 0.05, **p < 0.01, ***p < 0.001 versus the NC group. #p < 0.05, and ##p < 0.01 versus the DC group.

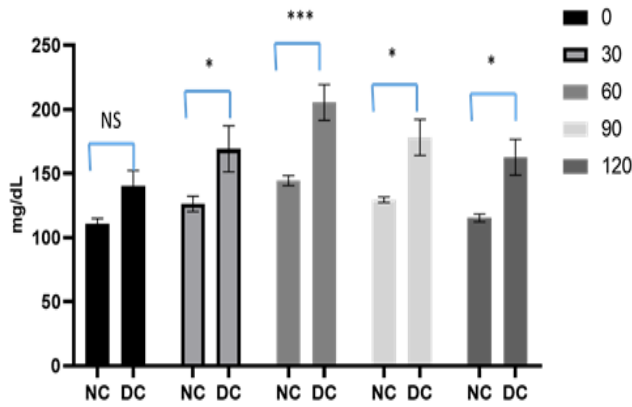


Figure 1. The GTT depicting the effect of 0.2 g/100gram ip, glucose (30%) on blood glucose levels in normal control (NC), and high-fat diet-fed diabetic rats (DC) at 0, 30, 60, 90, and 120 min after glucose administration. Values are means (\pm SEM) of six animals. Comparison with NC group * $p < 0.05$, *** $p < 0.001$ (Unpaired Student's *t*-test).

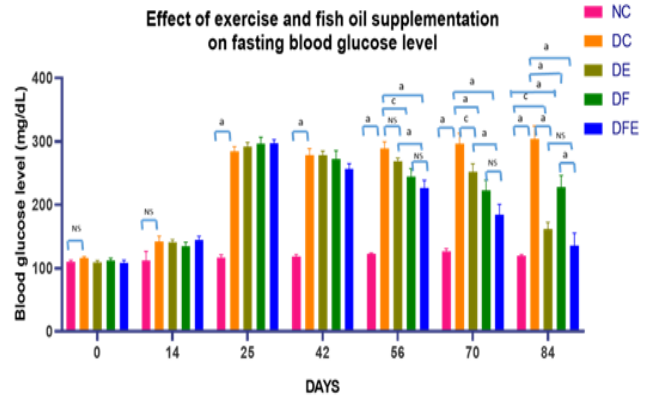


Figure 3. Fasting blood glucose levels. NC: normal control; DC: diabetes control group; DE: diabetic rat with exercise training; DF: diabetic rat with fish oil supplementation; DFE: diabetic rat with exercise training and fish oil supplementation. The values are reported as the mean \pm SEM (n = 10). cp < 0.05; * $p < 0.01$; ^a $p < 0.001$. NS = Not significant.

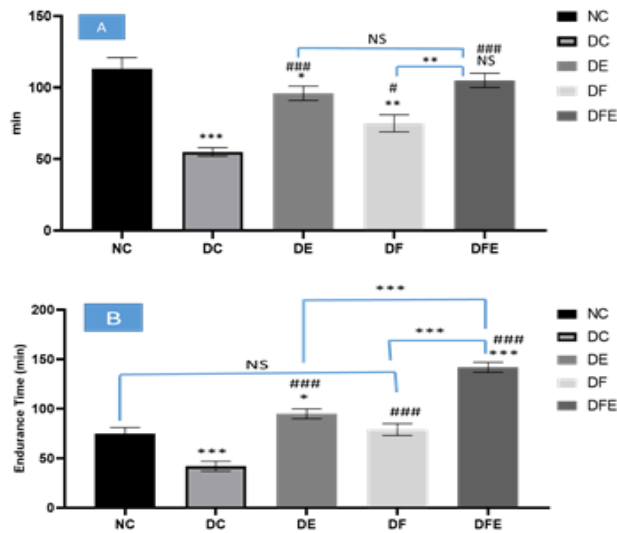


Figure 2. (A) exercise performance and (B) fatigue in diabetes mellitus rats. NC, normal control; DC, diabetes control group; DE, diabetic rats with exercise training; DE, the diabetic rat with fish oil supplementation; DFE, the diabetic rat with exercise and fish oil supplementation group. The data is reported as the mean \pm SEM (n = 6). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus the NC group. # $p < 0.05$; and ### $p < 0.001$ versus the DC group.

