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Effect of Phosphatidylcholine on Dyslipidemia and Atherogenic Index in High Fructose Exposed Rats

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A B S T R A C T

The purpose of this research was to investigate the beneficial effects of phosphatidylcholine in reducing changes in both lipid and protein profiles in addition to atherogenic index in adult rats with fructose-induced metabolic syndrome. Thirty-six mature Wistar Albino female rats (*Rattus norvegicus*) (aged 12-15 weeks and weighing 200±10 g) were divided randomly into four groups (G1, G2, G3, and G4); then variable treatments were orally administered for 62 days as follows: G1 (Control group), received distilled water; G2, treated with phosphatidylcholine (PC) orally (1 g/kg BW); G3 (Fr), orally dosed with 40% fructose and 25% fructose mixed with drinking water; G4 (Fr+PC), were also intubated with 40% fructose and 25% fructose in drinking water, and received PC at 1 g/kg BW by oral tube. At the end of the research, specimens were taken by cardio puncture approach after fasting for 8-12 h. Serum was obtained to measure lipid criteria (total serum cholesterol, triacylglycerol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, non-high-density lipoprotein-cholesterol, and Atherogenic index) and protein profile (total protein, albumin, and globulins). The results showed that the occurrence of dyslipidaemia (hypercholesterolemia, triacyleglycerolemia) increase in low density of lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, no-high density lipoprotein-cholesterol concentrations and atherogenic index and reduce the concentration of high-density lipoprotein-cholesterol) in fructose treated animals in addition to disturbance in protein profile (lowered in total protein and globulins level).PC treatment resulted in decreased changes in lipid profile, protein profile, and atherogenic index in rats, whereas fructose induced metabolic syndrome. In conclusion, using Phosphatidylcholine treatment in rats may reduce the changes of lipid and protein profiles and atherogenic index while fructose may lead to metabolic syndrome.

Keywords: lipid profile, phosphatidylcholine, hypercholesterolemia, total protein, non-HDL-c, LDL

INTRODUCTION

There seems to be a worldwide rise in the demand for unsafe high-calorie diets, as well as big differences in meal nutrient composition, such as higher consumption of processed carbs, leading to speculation that influence on food lifestyles has contributed to the contemporary obesity and type 2 diabetes epidemic, with an elevated danger of developing cardiometabolic syndrome (CMS) and cardiovascular disease (CVD) independent on caloric intake (1, 2). A fundamental sugar called fructose is present in fruits, plants, and honey. Due to its high relative saccharinity, low cost, palatability, and taste enhancement, it is utilized commercially in foods and beverages (3). The main constituent of fructose is the disaccharide sucrose. Fructose is also available as a free monosaccharide in high-fructose corn syrup (typically composed of 55% fructose

and 45% glucose) that would be used for flavoring soft drinks and a variety of other meals. Honey and fruits (for example, apples) have free fructose, glucose, and sucrose (4).

Sugar is generally termed as a toxic substance that considerably leads to non-communicable diseases, getting oxidative stress, and metabolic effects of fructose and its metabolites (5). Long fructose consumption may result in an overload of endogenous antioxidants, producing a redox shift by boosting ROS production and resulting in oxidative stress (6, 7). After months of fructose intake in normal rats, oxidative stress is thought to be caused by an imbalance between the generation of free radicals and antioxidant efficiency (8). Overweight, non-alcoholic drinks, liver cirrhosis disease, type 2 diabetes, renal dysfunction, and heart disease have all been associated with a high dietary fructose intake in epidemiologic research (9,10). Moreover, comparable illnesses may happen as a result of excessive use of table sugar and corn syrup, both of which contain significant levels of fructose (11). The hepatic appears to be a key organ in the evolution of metabolic disorders linked to fructose-rich meals (12,13). Insulin resistance, inflammation, hepatic stress, ATP depletion (14, 15), DNL (triglyceride and fatty acid production) non-alcoholic fatty liver (NAFLD) (16, 17) are the main detrimental effects of fructose on the hepatic and enterprise-level (18). The metabolic syndrome (MetS) produced by a high fructose diet is linked to increased intestinal permeability (19), bacterial endotoxin transfer (20), and alterations in intestinal bacterial composition (21), all of which led to endotoxemia (22). Fructose is metabolized in various brain regions, including the cerebellum, hippocampus, cortex, and olfactory bulb, all of which express Glucose transporters (GLUTs) and all the fructolysis enzymes (23), resulting in a central inflammatory response. Through the inflammatory process, fructose consumption also causes psychological stress (24). In MetS, there is an intracellular inflammatory response in the brain, notably in the hypothalamus (25). Phospholipids are polar, ionic molecules made of alcohol linked to either diacylglycerol (DAG) or sphingosine via a phosphodiester linkage. Phospholipids, like fatty acids, are amphipathic in nature (4). Phosphatidylcholine (PC) seems to be the most common phospholipid in mammalian cells (26). It is usually available from soybeans, egg yolk, milk, marine sources, organ and lean meat, rapeseed, cottonseed, and sunflower oil. PC is the primary component of Polyene PC and is an essential component of cytomembrane and organelle membranes. In previous decades, PC was used to protect the health, with its functions of nourishing the brain, beautifying the features, lowering weight, and scavenging blood vessels and it was even regarded as the third nutrient after protein and vitamin D (27). Previous research (28, 29, 30) referred to oral lecithin intake at a dose of 1-3 g/day may utilize to portray its effects for hyperlipidemia, and cardiovascular diseases; and oral bioavailability of phospholipids was shown to be relatively safe (31). This research sought to see whether PC has a positive impact on mature rats with fructose-induced metabolic syndrome by decreasing abnormalities in their lipid profiles, protein characteristics, and atherogenic index.

