ROLE OF CELL MEMBRANE FATTY ACIDS IN INSULIN SENSITIVITY IN DIABETIC RATS TREATED WITH FLAXSEED OIL

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ABSTRACT

Introduction: The cell functions involved in the action of insulin receptor binding enzyme and transporter activities are controlled by membrane properties, and the amount of dietary fat as well as the nature of fatty acids regulates various steps in the biosynthesis of membrane phospholipids.

Objective: To investigate the effect of flaxseed oil on improving erythrocyte membrane components and insulin sensitivity in diabetic rats.

Methods: Thirty two adult male albino rats were used in this study and classified into four groups control, flaxseed oil, diabetic and treated groups. Fasting blood glucose and plasma insulin were estimated. Total lipids in the red blood cells membrane were extracted with chloroform/methanol method. Erythrocyte membrane total lipids, total cholesterol and triglycerides were determined. Fatty acids and phospholipids fractions were measured by HPLC.

Results: Flaxseed oil administration effectively improved cell membrane components.

Conclusion: Flaxseed oil has an important role in enhancing insulin sensitivity and decreasing blood glucose in diabetic rats.

Keywords: Cell membrane, Diabetes, insulin, Fatty acids, Flaxseed oil

INTRODUCTION

Diabetes mellitus is a complex of metabolic disease characterized by hyperglycemia , diminished insulin production, impaired insulin action , or a combination of both resulting in the inability of glucose to be transported from the blood stream into the tissues, which in turn results in high blood glucose levels and excretion of glucose in the urine [1].

In diabetes mellitus, the high incidence of microvascular and atherosclerotic disorders has been associated with abnormalities of erythrocyte composition and rheological function [2].

The cell functions involved in the action of insulin receptor binding enzyme and transporter activities are controlled by membrane properties [3].

Fatty acids (FA) composition of membrane phospholipids such as sphingomyelin (SM), phosphatidylethanolamine (PE) and phosphatidylcholine (PC) are tissue specific but are affected by the composition of the dietary fat [4]. Changes in the fatty acids composition of erythrocyte, which are easily accessible cells, reflect changes in that of membrane phospholipids of less accessible tissues [5].

The fatty acids composition of cell membranes can influence membrane associated phenomena such as the interaction between insulin and its receptors [6].

It was found that, fatty acids composition of the membrane phospholipids of insulin target tissues, such as liver and skeletal muscle, is a critical factor that influences both insulin secretion and its biological actions [7], thus membranes enriched in unsaturated fatty acids tend to bind more insulin than membranes enriched in saturated fatty acids [8].

Since natural products have played an important role throughout the world in treating and preventing human diseases [9] and flaxseed is the best plant that contain high amount of polyunsaturated fatty acids especially omega-3 [10], thus, this study aimed to investigate the effect of flaxseed oil on improving erythrocyte membrane components and insulin sensitivity in diabetic rats.

MATERIALS AND METHODS

Materials

Streptozotosin (STZ) was purchased from Sigma Chemicals Co. (Munih,Germany).

α–linolenic acid (ALA), arachidonic acid (AA), linoleic acid (LA) and oleic acid (OA) standards (HPLC grade) were purchased from Sigma Chemicals Co. (Munih,Germany).

Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and sphingomyelin (SM) from bovine sources as phospholipids standards for HPLC analysis were purchased from Sigma Chemicals Co. (Munih,Germany).

Experimental Animals

Thirty two adult male albino rats weighing (180-200 g) were used in this study. The animals were obtained from the animal house of the National Research Center (Cairo, Egypt). They were housed in stainless steel cages under environmentally controlled conditions. The ambient temperature was 25 ± 2 °C and the light/dark cycle was 12/12 hours. The animals had free access to water and standard rodent chow diet (NRC rodent chow). All animals received human care in compliance with guidelines of the Ethical Committee of National Research Centre, Egypt and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Methods

Induction of diabetes mellitus

Streptozotocin (STZ) was dissolved in 50 mM sodium citrate (PH 4.5) solution containing 150 mM NaCl. The solution (6.0 mg/0.5 ml/100g body weight) was subcutaneously administrated into rats; fasting blood sugar was estimated after 3 days to confirm the development of diabetes mellitus [11].

Experimental design

Thirty two male albino rats were used in this study and divided into the following groups:

Group I (control group): healthy rats received 1.2 ml corn oil / kg b.w. / day orally.