sedentary lifestyle plays a vital role in making the disease epidemic. Rats fed with a modified diet, i.e. both high fat and high fructose in their diet renders the rats with an increase in weight, insulin resistance, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia with a compensatory increase in insulin levels, a condition similar to insulin resistance state. Our study demonstrates that, in insulin-resistant diabetic rats, combination intervention of physical exercise and a daily dose of fish oil supplementation improves insulin sensitivity and relieves fatigue. The advantage of swimming as an exercise or diets enriched with polyphenols on

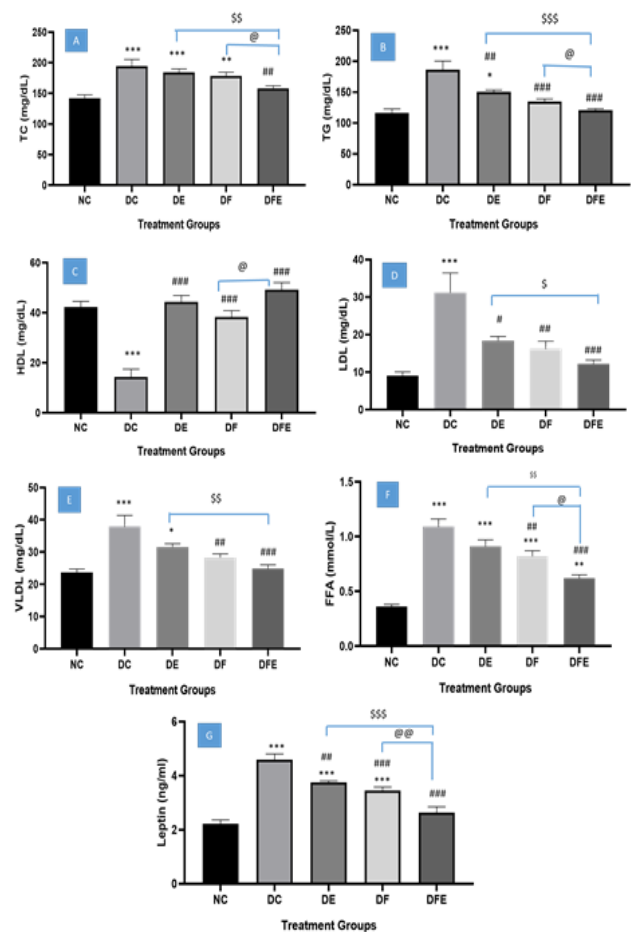


Figure 4. Impact of exercise, consumption of fish oil, and dual combination intervention on plasma A: Total Cholesterol (TC), B: Triglycerides (TG), C: High-density lipoprotein (HDL), D: Low-density lipoprotein (LDL), E: Very low-density lipoprotein (VLDL), F: Free fatty acid (FAA) and G: Leptin]. The data is reported as the mean \pm SEM (n = 10). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus the NC group. # $p < 0.05$, ## $p < 0.01$ and ### $p < 0.001$ versus the DC group. \$\$ $p < 0.01$ and \$\$\$ $p < 0.001$ versus the DE group, @ $p < 0.05$ and @@ $p < 0.01$ versus the DF group.

physiologic parameters in metabolic syndrome has been studied enormously, but none have studied the combination in rats.

In the past, the ability of polyphenol to prevent the development of diet-induced metabolic alterations was studied as a prophylactic, as the rats were treated with polyphenols before disease induction. In the present study, a combination of fish oil supplementation and swimming was used after the development of insulin resistance to understand the curative potential of fish oil and as a dual strategy for life-style modification. Nutritional supplementation of fish oil was sufficient to decrease rats' body weight gain by 6%. The incidence of diabetes mellitus reduces drastically with an even 5% decrease in body weight.^{26,27} Additionally, our study revealed the prevention of weight gain and promoting overall metabolic improvement with a dual lifestyle intervention with exercise and diet. Such prevention of weight gain is not observed in humans on either polyphenol intake or exercise.

