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Modulation of Renal Aquaporin-3 by Swimming Exercise in Fructose Induced Metabolic Syndrome

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Abstract

Background: Metabolic syndrome is cluster of cardiovascular and metabolic pathologies, caused by high fructose in modern times.

Aim of Study: We investigated the possible beneficial role of exercise on fructose induced metabolic syndrome in rats with special focus on the role of renal aquaporin-3 (AQP3).

Material and Methods: Forty rats were divided into four groups; control, exercised control, MetS (Metabolic Syndrome), and MetS with exercise. MetS was induced by fructose rich diet and swimming was practiced 3 days per week for 6 weeks, one hour each session.

Results: Fructose consumption significantly increased fact accretion, systolic blood pressure, serum lipids, insulin levels and insulin resistance. Also serum MDA, uric acid and renal AQP3 expression increased compared to the control group. Swimming exercise significantly decreased the previously measured parameters compared to fructose group but overexpressed renal AQP3.

Conclusion: Increased AQP3 expression may be implicated in fructose induced MetS. Swimming exercise efficiently counteracted metabolic disruption and vascular affection via lowering effect on oxidant and dyslipidemic stresses with renal aquaglyceroporin-3 overexpression.

Key Words: *Swimming exercise – Fructose – Metabolic syndrome – Insulin resistance – Aquaglyceroporin-3.*

Introduction

METABOLIC syndrome or "syndrome X" is cluster of pathologies comprising plethora of negative cardiovascular and metabolic conditions like dyslipidemia, obesity, insulin insensitivity, atherosclerosis, and hypertension [1]. Fructose consumption has risen dramatically in modern times and its high consumption has developed metabolic syndrome profile [2].

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Fructose is the sweetest tasting carbohydrate, found in many fruits and vegetables. But lastly its consumption increased in industrialized foods and soft drinks [3]. Fructose is taken up by the liver and enters the metabolic pathway for glycerol synthesis that constitute the carbon backbone of fats (triacylglycerol), so, the sources of circulating glycerol are fat lipolysis, diet-derived glycerol or glycerol reabsorbed in renal tubules [4].

AQPs are a family of integral membrane water channels namely 13 members have been identified in human. AQP3 is one of aquaglycerporins that has an additional permeability to glycerol [5]. It had been demonstrated by immunohistochemical studies that renal AQP3 is localized along the basolateral membranes of principal cells, in cortical distal convoluted tubules and collecting ducts in the renal medulla [6]. Glycerol transport regulation by aquaglyceroporins can play a pivotal role in control of fat accumulation, glucose homeostasis, cardiomyocytes energy production and pancreatic insulin secretion, among other functions [7]. These novel metabolic mechanisms helped in shifting the focus of obesity and insulin resistance development to design new therapeutic strategies for metabolic syndrome [8].

Physical exercise was preferred among nondrug treatment strategies for the control of energy balance and obesity [9]. Exercise is fueled mostly by fatty acids provided by the adipose tissue, circulating lipoproteins, and the triglycerides stored in the muscle cells themselves [10].

Continuous physical exercises performed at low/moderate intensities and high volume can effectively produce several cardiorespiratory and muscular systems adaptations, favoring body fat oxidation and body mass loss [9].

This study aimed to clarify the metabolic consequences of increased fructose intake, mechanisms leading to fructose-induced insulin resistance, metabolic dyslipidemia and vascular affection. And also the effects of physical exercise on free radicles, renal AQP3 expressions and dyslipidemia in fructose induced metabolic disorder.

Material and Methods

Animals and experimental design:

This study was carried out in accordance with the regulations of Animal Experimentation Ethics Committee of Faculty of Medicine Menoufia University September 2017. Thirty adult male Wister albino rats weighing 120-150g were used. The animals were housed at 20-24ºC with a 12-h light, 12-h dark cycle and they were provided with standard rat chow and tap water freely available.

Forty rats were randomly divided into four groups (n=10) as follows; control: Rats in this group received standard rodent diet. Swimming Exercise-trained Control (EC) group: Rats of this group practiced swimming exercise as described below. MetS: Rats in this group were fed fructose rich diet (60% fructose (Techno Gene Company, Egypt) mixed with standard rat chow) [11,12]. MetS with exercise (MetS-E): Swimming were practiced by rats of this group as described below.