Group II (flaxseed oil group): healthy rats received 1.2 ml flaxseed oil / kg b.w. / day orally.

Group III (diabetic group): diabetic rats received 1.2 ml corn oil / kg b.w. / day orally.

Group IV (treated group): diabetic rats received 1.2 ml flaxseed oil / kg b.w. / day orally [12].

After the experimental period (8 weeks), animals were kept fasting for 12 hours before blood sampling, blood was withdrawn from the retro-orbital venous plexus of the eye using capillary tubes and collected in:

a- Tubes contain sodium floride for blood glucose.

b-Heparinized tubes for other biochemical parameters.

Blood was centrifuged at 2000 rpm for 10 minutes using cooling centrifuge. Plasma was separated and immediately frozen. Packed RBCs were used for isolation and extraction of erythrocyte membrane lipids.

The following parameters were estimated:

Blood glucose and plasma insulin

Fasting blood sugar was determined using enzymatic colorimetric method. Centronic, Germany, according to Trinder (1969) [13].

Plasma insulin level was estimated by ELISA according to Yalow and Bauman (1983) [14]. Using BioSoure INS-EASIA Kit.

Insulin resistance was calculated from the equation:

Insulin resistance = fasting glucose (mg dl–1) X fasting insulin (μIU ml–1)/405 According to Matheus et al. (1985) [15].

Erythrocyte membrane lipids

Total lipids in the red blood cells membrane were extracted with Chloroform: methanol method [16], modified from the method described by Bligh and Dyer (1959) [17].

Erythrocyte membrane total lipids were determined [18], using FAR (Italy) Kit. Membrane total cholesterol and triglycerides were estimated according to the previous methods [19, 20] respectively using enzymatic colorimetric method Centronic, Germany kit. Erythrocyte membrane phospholipids levels were estimated colorimetrically according to the method described before [21].

Analysis of cell membrane fatty acids by HPLC

Cell membrane was homogenized in 2 % acetic acid- ethyl ether mixture (2:1 volume ratio). The solution was then filtered and centrifuged at 500 xg, the organic phase was evaporated to dryness. The extract was dissolved in 200 ul acetonitrile [22].

HPLC Condition

This method was carried out after modification of the method described previously [23]. HPLC column C 18 (260 X 4.6 , particle size 5 μl) , mobile phase was acetonitrile / water mixture (70/30) v/v by isocratic elution with flow rate 1 ml / min and 200 nm wave length. Serial dilutions of standards were injected and their peak areas were determined. A linear standard curve was constructed by plotting peak areas versus the corresponding concentrations. The concentration in samples was obtained from the curve.

Estimation of phospholipids fractions by HPLC

Fractionation of phospholipids was carried out using high performance liquid chromatography (HPLC) system, Agilent technologies 1100 series, equipped with a quaternary pump (Quat pump, G131A model). Separation was achieved on a stainless steel phenomenx bond with 300x 390x mm silica analysis column (with 10 μm spherical particles). The mobile phase was acetonitrile–methanol-85%phosphoric acid (1000:40:0.4) v/v, degassed in an ultrasonic bath. It was delivered to the column at flow rate of 1.5 ml/min at room temperature (25ºc). Photodiode array UV-visible detector was used and set at 203 nm. The sample was dissolved in 2ml (n-hexane -2 propanol) (3:1) v/v. 20 μl of the standard and each sample was injected and the phospholipids area resulted in a graph [24].

Statistical analysis

Results were expressed as mean ± standard error. Data were analyzed by independent sample t test (SPSS) version 15 followed by (LSD) test to compare significance between groups. Difference was considered significant when P value <0.05.

RESULTS

In this study, fasting blood glucose and insulin resistance were elevated in diabetic group compared to control, while this value decreased by flaxseed oil administration in treated group (Table1).

Erythrocyte membrane total lipids were significantly increased in diabetic group, although they decreased in flaxseed oil treated group as compared to diabetic group that may be due to the concomitant decrease in membrane cholesterol , triglycerides and phospholipids (table:2).

Phospholipids fractions (PE, PC and SM) were significantly increased in diabetic group compared to control group and decreased by flaxseed oil administration in treated group, while the mean value of PS was not changed during the experimental period (Table3).