MATERIALS AND METHODS

Ethics and Animals

All procedures used in this study were reviewed and approved by The Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq, and the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq in compliance with the ethical principles of animal welfare.

Thirty-six (36) female Albino Wister rats (Rattus norvegicus) (aged 12-15 weeks and weighing 200±10 g). They were selected after two weeks of acclimation in the animal house of the College of Veterinary Medicine, University of Baghdad, during the experimental phase (62 days). Experimental animals were housed in a well-ventilated room in plastic cages, and they were free access to food and water during the experimental period. Room temperature was kept at 22±2 °C and 12-h Light/Dark cycle along the period of acclimatization and experiment.

Study Design, Sampling, and Laboratory Tests

Animals were given the following treatments on a daily basis for a total of 62 days: G1 (control group): rats in this group were given distilled water; G2 (PC): rats were given 1 g/kg BW of PC orally, animals in group G3 (Fr): were given 40% fructose through the oral tube and 25% fructose in drinking water, rats in group G4 (Fr+PC): were given 40% fructose via oral tube and 25% fructose in drinking water in addition to 1 g/kg BW of PC by oral tube.

After fasting the rats for 8-12 h, blood samples were taken by heart puncture method from rats after sedated with intramuscular injections of ketamine-HCl 90 mg/kg BW and xylazine 40 mg/kg BW (Switzerland); Serum was extracted by centrifugation at 3000 rpm for 15 min and stored in deep freezer for later examination of the following parameters.

Determination of lipid profile (total serum cholesterol (TC), triacylglycerol (TG), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), very low-density lipoprotein-cholesterol (VLDL-c), non-high-density lipoprotein-cholesterol (non-HDL-c) was performed using a commercially available kit (BioSystems Chemical, Spine). Atherogenic index was calculated mathematically as TG/HDL-c). Determination of protein profile, total protein (TP), albumin (AL) was performed using a commercially available kit (Linear Chemical, Spine). Globulins was calculated mathematically as Globulin

concentration = serum total protein concentration - serum albumin concentration) (32).

Statistical Analysis

Data were analyzed using SAS (Statistical Analysis System, version 9.1). One-way-ANOVA was considered with Least Significant Differences (LSD) in addition to post hoc test were used to investigate significant differences among means at $P \leq 0.05$ (33).

RESULTS

Effect of PC, Fructose and/or their Combination on Serum Lipid Profile

PC-treated groups (PC and Fr+PC) showed a significant ($P<0.05$) reduction in total cholesterol, triglycerides, VLDL-c, LDL-c, non-HDL-c, and atherogenic index when compared to control. There was a significance ($P<0.05$) increase in total cholesterol, triglycerides, VLDL-c, LDL-c, non-HDL-c and Atherogenic index in fructose-treated groups (Fr) when compared to other groups (Figures 1-6). Besides, a significant ($P<0.05$) decrease in serum HDL-c concentration was observed in fructose treated group (Fr) when compared to other groups (Figure 7). However, oral intubation of PC, concurrently with fructose (G4 or PC+Fr treated groups) caused alleviation of dyslipidemia induced by fructose (correlation of lipid profile and lowering atherogenic index) compared to G3 group.