Swimming exercise training:

Swimming was practiced in temperature-controlled water (30º-32ºC), 3 days per week for 6 weeks, one hour each session (10:00-11:00a.m.). At the end of each exercise session, animals were dried and kept in a warm environment. Sedentary rats of C and F groups were restricted to cage activity. However, on the days of exercise practice, the sedentary animals were removed from their cages and kept for one hour in the container (previously cleaned and dried), where the swimming sessions had taken place, in order to handle stress. To minimize the acute effect of the exercise, the trained animals were sacrificed 48 hours after the end of the last swimming training session [13].

At the end of the experiment (after 6 weeks), body weight was assessed, animals were fasted overnight and animals then retro-orbital blood samples were collected and left for clotting for 10min and centrifuged at 4000rpm for another 10min to isolate the serum and kept at 20ºC for further analysis.

Thereafter, rats were subjected for measurement of arterial blood pressure by invasive method.

Lastly, rats of all groups were sacrificed and the visceral, epididymal and retroperitoneal fats were estimated. The kidneys were excised, fixed in 10% phosphate-buffered formalin solution, processed through paraffin embedding and prepared for immumohistochemical studies.

Measurement of invasive blood pressure:

Rats were anesthetized by Thiopental sodium 50mg/kg i.p. The aorta is identified and cannulated using a cannula pre-filled with heparinized normal saline and the other end of the cannula was connected to a three-way stopcock saline filled syringe which was connected to a pressure transducer and the invasive blood pressure was recorded using physiography system (Narco Bio-Systems, U.K.).

Serum biochemical analysis:

Lipid profile:

Total cholesterol (mg/dl) and HDL-C (mg/dl) levels were determined following their hydrolysis and oxidation to yield colored quinoneimine derivatives using test reagent kits (Biodiagnostics, Egypt). Triglycerides (TGs) level (mg/dl) was estimated by a reagent kit (EMAPOL, Poland), in which TGs were hydrolyzed with lipoprotein lipase to form glycerol, which forms a complex with H_2O_2 giving a colored derivative. The obtained levels of total cholesterol, HDL and TGs were then used to calculate the serum level of LDL-C as that described by Friedewald et al., [14].

LDL = Total Cholesterol – (HDL + Triglycerides/5).

Blood glucose:

FBG level (mg/dl) is oxidized enzymatically to yield a red violet quinoneimine that can be determined calorimetrically using a test reagent kit (EMAPOL, Poland) [15].

Insulin levels:

Insulin level (µU/ml) was measured following a solid phase two-site enzyme immunoassay (DRG Instruments GmbH, Germany) [16].

Homeostasis Model Assessment Index (HOMA-IR):

Insulin resistance was evaluated by the HOMA-IR using the formula: Insulin (µU/ml) X glucose (mg/dl) / 405 [17].

Serum Malondialdehyde (MDA):

Colorimetric method for estimation of Malondialdehyde (MDA) using test reagent kits (Biodiagnostics, Egypt) was done according to protocol

described in Ohkawa et al., [18], by using thiobarbituric acid reactive substance for measuring the peroxidation of fatty acids as oxidative stress marker.

Serum uric acid:

Colorimetric method was performed using test reagent kits (Biodiagnostics, Egypt) by using the protocol described in Braham and Trinder [19].

Renal immunohistochemical staining with AQP3:

Paraffin-embedded blocks were sectioned then all slides were de-paraffinized using xylene and then rehydrated in decreasing concentrations of ethanol. Antigen retrieval using microwave heating (20 minutes; 10mmol/citrate buffer, pH 6.0) after inhibition of endogenous peroxidase activity (hydrogen peroxidase for 15min) was used followed by cooling at room temperature. The primary antibody (purified rabbit polyclonal to Aquaporin 3 [Abcam (ab125219)]) was applied to the slides, incubated overnight at room temperature in humidity chamber. Sections were then washed by PBS with optimal dilution 1:500. Sections were then incubated with secondary antibody for 15 minutes followed by PBS wash. Finally, the detection of bound antibody was accomplished using a modified Labeled Avidin-Biotin (LAB) reagent for 20 minutes then PBS wash. A 0.1% solution of Diaminobenzidine (DAB) was used for 5 minutes as a chromogen. Slides were counter-stained with Mayer's hematoxylin for 5-10 minutes. Rat kidney tissue specimens were used as positive controls. Omission of the primary antibody served as a negative control.