In this study, flaxseed oil significantly increased the mean value of membrane α-Linolenic acid in flaxseed oil treated group compared to the diabetic group while it significantly decreased the mean value levels of Arachidonic acid, Linoleic acid and Oleic acid indicating the role of flaxseed oil in improving the membrane fatty acids components (Table 4).

Table 1: Blood glucose, insulin and insulin resistance levels in different studied groups

Groups	Glucose (mg/dl)	Insulin (μIU/ml)	Insulin resistance (mgdl⁻¹ μIU ml ¹)
Control Mean ± SE	79.87 ± 4.1	11.1 ± 0.9	2.19 ± 0.1
Flaxseed Mean ± SE	79.62 ± 2.7 *	11.5 ± 1.6	2.26 ± 0.1*
Diabetic Mean ± SE	243.87 ± 9.3 ♦	8.8 ± 1.0	5.30 ± 0.2♦
Treated Mean ± SE	177.50 ± 5.1 ♦,*	10.3 ± 2.0	3.63 ± 0.1♦,*

Significant *p* value < 0.05

♦ = significant difference compared to control group

* = significant difference compared to diabetic group

Number of cases = 8

Table 2: Membrane lipid profile in different studied groups.

Groups	Total Lipids (mg/mlRBCs)	Cholesterol (mg/ml RBC's)	Triglycerides (mg/ml RBC's)	Total Phospholipids (mg/ mlRBCs)
Control Mean ± SE	4.6 ± 0.1	1.9 ± 0.1	0.23 ± 0.02	0.74± 0.1
Flaxseed Mean ± SE	4.4 ± 0.1*	1.7 ± 0.3*	0.18 ± 0.01 *	0.63 ± 0.2 ♦,*
Diabetic Mean ± SE	6.9 ± 0.1♦	2.9 ± 0.1♦	0.31 ± 0.02 ♦	0.80 ± 0.006 ♦
Treated Mean ± SE	5.2 ± 0.2♦,*	2.3 ± 0.2 *	0.24 ± 0.02 *	0.71 ± 0.007 *

Significant *p* value < 0.05

♦ = significant difference compared to control group

* = significant difference compared to diabetic group

Number of cases = 8

Table 3: Phospholipids fractions in different studied groups.

Groups	PS (µg/ ml RBCs)	PE (µg/ ml RBCs)	PC (µg/ ml RBCs)	SM(µg/ ml RBCs)
Control mean ± SE	8.15± 0.08	84.2 ± 0.5	133.9 ± 0.9	82.3 ± 0.4
Flaxseed mean ± SE	8.48 ± 0.18	81.2 ± 0.6 ♦,*	129.7 ± 3.8 *	79.2 ± 0.5♦,*
Diabetic mean ± SE	8.31 ± 0.12	94.9 ± 0.7♦	140.6 ± 0.5 ♦	95.9 ± 0.8♦
TreatedMean ± SE	8.30 ± 0.96	85.3 ± 0.8♦,*	138.1 ± 0.8	85.2 ± 0.6♦,*

Significant *p* value < 0.05

♦ = significant difference compared to control group

* = significant difference compared to diabetic group

Number of cases = 8

Table 4: Fatty acids in different studied groups.

Groups	α- Linolenic acid (mg/ml RBCs)	Arachidonic acid (mg/ml RBCs)	Linoleic acid (mg/ml RBCs)	Oleic acid (mg/ml RBCs)
Control mean ± SE	0.77± 0.01	0.04 ± 0.007	0.61 ± 0.04	0.14 ± 0.008
Flaseed mean ± SE	0.82 ± 0.2♦,*	0.02 ± 0.002 ♦,*	0.23 ± 0.006 [a],*	0.06 ± 0.004♦,*
Diabetic mean ± SE	0.34 ± 0.1 ♦	0.09 ± 0.005♦	0.79 ± 0.04 [a]	0.18 ± 0.007♦
TreatedMean ± SE	0.77 ± 0.4 *	0.06 ± 0.004 ♦,*	0.34 ± 0.009 ♦,*	0.12± 0.008 *