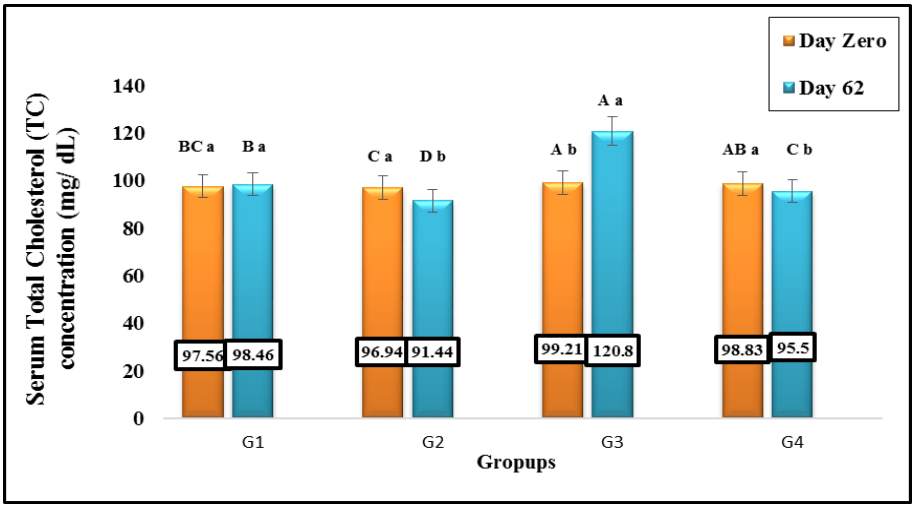

Figure 1. Effect of phosphatidylcholine, fructose and/or combination on serum total cholesterol concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

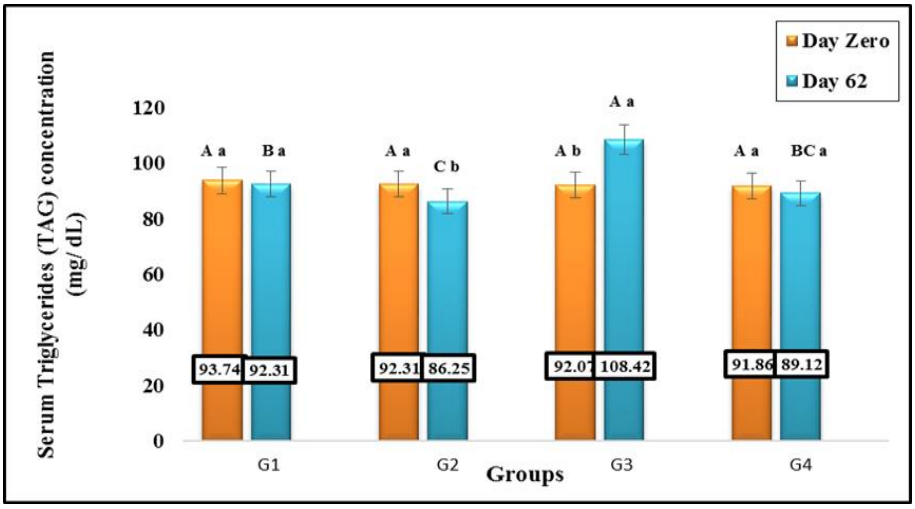

Figure 2. Effect of phosphatidylcholine, fructose and/or combination on triglycerides concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