The reduced glucose uptake and utilization (insulin resistance) can be explained by the fatty acid-glucose cycle, wherein the hyperglycemia state had occurred due to an increase in FFA.²⁸ The untreated diabetic rats (DC) showed a significant increase in free fatty acid, TC, TG, LDL, and VLDL (Figure 4) but the combination of fish oil supplementation and exercise (DFE), resulted in lower insulinemia and insulin resistance compared to the untreated rats of the diabetic group (DC), suggesting an improvement in insulin sensitivity (Table 1). The other possible mechanism in the improvement of insulin sensitivity might be due to an increase in glycogen storage in skeletal muscle. Insulin sensitivity increased in rats belonging to the DFE group because these rats had an increase in glycogen content when compared with other treated groups.

Visceral adiposity causes an increase in insulin as well as leptin levels and severe metabolic consequences.^{29,30} This demonstrates that these untreated diabetic rats had unfavorable metabolic disturbances, like intolerance in glucose during a GTT test, insulin resistance, leptin resistance, and hyperlipidemia. The synergistic effect of swimming exercise on fish oil supplementation that helped to normalize the metabolic abnormalities such as serum TC, TG, HDL, LDL, VLDL, and leptin. The probable mechanism may be blocking the synthesis of adiponectin that is directly influenced by the concentrations of free fatty acids.

The lipid profile and leptinemia were significantly reduced by the combination treatment of fish oil and exercise, thereby ameliorating the levels of FFA and insulin resistance. Past research³¹ had proven the

efficiency of adiponectin in controlling FFA, lipids, and insulin sensitivity. The ameliorating effect of the DFE group on the FFA levels was significant when compared to DE and DF groups and might have increased the insulin sensitivity due to improvement in adiponectin. Improvement in adiponectin levels improves insulin resistance.³² The increase in insulin sensitivity in the DFE group correlates with a significant (49.44%) increase in the endurance time, indicating the higher exercise capacity when fish oil was administered in addition to exercise training. The current study also demonstrated a significant decrease in FBG level on completion of therapy in the DFE group which indicates a higher peripheral utilization of glucose which correlates with an increase in endurance time. Regular intake of diet (Western diet) rich in fat (saturated) has led to a state of insulin resistance¹¹ and on the other hand diet rich in PUFA would have a positive impact on insulin resistance.¹² Feeding fish oil to rats on diet with high fat has reduced the occurrence of resistance towards insulin, especially in skeletal muscle.¹³

The DFE group also demonstrated the synergistic effect of exercise and fish oil supplementation in reducing the oxidative stress as observed from reduced MDA levels and simultaneously increased the levels of endogenous antioxidant enzymes; SOD and GSH (Table 2). The improved insulin resistance and hyperglycemic state might be the reason for this effect. Oxidative stress associated with diabetes is the leading cause of obesity that further aggravates lipid peroxidation and suppresses antioxidant activities. A high-fat diet is responsible for increasing the burden on the endogenous antioxidative system.⁷ Therefore, the impaired endogenous antioxidative system leads to insulin resistance in peripheral metabolic tissues.⁸ *In vivo* studies have demonstrated the effect of fish oil as a free radical scavenger.³³ and Chautan *et al.*,³⁴ demonstrated stimulation of vitamin E incorporation into membranes modulated by Omega 3 fatty acid and thus prevention of lipid peroxidation. Regular controlled exercise maintains a balance between inflammatory and pro-inflammatory cytokines, lowers the leptin levels, and oxidative stress.³⁵ The etiology behind the tiredness and fatigue symptoms in diabetes patients is still not very clear. Associated obesity and insulin resistance are the responsible factors for fatigue^{36,37} and as observed from the swimming exercise test, the dual intervention of physical training and dietary modification with fish oil could overcome the fatigue as observed from in DFE group (Figure 2A and B).