Significant *p* value < 0.05

♦ = significant difference compared to control group

* = significant difference compared to diabetic group

Number of cases = 8

In the current study, there was a positive correlation between insulin resistance and PE,PC and SM. Also there was a positive correlation between insulin resistance and Arachidonic acid, Linoleic acid and Oleic acid concomitant with a negative correlation between insulin resistance and α-Linolenic acid (Figures 1-8).
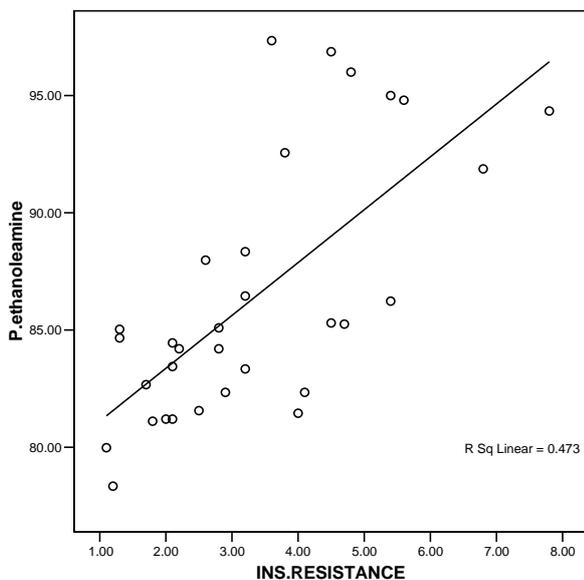

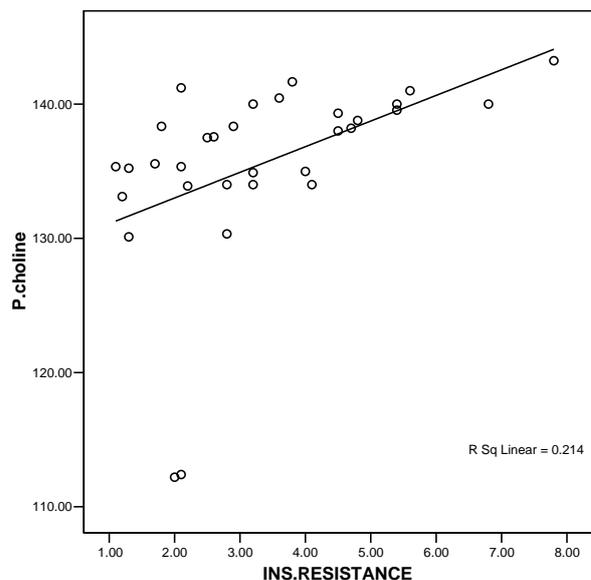Fig. 1: Correlation between insulin resistance and PE.

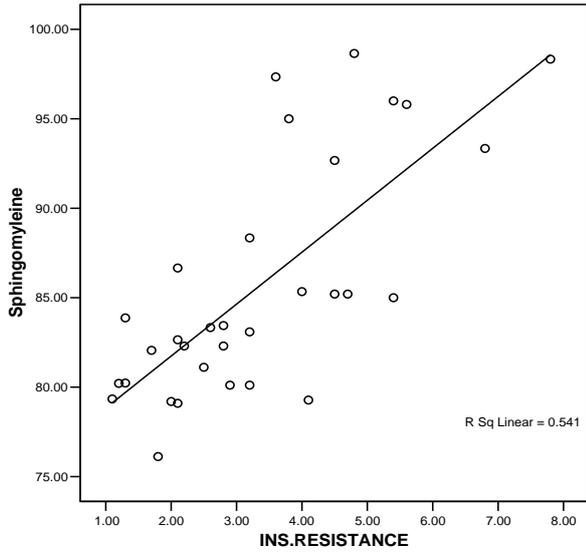Fig. 2: Correlation between insulin resistance and PC.