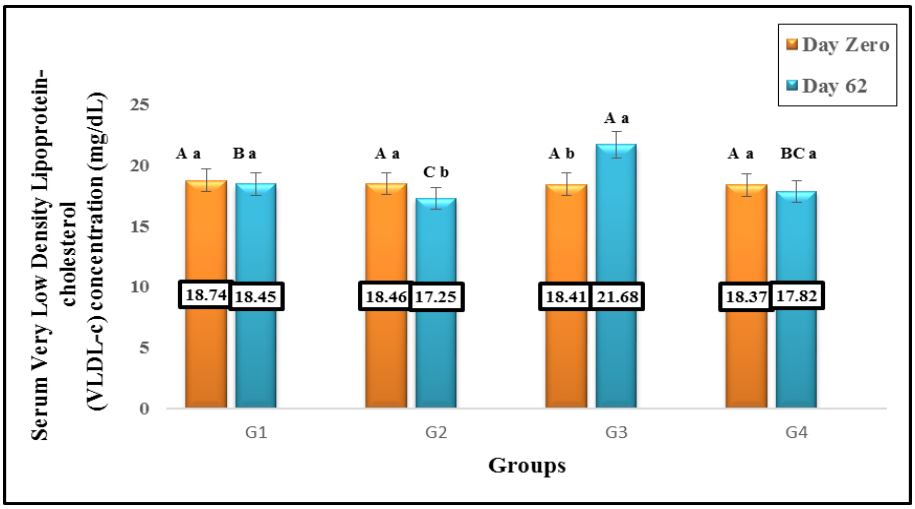

Figure 3. Effect of phosphatidylcholine, fructose and/or combination on serum very low density lipoprotein-cholesterol (VLDL-c) concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

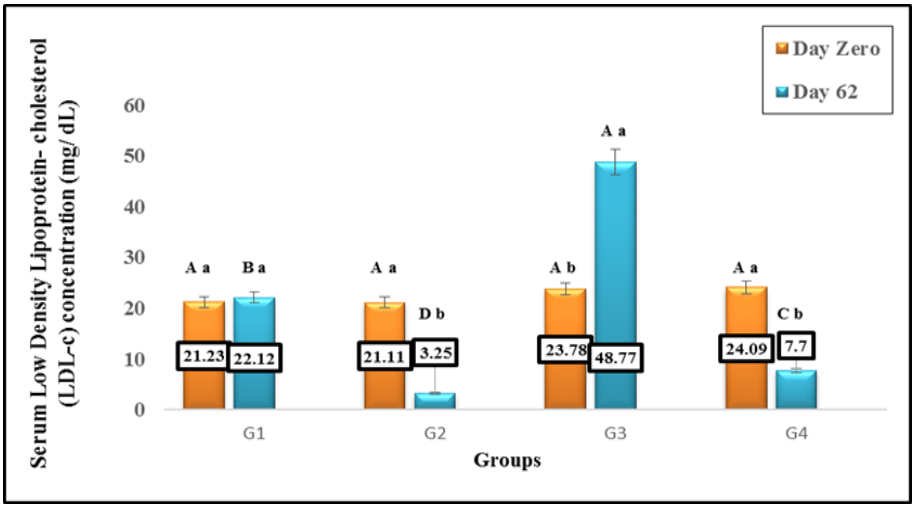

Figure 4. Effect of phosphatidylcholine, fructose and/or combination on serum low density lipoprotein-cholesterol (LDL-c) concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

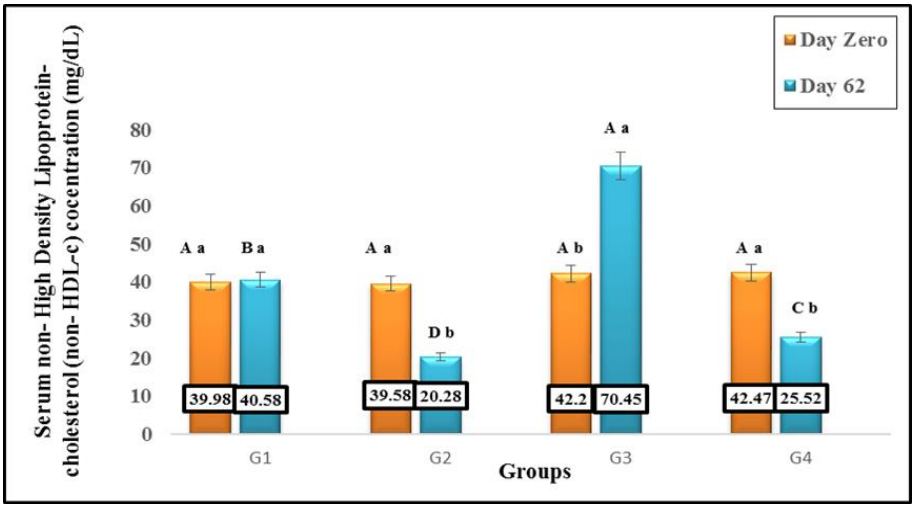

Figure 5. Effect of phosphatidylcholine, fructose and/or combination on serum non-high density lipoprotein-cholesterol (non-HDL-c) concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