Interpretation of immunohistochemical results:

A brown membranous staining in any number of cells was considered positive in the studied cases and control specimens [20].

Renal tissue in the 4 studied groups (control, exercised control, metabolic syndrome, and metabolic syndrome with exercise) was assessed for the expression percentage of positive cells, which were counted and given a percentage over 200 cells of the whole section at 200X magnification in renal tissue [21].

Statistical analysis:

The data were tabulated and analyzed by SPSS (statistical package for the social science software) using statistical package Version 20 on IBM compatible computer. Quantitative data were expressed as mean ± standard error of mean (X ± S.E.M). Data from control and test groups were compared using one way ANOVA, followed by Tukey post Hoc test, probability value of less than 0.05 was considered as statistically significant ($p<0.05$).

Results

Body weight and fat accretion:

The body weight of MetS group was found to be significantly higher ($p<0.05$) than that of the control and exercised control groups while that of Met-E group was found to be significantly lower ($p<0.05$) than that of the MetS group.

With regard to the major fat pad accretion, the MetS rats showed a significantly higher amount of visceral ($p<0.05$), retroperitoneal ($p<0.05$) and epididymal ($p<0.05$) fat mass compared to their control and exercised control counterparts indicating abdominal obesity, while MetS-E group showed a significantly lower amount of visceral ($p<0.05$), retroperitoneal ($p<0.05$) and epididymal ($p<0.001$) fat mass compared to MetS rats (Table 1).

Serum biochemical analysis:

Serum lipid profile (cholesterol, TGs and LDL) in exercised control group were significantly lower ($p<0.001$) but that of MetS group were significantly higher ($p<0.001$) compared to control group. While HDL level in exercised control group was significantly higher ($p<0.001$) but that of MetS group was significantly lower ($p=0.001$) compared to control group. Serum lipid profile (cholesterol, TGs and LDL) in MetS group were significantly higher ($p<0.001$) while HDL level was significantly lower ($p<0.001$) compared to exercised control group. In MetS-E group, serum lipid profile (cholesterol, TGs and LDL) were significantly lower ($p<0.001$, 0.05, 0.001) compared to fructose fed group but still significantly higher ($p<0.001$) compared to exercised control group, while HDL level in MetS-E groups was significantly higher ($p<0.05$) compared to MetS group but still significantly lower ($p<0.001$) compared to exercised control group and all these parameters were insignificantly different compared to control group (Table 2).

Blood glucose in exercise control was significantly lower ($p=0.001$) compared to control group. In MetS group, blood glucose, serum insulin and HOMA index were significantly higher ($p<0.001$) compared to their corresponding levels in control group and were significantly higher ($p<0.001$, 0.001, 0.005) compared to exercised control group. In MetS-E group blood glucose and HOMA index were significantly higher ($p<0.05$) compared to control group and were significantly higher

(p<0.001, 0.05) compared to exercised control group, while these parameters plus serum insulin were significantly lower (p<0.001) compared to their corresponding values in MetS group (Table 2).

Serum MDA and uric acid in MetS group were significantly higher (p<0.001) compared to their corresponding levels in control group, and serum MDA only was significantly higher (p<0.05) compared to exercised control group. In MetS-E group, these parameters were significantly lower (p<0.05, 0.001) compared to their corresponding levels in MetS group but still significantly higher (p<0.05) compared to control group but serum uric acid only was significantly higher (p<0.001) compared to exercised control group (Table 2).

Table (1): Body weight and fat accretion (visceral fat, retroperitoneal fat and epididymel fat weights) (gm.) in control, exercise control, MetS and MetS-E groups.

	Control	Exercised control	MetS	MetS-E
Body weight (gm.)	213±6.5	209.8±18.3	272±12.8*$	218±14.5#
Visceral (gm.)	2.9±0.2	2.2±0.17	3.9±0.28*$	3.02±0.19#
Retroperitoneal fat (gm.)	4.2±0.18	3.7±0.15	5.5±0.35*$	3.8±0.27#
Epididymal fat (gm.)	2.9±0.12	2.7±0.15	4.8±0.23*$	3.1±0.52#

Data were expressed as mean ± S.E. (n=10). One way ANOVA:
*: p<0.05 vs. control.
$: p<0.05 vs. exercise control.
#: p<0.05 vs. MetS group.