A decrease in glycogen content of untreated diabetic rats were noted (Table 3). DE group showed a tendency

toward an insignificant increase in glycogen content and significantly raised in DF and DFE groups. Loss of weight was seen in untreated diabetic rats and not in treated groups because these groups have increased the glycogen content in both the tissues and the same would have been utilized for energy expenditure instead of storage, which in turn prevented the loss of weight.

CONCLUSION

Dietary supplementation of fish oil has could repair the abnormal free radical-induced oxidative changes and reduced lipid peroxidation. Therefore, fatty acids like EPA and DHA are effective ingredients for food functionalization for added therapeutic benefits. Food fortification and dietary supplementation in controlling the disease-induced damage caused by chronic diseases like diabetes resulting from the imbalance between oxidant/antioxidant defense mechanisms would play a significant role. Decreased glycogen content in liver and skeletal tissue in diabetes leading to fatigue was significantly altered when the lifestyle was modified with diet as well as exercise. Moderate physical training along with healthy dietary modifications could reverse the metabolic damage and enhance exercise endurance capacity thus facilitating early recovery from fatigue. Therefore, a combination of moderate physical exercise and incorporation of any source of omega 3 fatty acids like fish oil in the diet would be a new, effective, and powerful treatment modality for the management of chronic diabetic complications.

Author Contributions

Conceptualization, A.H.A, P.K.N, U.C and R.S.T ; Data curation, A.H.A, P.K.N, G.M.B, N.S and U.C; Formal analysis, G.M.B; Funding acquisition, A.H.A, G.M.B, N.S and R.S.T ; Investigation, A.H.A, P.K.N, G.M.B, N.S, U.C and R.S.T ; Methodology, A.H.A, P.K.N, G.M.B, N.S, U.C and R.S.T ; Project administration, A.H.A, P.K.N, G.M.B, N.S and U.C; Resources, A.H.A, P.K.N, N.S, U.C and R.S.T ; Software, P.K.N and U.C; Supervision, G.M.B, N.S and R.S.T ; Validation, A.H.A, P.K.N, G.M.B, N.S, U.C and R.S.T ; Writing – original draft, A.H.A, P.K.N, G.M.B, N.S, U.C and R.S.T ; Writing – review & editing, A.H.A, P.K.N and N.S.

Funding

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number IFT20115.

ACKNOWLEDGEMENT

The authors thank the Deanship of Scientific Research, King Faisal University, Al-Ahsa, Saudi Arabia for their support.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

GTT: Glucose Tolerance Test; **GOD-POD:** Glucose Oxidase Peroxidase; **DC group:** Type 2 Diabetic Control; **DFE:** Oral Dose Of Fish Oil And Exercise Training; **FBG:** Fasting Blood Glucose; **TC:** Total Cholesterol; **TG:** Triglyceride; **TBARS:** Thiobarbituric Acid Reactive Substances; **SOD:** Superoxide Dismutase; **TBA:** Thiobarbituric Acid.

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PICTORIAL ABSTRACT



SUMMARY

Dietary intervention and physical exercise are necessary to reduce the incidences of insulin resistance Diabetes being a chronic disease requires long-term treatment and therefore, administration of fish oil by oral route will be convenient for the patient.

About Authors



Dr. Afzal completed M.B.B.S. from Nishtar Medical University, Multan, in 1984 and M.Phil. from Postgraduate Medical Institute, University of Punjab, Lahore, Pakistan in Pharmacology in 1995. He is deeply involved in teaching, training, curriculum development and quality management in College of Clinical Pharmacy, King Faisal University, Saudi Arabia since 2005. His area of interest in research is nephrotoxicity of drugs and its protection and internal medicine. He is also working on antidiabetic activity of indigenous plants. He is member of research group working on development of novel pharmaceutical formulations of various drugs. He has about 40 publications on his credit.

Cite this article: Asif AH, Nanjundan PK, Basavarajappa GM, Sreeharsha N, Chandur U, Roopashree TS. Insulin Resistance Modulation with Lifestyle Modification- Proof-of-Concept Study in Rats. *Indian J of Pharmaceutical Education and Research*. 2020;54(4):999-1006.