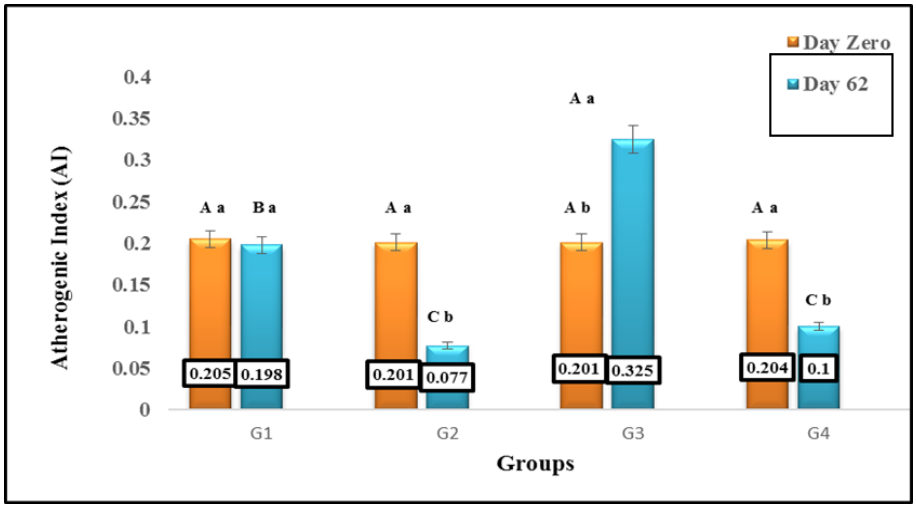

Figure 6. Effect of phosphatidylcholine, fructose and/or combination on Atherogenic Index. Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

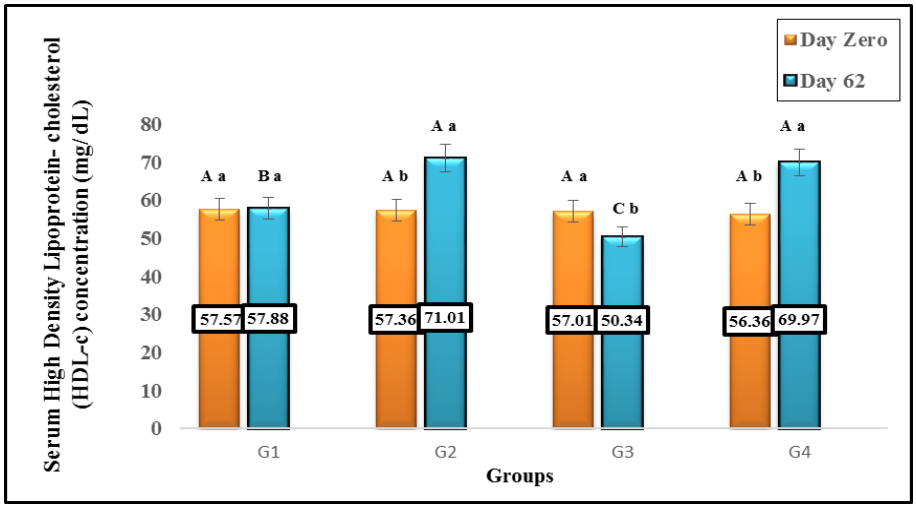

Figure 7. Effect of phosphatidylcholine, fructose and/or combination on serum high density lipoprotein-cholesterol (HDL-c) concentration (mg/dL). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