Table (2): Serum lipid profile, glucose, insulin, HOMA-IR, MDA and uric acid levels in control, MetS and MetS-E groups.

	Control	Exercised control	MetS	MetS-E
Cholesterol (mg/dl)	103±3.7	79.8±1.9	127±2.1*$	110±1.2$#
Triglycerides (mg/dl)	61.2±2.6	38.8±1.01*	64.7±1.9*$	66±2.1$#
HDL (mg/dl)	39.8±1.1	50.5±0.8*	31±1.6*$	37.8±1.7$#
LDL (mg/dl)	50.9±3.7	21.5±2.6*	83±2.2*$	59±2.5$#
Glucose level (mg/dl)	91±2.1	74.1±3.1*	116.2±4.2*$	98.5±2.0$#
Insulin level (µU/ml)	17.2±1.2	18.4±1.4	34.2±1.8*$	19.9±1.8#
HOMA-IR	3.8±0.29	3.2±18	9.8±0.51*$	4.8±44$#
MDA (nmol/ml)	3.3±0.26	3.4±.35	8.0±1.4*$	5.2±0.42#
Uric acid (mg/dl)	1.6±0.08	1.5±0.08	3.4±0.13*	2.3±18$#

Data were expressed as mean ± S.E. (n=10). One way ANOVA:
*: p<0.05 vs. control.
#: p<0.05 vs. MetS group.

Invasive blood pressure:

Systolic, diastolic and mean arterial blood pressure (measured by invasive technique) in MetS rats showed significant increase (p<0.05) compared to control and exercised control groups. These parameters showed significant decrease (p<0.05) in MetS-E rats compared to MetS rats, but systolic and mean arterial pressure were still significantly higher (p<0.05) compared to control group Fig. (1).

Aquaporin-3 (AQP-3) immunohistochemistry:

Expression of aquaporin-3 was detected as basolateral membranous in the collecting tubules in the medulla, the control group showed AQP-3 expression of (27.5%) but it was found in the exercised control group (77.5%). The MetS group showed expression of (30%) while the MetS-E group showed expression of (45%).

So, results revealed AQP3 overexpression in the the exercised groups (exercised control and MetS-E) in comparison with control and MetS groups Fig. (2).

Some cortical cytoplasmic expression was displayed, however, the expression was considered as a non-specific stain, according to the data sheet of the primary antibody provided by the company.