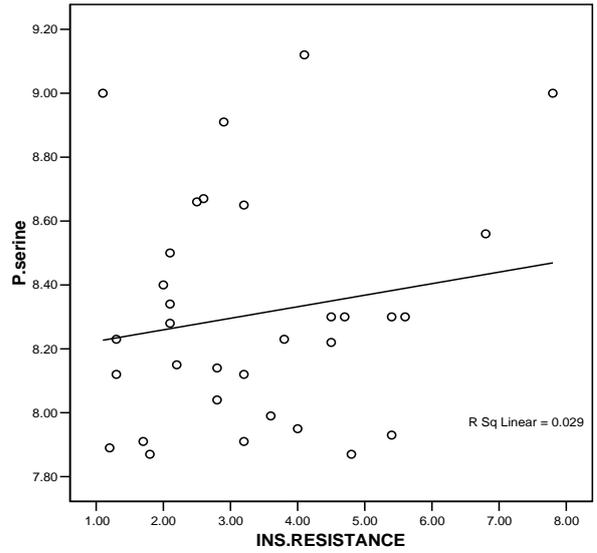**Fig. 3: Correlation between insulin resistance and SM.**
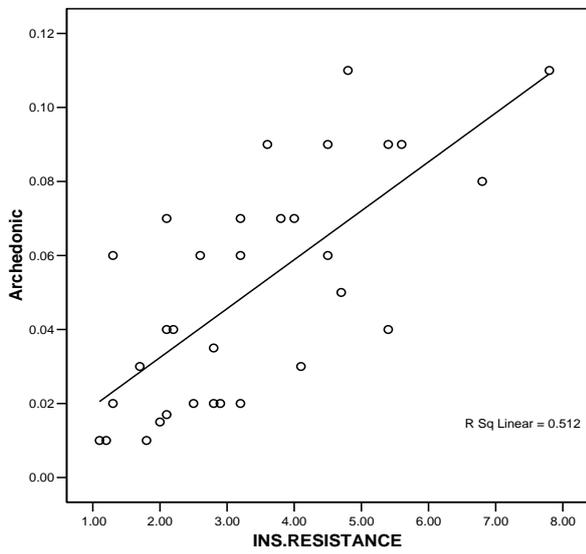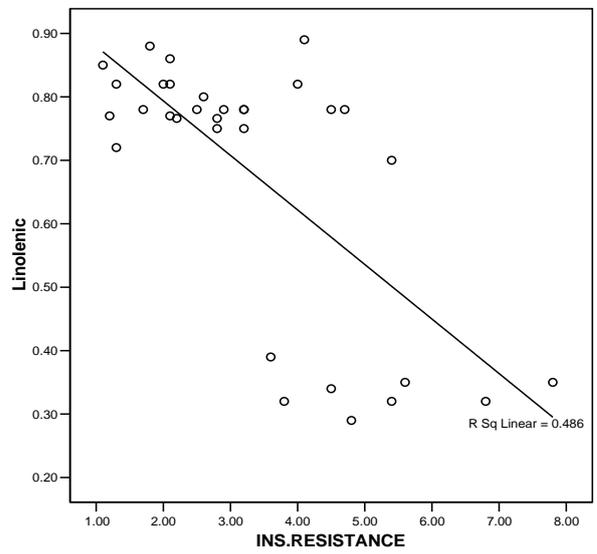

Fig. 4: Correlation between insulin resistance and PS.

Fig. 5: Correlation between insulin resistance and AA.

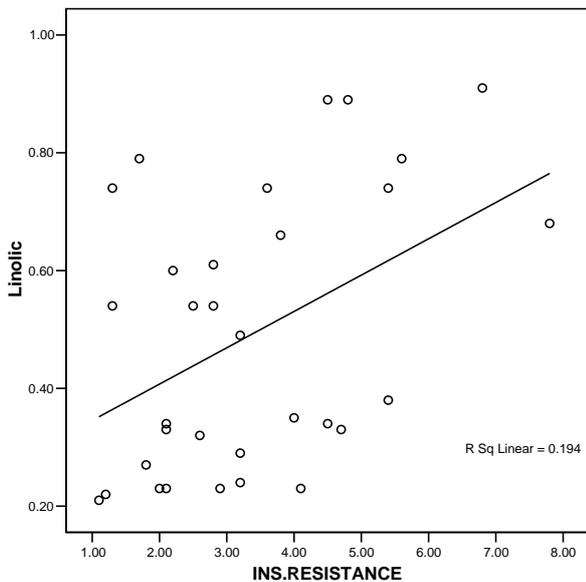**Fig. 6: Correlation between insulin resistance and α-LA.**