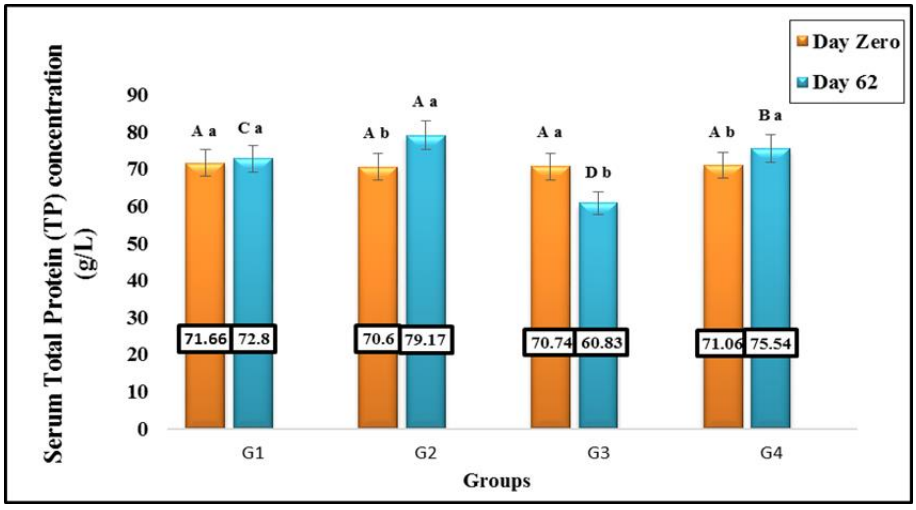

Figure 8. Effect of phosphatidylcholine, fructose and/or combination on serum total protein (TP) concentration (g/L). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations $P \leq 0.05$ between peroids

Effect of PC, Fructose and /or Combination on Serum Protein Profile

After 62 days of treatment, there was a significant (P<0.05) increase in the serum total protein and globulins concentration of PC treated groups (PC) compared to other treated groups. There was a marked drop in total serum protein and globulin levels in fructose treated group (Fr) compared to other groups. Albumin concentration remained steady in both (Fr) and (C) groups, while there was a significant (P<0.05) decrease in serum albumin concentration in Fr+PC-treated groups compared to other groups (Figures 8-10).

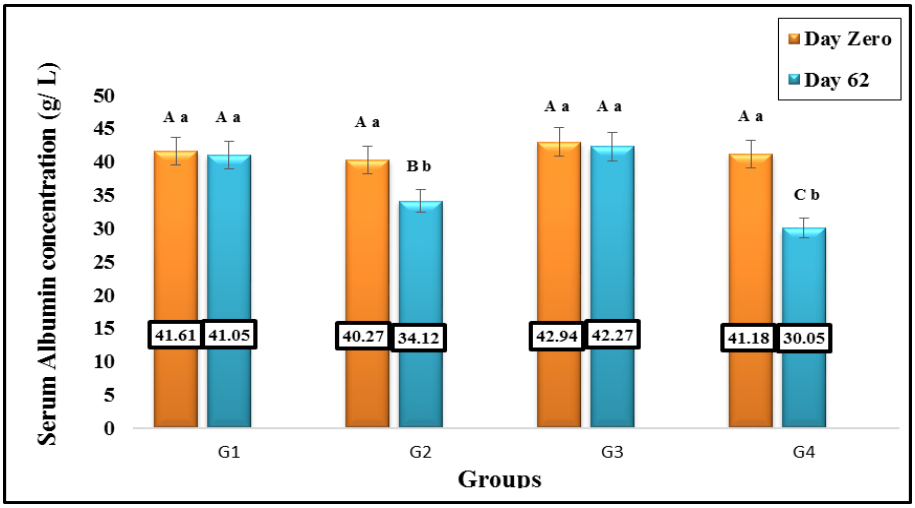

Figure 9. Effect of phosphatidylcholine, fructose and/or combination on serum albumin concentration (g/L). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations P≤0.05 between peroids

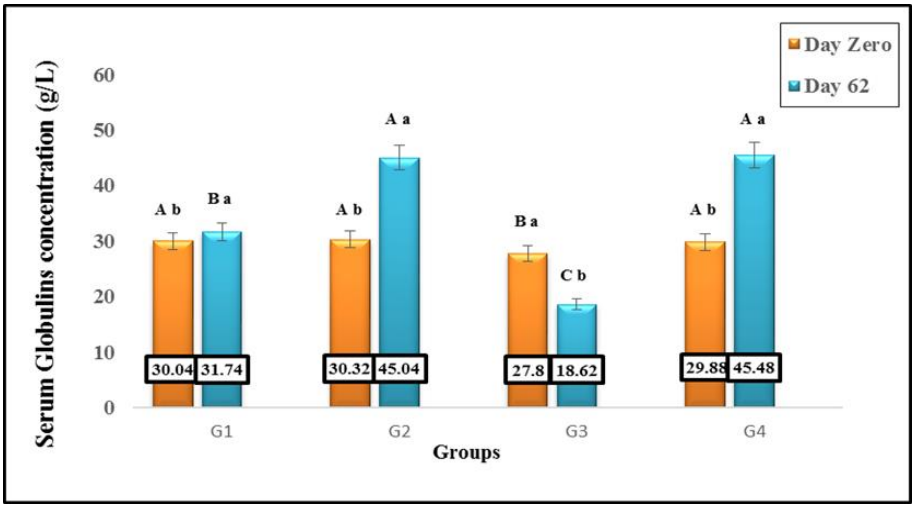

Figure 10. Effect of Phosphatidylcholine, Fructose and/or their combination on serum globulin Concentrations (g/L). Mean ± SE, n = 9 in a group. G1 control groups (C), G2: (Pc), G3: (Fr), G4: (Fr + Pc). [A-C] Significant variations P≤0.05 between peroids