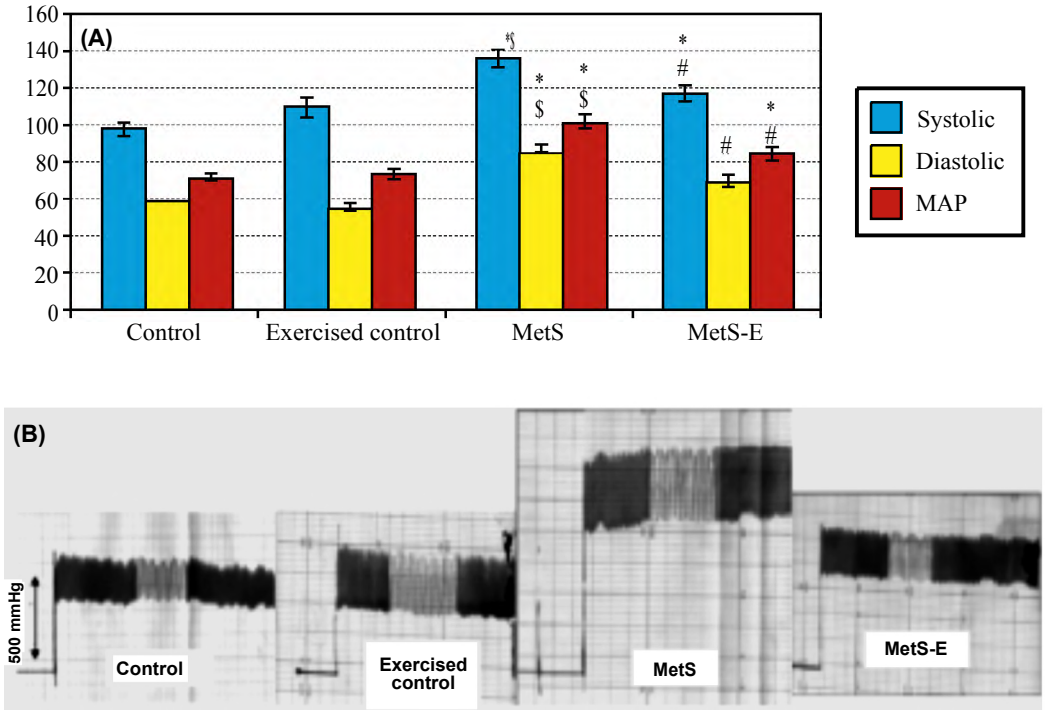

Fig. (1): Invasive blood pressure amomg control, exercised control, MetS and MetS with exercise groups. A and B show level of systolic, diastolic and mean arterial blood pressure (mmHg) among groups.

Data were expressed as mean ± S.E. (n=6-8). One way ANOVA: *: $p<0.05$ vs. control; #: $p<0.05$ vs. MetS group.

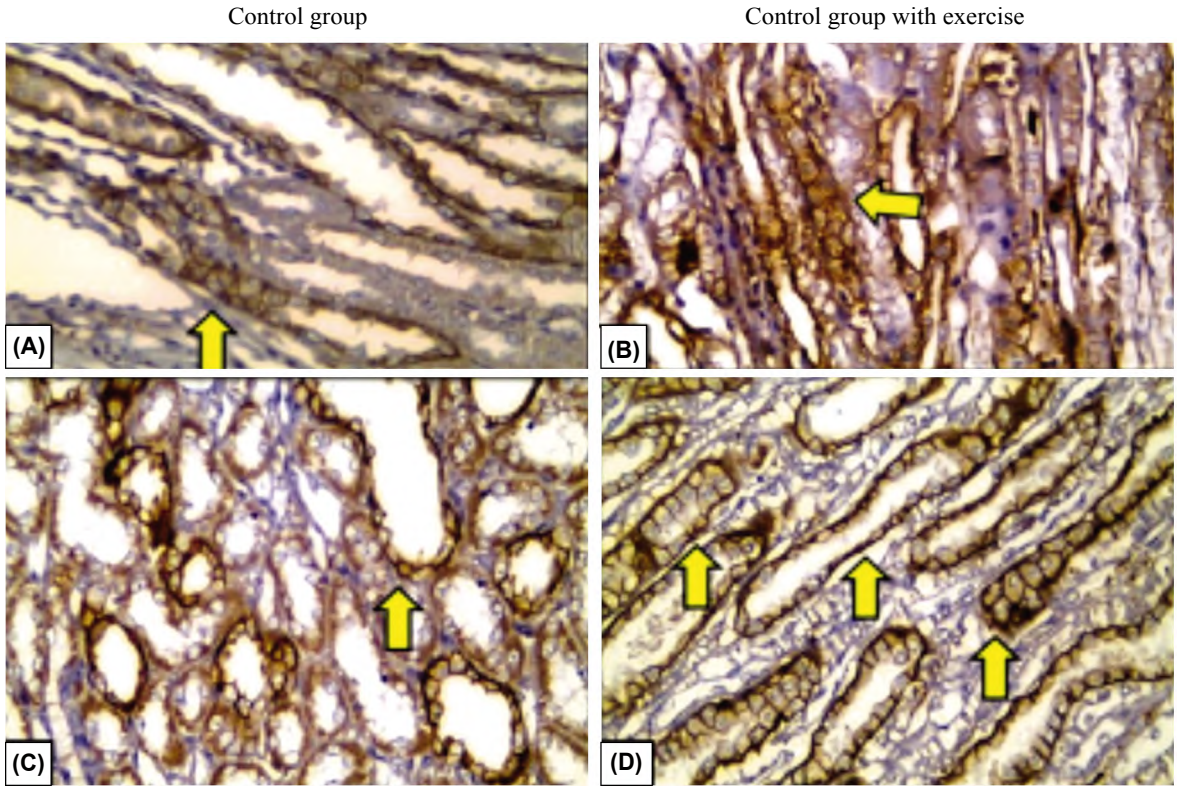

Fig. (2): Immunohistochemistry staining of renal AQP-3 in renal medulla: Basolateral membranous expressionof AQP-3 (yellow arrows) were more evident in the control group with exercise (B) and the fructose metabolic syndrome with exercise (D) in comparison with both the control group (A) and the fructose metabolic syndrome group (C). (A, B, C and D): Immunoperoxidase X400 HPE).