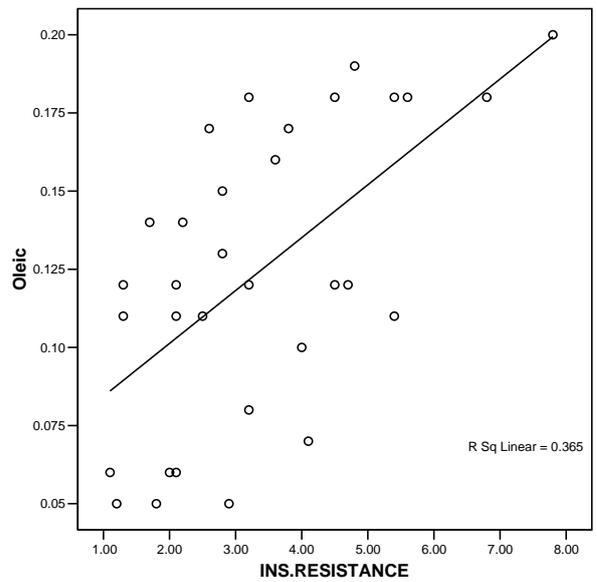**Fig. 7: Correlation between insulin resistance and LA.**

Fig. 8: Correlation between insulin resistance and OA.

DISCUSSION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both [25]. It has been suggested that insulin resistance is associated with alterations in cell membrane properties [26, 27]. Some studies have demonstrated relationships between the fatty acid composition of phospholipids in skeletal muscle and the action of insulin [28, 29].

In the current study, the mean value levels of erythrocyte membrane total cholesterol, triglycerides and phospholipids were increased in diabetic group and decreased again by flaxseed oil administration. These results were in agreement with Hussein et al. (2011*)* [24] who found a positive correlation between blood glucose and membrane cholesterol & triglycerides in diabetic rats treated with omega-3.

It was suggested that, enrichment of cholesterol in the membrane lowers the passive permeability of solutes and depletion of cholesterol enhances glucose permeability. This indicates that reduced glucose permeability of diabetic erythrocytes is due to enhanced cholesterol content in their membranes and thus the diabetic cells might have starved from glucose [30]. In addition, TG might influence the binding of insulin to its receptor or interfere with early post binding steps [31], higher serum triglycerides leads to a resistance to the antilipolytic effect of insulin, therefore, a reduction in serum TG levels might improve insulin sensitivity [32].

In our study, we observed some changes in membrane fatty acids in flaxseed oil group which reflect the composition of flaxseed oil, while in diabetic group the change in AA content was more significant than changes in the other fatty acids. Two clinical investigations reported a significant increase in plasma and tissue AA concentrations in patients compared with controls [33, 34] which could be the result of enhanced lipid peroxidation in disease [35]. Alternatively, the increased AA levels could be due to elevated desaturase activity on LA leading to increased formation of prostaglandins and other lipoxygenase products [36] .These values of fatty acids were regulated in our experiment by flaxseed oil administration probably due to its high content of omega-3.

In the current investigation, phospholipids fractions increased in diabetic group while decreased by flaxseed oil administration except PS was not changed during the experimental period.

Positive correlation was observed between insulin resistance and phospholipids fractions (PE, PC and SM) in this study which confirmed the finding of Zeghari et al. (2000) [3].

There may be several links between an increase in membrane SM content and impaired insulin action. Studies in artificial membranes support this assumption [37, 38]. Enrichment in SM inhibits the tyrosine kinase activity in rat liver plasma membranes [39], decreases the phosphatidylinositol phosphodiesterase activity activated by diacylglycerol [40] and glucose transport in phospholipid vesicles [38]. These effects of SM are probably due in part to the ability of this phospholipid to stabilize a bilayer structure and to increase membrane rigidity.

Membrane PE content is also strongly correlated with markers of insulin resistance and may be an important regulator of insulin action. A high membrane PE content leads to an increase in the head group spacing of phospholipids in lipid bilayers of defined composition is closely correlated with decreased protein kinase C activity, a key enzyme in insulin action. Moreover, PE could affect the activity of the hormone-sensitive lipase (HSL). Phosphatidylcholine (PC) content is also correlated with the insulin resistance but the possible links between PC and insulin are not clear [3].

Finally, factors such as the diet must also be taken into consideration. It has been suggested that the amount of dietary fat as well as the nature of fatty acids regulate various steps in the biosynthesis of membrane phospholipids. Total PL, PC, PE and SM in rats fed a diet high in saturated fat were 1.7, 1.5, 2 and 5-fold respectively higher than in rats fed on an unsaturated, high fat diet [3].

We concluded that diet with high content of polyunsaturated fatty acids such as flaxseed oil is very effective in improving cell membrane lipid structure especially fatty acids and phospholipids which have an important role in enhancing insulin sensitivity and decreasing blood glucose in diabetic rats.

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