DISCUSSION

A case of dyslipidemia and elevation in atherogenic index detected after fructose consumption was ameliorated after PC treatment. Several studies demonstrated variations in lipid levels after fructose supplementation, including high circulating levels of LDL-c, TAG and increased risk of obesity (34, 35). Furthermore, a negative connection has been seen between fructose consumption and TC, TG, non-HDL, and TG/HDL, particularly when this carbohydrate was obtained via sweetened drinks (36). Fructose has been connected to elevated serum de-novo lipogenesis, triglyceride production, and excess supply of VLDL particles enriched in apoC-III, a shift associated with greater small dense LDL (37-39). Additionally, hepatic fructose could raise TAG via encouraging the expression of the genes for GLUT2-GLUT5, fatty acid synthesis, and acetyl

CoA carboxylation in the liver (40). Atherogenic index elevation is correlated with size of lipoproteins LDL and is indication of oxidative stress that cause LDL oxidation, which is an indicator of atherogenic lipoproteins status, lead to early stage of atherosclerosis (51). Accordantly, the well-known oxidative stress produced by fructose exposure could lead to an elevation of AI in G3 group. Which is regarded as predictors of atherogenic risk at an earlier stage (52). Regarding the hypolipidemic impact of PC, it has been shown that the effects of PC on fat were mostly mediated by a decline in adipocyte viability and induction of adipocyte cell death, making it a potentially useful agent for targeting the amount of adipose tissue (53). Using different phospholipid preparation for hyperlipidemic patient resulted in significant reductions in total cholesterol, triglyceride and LDL-cholesterol, in association with a significant (12%) increase in plasma HDL-cholesterol (54,55). One of the most spectacular properties of lecithin is the ability to reduce the excess of LDL cholesterol, it also promotes the synthesis in the liver of great amount of HDL and elevated its serum concentration (56, 57). PC has also recently been used for fat lipolysis in treating obesity via mesotherapy (41). In a dose-dependent way, it caused adipocyte lipolysis and apoptosis (42). The intestinal lumen appears to be the primary site of action for the PC hypolipidemic response, where ingested phospholipids can block neutral sterol absorption. More proof points to the possibility that dietary phospholipids can increase the synthesis of bile acids and cholesterol, possibly by reducing intestinal absorption or boosting bile acid production (43). Antioxidant paly role in reducing atherogenic index, which is a positive physiological effect, by protection LDL from oxidation (58). Atherogenic index was reduced in PC in high fats diet induced obesity (59). The possible role of PC in lowered atherogenic index could be due to its antioxidant's activity. Generally, the antioxidant capacity of natural antioxidant act as strong inhibitors of ROS and is consequently counteract as loosen LDL oxidation and thus decrease AI and Could contribute to defense against CVD correlated with oxidative status (60). Production in TAG level potentiated ability of PC in reducing cardiovascular decrease. This also support observed decrease in atherogenic index by PC (61). The significance elevation in total serum protein and globulins concentration was detected in PC treated groups compared to fructose treated groups. It is known that several oxidative products such as peroxide can disturb endoplasmic reticulum ER and redox homeostasis (44, 45), resulting in ER stress and then disruptions in protein synthesis PC, like other antioxidants, may play an important role in regulating protein folding, activating ERs, maintaining redox homeostasis (46), and restoring protein synthesis. It has been documented that membrane lipid replacement therapy (LRT) including lecithin which contain glycerol phospholipids caused protection against oxidative damage and restore organelle and cellular organ function (62, 63). Such LRT also restore mitochondrial function in animal and human, elevated ATP necessary for cellular function including protein synthesis (64). It should be mentioned that this is the first research concerning the effect of PC on protein profile, so no scientific literature or research were available. After fructose treatment, total serum protein (TP) and globulin concentrations decreased as well. Wistar rats fed diets containing 65% fructose promoted liver apoptosis, ER stress, and an inflammatory process that could lead to hypoproteinemia (47). Malondialdehyde (MDA), and other lipid peroxidation metabolic end products can covalently bind to protein thiol groups and other cellular components, impairing protein and enzyme activities or functions (48), which could be a mechanism leading to hypoproteinemia.