Discussion

There is a growing evidence that high dietary intake of fructose could be considered an important factor in the development of current metabolic disorder epidemic [22] and its associated complications [23].

It is important to focus on lifestyle changes for treatment of metabolic syndrome; especially increased physical activity and weight reduction [24].

In the current study fructose fed rats showed evidences of metabolic syndrome as the significant increase in body weight and fat accretion, dyslipidemia, hyperglycemia, hyperinsulinemia, insulin resistance, hypertension, which were associated by hyperuricemia increased lipid peroxidation parameter (MDA), and increased expression of renal aquaporin-3 (AQP3).

Fructose promoting ability of metabolic syndrome was currently proved by its lipogenic nature that increase deposition of TG in adipose tissue and ectopic tissues, eventually resulting in impaired insulin signaling and dyslipidemia [25].

There is evidence that fructose rich diet created an unfavorable lipid profile in blood via hepatic de novo lipogenesis that increases plasma triglycerides, and a delayed triacylglycerol clearance with palmitic acid production, a fatty acid specifically was shown to increase the risk of atherosclerosis [26].

As a small solute, glycerol should be freely filtered in the renal glomeruli, thus it is likely to be reabsorbed after glomerular filtration [27]. Glycerol is the backbone of triglycerides [4].

Interstingly, overexpression of renal AQP3 revealed in this study may have a role in the dyslipedemic complications, being channels in the basement membrane of distal convoluted tubules and collecting ducts of the kidney, that are responsible for glycerol reabsorption [6].

Hyperuricemia of fructose fed rats might be attributed to the stimulation of adenosine monophosphate deaminase activity triggered by fructose metabolism and resulted in development of metabolic syndrome. Also it played a pivotal role in the development of associated insulin resistance and hypertension probably through uric acid-induced endothelial dysfunction [28].

Regarding fructose induced hypertension, the current study demonstrated higher membranous expression of renal AQP3 with hypertension in fructose induced metabolic syndrome rat model which agreed with Lee and colleagues [29] who reported a similar expression in the kidney of spontaneously hypertensive rats.

Swimming exercise was efficient in counteracting some disrupting effects seen in fructose induced metabolic syndrome in particular, insulin resistance, hyperuricemia, oxidative stress markers, and obesity. It prevented the increase of fasting blood glucose, serum insulin in high fructose-fed rats with better overall lipid profile as agreed with Sakr [30]. Moreover, swimming exercise was able to return some parameters to normal values as presented by their insignificant difference between exercised fructose fed rats and exercised control groups as serum insulin and MDA.

A large scientific evidence is available regarding the positive effects of swimming as a moderate intensity aerobic exercise on the lipid profile, with favorable modifications to lipoprotein metabolism (increase in the cardioprotective HDL-C fraction, decrease triglyceride level and small atherogenic LDL particles levels [31]. Sports with a high dynamic component but with concentric muscular contraction and low joint impact, such as swimming, could be more beneficial for better lipogram [10].

Exercise had beneficial clearing effect on triglycerides through increasing skeletal muscle lipoprotein lipase, activation of PPAR- a, which promotes transcription of fatty acid catabolic genes and lastly through fructose conversion to muscle and liver glycogen instead of triglycerides since exercise depletes muscle and liver glycogen [31].

Additionally, moderate intensity exercise leads to activation and recruitment of type I oxidative muscle fibers with preferential fatty acids oxidation, mediating exercise improved lipid profile [10].

Also, physical activity was able to prevent some of the maladaptive changes associated with chronic fructose feeding as the significant decrease of body mass and fat accretion with normalization of retroperitoneal and subcutaneous fat pad mass which agreed with our results [32]. These changes might be mediated by decreased acylated ghrelin (active appetite stimulating protein), and increased both leptin (appetite suppressor) and activity of adiponectin (cytokine that increases insulin sensitivity, and reduces inflammation along with having antiatherogenic effects). Thus, exercise has a very strong effect in mediating hunger (and, subsequently, food intake) and energy expenditure [30].

Additionally, swimming exercise in the current study effectively reduced serum MDA levels which is a key player in the pathophysiology of many diseases including metabolic syndrome and its vascular complications **[33]**.