Furthermore, in high fructose in humans, an increase in nitro-tyrosine (N-Tyr), a marker of protein oxidative alterations, was identified in hepatic homogenates and mitochondria, resulting in a decrease in serum protein content (49). Endoplasmic reticulum stress (ERs), often known as oxidative stress, has been linked to the pathogenesis of multiple diseases. By lowering the effectiveness of protein packing mechanisms and promoting the synthesis of misfolded proteins, oxidative stress can make ERS worse (45, 50).

In conclusion, using PC treatment in rats caused reduced changes in lipid profile, protein profile and the atherogenic index, while fructose caused induced metabolic syndrome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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تأثير فوسفاتيديل كولين على عسر شحميات الدم ومؤشر تصلب الشرايين في الجرذان المعرضة لارتفاع نسبة الفركتوز

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الخلاصة

صممت هذه الدراسة للنظر في الآثار المفيدة للفوسفاتيديل كولين في تقليل التغيرات في ملف الدهون، البروتين، ومؤشر تصلب الشرايين في الجرذان البالغة المصابة بمتلازمة التمثيل الغذائي التي يسببها الفركتوز. تم تقسيم الحيوانات البالغة ستة وثلاثين (36) أنثى من الجرذان إلى أربع مجاميع G1، G2، G3، G4 وأعطيت العلاجات التالية لمدة (62) يوم، المجموعة الاولى: مجموعة السيطرة تلقت الماء المقطر بانتظام. المجموعة الثانية: تم تجريع الجرذان بـ 1 جم/كجم من وزن الجسم من فوسفاتيديل كولين؛ ومن ثم تجريع الحيوانات في المجموعة الثالثة بنسبة 40٪ من الفركتوز فمويا و25٪ من الفركتوز في مياه الشرب؛ تم تجريع الجرذان في المجموعة الرابعة أيضًا بنسبة 40٪ من الفركتوز فمويا و25٪ من الفركتوز في مياه الشرب، مع 1 جم/كجم من وزن الجسم من الفوسفاتيديل كولين عن طريق الفم. بعد صَوَمَ الحيوانات (8-12 ساعة)، تم جمع عينات الدم بتقنية ثقب القلب في نهاية هذه الدراسة، وتم الحصول على مصل الدم لقياس معايير الدهون في الدم (الكوليسترول الكلي في الدم، الدهون الثلاثية (ثلاثي الجلسرين)، البروتين الدهني عالي الكثافة، البروتين الدهني منخفض الكثافة، البروتين الدهني منخفض الكثافة جدا، البروتين الدهني غير عالي الكثافة، مؤشر تصلب الشرايين) لبروتينات الدم (البروتين الكلي، الألبومين والجلوبيولين). أظهرت النتائج حدوث عسر شحميات الدم (فرط كوليسترول الدم، ثلاثي الجلسرين في الدم، زيادة في البروتين الدهني منخفض الكثافة ، زيادة كوليسترول البروتين الدهني منخفض الكثافة، زيادة تراكيز البروتين الدهني غير عالي الكثافة ومؤشر التصلب العصيدي وانخفاض تركيز البروتين الدهني عالي الكثافة). الحيوانات المعالجة لوحظ اضطراب في تكوين البروتين (انخفاض في مستوى البروتين الكلي والجلوبيولين). أظهرت النتائج كذلك أن العلاج بالفوسفاتيديل كولين خفف من التغيرات في المعلمات او المعايير المذكورة أعلاه. أدى استخدام الفوسفاتيديل كولين في الجرذان إلى تقليل التغيرات في مستوى الدهون، ومظهر البروتينات ومؤشر تصلب الشرايين بينما تسبب الفركتوز في حدوث متلازمة التمثيل الغذائي.

الكلمات المفتاحية: الدهون، فوسفاتيديل كولين، زيادة الكولسترول في الدم، البروتين الكلي، البروتين الدهني غير عالي الكثافة، البروتين الدهني قليل الكثافة