Physical activity successfully reduced the elevated BP following diet-induced obesity in rats **[34]**. That was consistent with results of current study which revealed the preventive effect of swimming exercise against elevation of ABP, and this was proved by insignificant difference between exercised fructose fed rats and exercised control groups.

Furthermore, the BP-lowering effect of training in hypertensive patients appears to be associated with improvement in insulin sensitivity. So, Swimming could be recommended as a lifestyle intervention by clinicians for prevention and treatment of hypertension **[35]**.

Swimming programme in the current study revealed higher overexpressed renal AQP3. Being a glycerol permeating pore, this overexpression seemed conflicted with decreased plasma triglycerides presented in exercised rats that can be explained by increased glycerol uptake by skeletal muscle many folds during exercise **[36]**. Skeletal muscle has GLK activity which enables muscle to incorporate glycerol into TAG, also its overexpression can divert glycerol to be incorporated into glycogen. This may be physiologically relevant pathway for muscle fuel stores in vivo, particularly post exercise **[37]**.

The physiologic significance of AQP3 is still less clear, so, extensive studies of aquaglyceroporins on the basic and clinical levels are needed.

In conclusion, fructose induces metabolic syndrome characterized by increase fat accretion, insulin resistance, metabolic dyslipidemia, increased oxidant level and complicated by hypertension and were associated with increased expression of renal AQP3.

Our study support the notion that exercise has many significant homeostatic promoting mechanisms that lead to improvements in metabolic and other dysfunctions caused by stressors such as high fructose intake, particularly increased ABP, hyperuricemia, insulin resistance, oxidative stress markers, body weight, visceral obesity.

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تحوير الاكوابورين-٣ الكلوى عن طريق ممارسة السباحة فى متلازمة الأيض المستحدث بالفركتوز

مقدمة: متلازمة الأيض هى مجموعة من الأمراض القلبية الوعائية والتمثيل الغذائى، والناجمة عن الوجبات الغذائية عالية الفركتوز فى العصر الحديث. لقد قمنا بالتحقق من الدور المفيد المحتمل للرياضة على متلازمة الأيض المستحدث بالفركتوز فى الفئران مع التركيز بشكل خاص على الأكوابورين-٣ الكلوى.

مواد وطرق: البحث تم تقسيم أربعين فئران إلى أربع مجموعات: مجموعة سليمة ضابطة، مجموعة ضابطة ممارسة لرياضة السباحة، مجموعة مصابة بمتلازمة الأيض ومجموعة مصابة بمتلازمة الأيض مع ممارسة رياضة السباحة. تم استحداث متلازمة الأيض باتباع نظام غذائى غنى بالفركتوز ورياضة السباحة ٣ أيام فى الأسبوع لمدة ٦ أسابيع، وساعة واحدة فى كل دورة. فى نهاية فترة البحث تم تقدير وزن الجسم وتراكم الدهون، تقييم ضغط الدم الشريانى وقياس الآتى: مستوى الدهون بالدم، نسبة الجلوكوز بالدم، الأنسولين بالدم، مقاومة الأنسولين، مستوى المالوندالديهيد، حمض اليوريك، كما تم لفحص الانسجة المناعى للاكوابورين-٣ الكلوى.

النتائج: أظهرت نتائج البحث أن استهلاك الفركتوز أدى إلى زيادة تراكم الدهون، ضغط الدم الانقباضى، شحوم الدم، ومستويات الأنسولين بالدم والمقاومة للانسولين. كما أدى إلى زيادة مستوى المالونديالدهايد وحمض اليوريك بالدم وتعبير الاكوابورين-٣ الكلوى مقارنة بالمجموعة الضابطة. وقد أدى تمرين السباحة بشكل ملحوظ إلى إنخفاض القياسات السابقة بينما زاد تعبير الاكوابورين-٣ الكلوى بشكل مفرط مقارنة مع مجموعة متلازمة الأيض المستحدث بالفركتوز.

الاستنتاجات: نستخلص من البحث أن زيادة تعبير الاكوابورين-٣ الكلوى قد تكون بفعل متلازمة الأيض المستحدث بالفركتوز وأن تمارين السباحة تصدت لاضطراب التمثيل الغذائى وتأثر الأوعية الدموية بشكل فعال عن طريق خفض تأثير الإجهاد المؤكسد وتعسر شحوم الدم وكذلك زيادة التعبير المفرط للأكوابورين-٣ الكلوى.