Effect of acrylamide and fructose on some parameters related to metabolic syndrome in adult male rats

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Summary

This study is designed to investigate the effect of acrylamide on some metabolic syndrome parameters in adult male rats relative to fructose. Forty adult male rats were randomly divided into four equal groups (ten rat/group) and treated for 60 days as follows: Control: Rats in this group were received distilled water orally, groups T1 and T2: rats of these groups were given orally 0.5 and 1mg/kg B.W acrylamide respectively. Animals in the fourth (T3) group were given 40% fructose in drinking water. Blood samples were collected by cardiac puncture technique at different periods 0, 30 and 60 day of the experiment for measuring serum concentration of the following parameters related to metabolic syndrome: Dyslipidemia (high density lipoprotein-cholesterol, and triacylglycerol), uric acid and glutathione. The result revealed that oral intubation of two concentration of acrylamide or exposure of rats to 40% fructose in drinking water caused disturbance in lipid metabolism manifested by triacylglycerolemia, lowered high density lipoprotein-cholesterol concentration, lowered serum uric acid and glutathione concentration with hyperuricemia. These functional changes were accompanied by structural changes in the kidney. Sections in rat's kidney showed renal damage manifested by desquamation and degeneration of epithelial cells of renal tubule as well as lymphocyte infiltration between renal tubules. The results of this study concluded that acrylamide succeeded to induce sever changes in parameters related to metabolic syndrome in rats as does the fructose (the well-known inducer of metabolic syndrome). According to the available literature it seems that this is the first study which showed the effect of acrylamide on some parameters related to metabolic syndrome.

Keywords: Acrylamide, Fructose, Metabolic Syndrome, Rats.

Introduction

Metabolic syndrome is a clustering of metabolic problems associated with insulin resistance including hyperglycemia, lipid regulation problems (hypertriacelglycerolemia decreased high density lipoprotein and increased low density lipoprotein), obesity (especially central obesity), hypertension and hyperuricemia occurs commonly together. This combination is referred to as either the metabolic syndrome or syndrome X. These clusters of metabolic disorders interact to promote the development of type2 diabetes (1), arteriosclerosis, cardiovascular and renal disease (2 and 3). In spite of the fact revealed that insulin resistance lie at the heart problem (4). All of these metabolic disorders could together or independently, contribute to health problems. Acrylamide (ACR) is a water-soluble, vinyl monomer that has multiple chemical and industrial applications: like waste water management or processing. Besides, ACR is used extensively in molecular laboratories for gel chromatography and is present in some foods that have been prepared at very high temperatures (5). It is a small organic molecule with very high water solubility; such properties facilitate its rapid absorption and distribution through the body (6).The primary source of human exposure to acrylamide is occupational; other sources include food, drinking water, and smoking (7). Acrylamide is produced in starchy foods that are baked, roasted or fried at high temperature (8). In fried potato chips, acrylamide concentration ranged from 376 to 2348 µg/ kg (9) ACR polymers with low residual acrylamide monomer levels are used in the USA for treatment of poultry, potato, corn and other wastes, resulting in concentrated solids used as components of blended animal feeds (10 and 11). Acrylamide is neurotoxic to experimental animal and human (12) and has mutagenic and carcinogen effect (13 and 14).Acrylamide also reported to cause hepatotoxicity (15), DNA damage (16), and

reproductive toxicity (17). Fructose is a simple sugar present in fruits and honey and is responsible for the sweet taste. Fructose metabolism is very unique in a sense that it is not regulated (18). The consequences of uncontrolled fructose metabolism could be harmful at the cellular level leading to depletion of intracellular ATP, oxidative stress, increased uric acid production, endothelial dysfunction, and increased lipogenesis (19). Fructose was advisable for patients with diabetes duo to its low glycemic index. However, chronically high consumption of fructose for long period in rodents leads to insulin resistance (20), hypertension, renal damage (21), obesity and type 2 diabetes mellitus (22) and other manifestation of metabolic syndrome in human and animals (23 and 24). The effect of high fructose diet on hypothalamic- pituitary- adrenocortical axis activity in rats were also studied (25). This study was aimed to evaluate the effect of ACR on some criteria related to metabolic syndrome relative to fructose.

Materials and Methods

Forty adult male rats were randomly divided into four equal groups and treated daily for 60 days as follows: Control: Rats in this group were received distilled water orally, groups T1 and T2: rats of these groups were administered orally 0.5 and 1 mg/kg B.W of ACR respectively. Animals in the fourth (T3) group were given 40% fructose in drinking water. Blood samples were collected by cardiac puncture technique at different periods 0, 30 and 60 day of the experiment for measuring serum concentration of the following parameters related to metabolic syndrome: triacylglycerol (TAG), High density Lipoprotein - cholesterol (HDL-C) concentrations were measured using enzymatic kits (Linear chemicals, Barcelona/ Spain); serum glutathione (GSH) was determined by method as described by (26), besides, serum uric acid concentration was measured enzymatically using uric acid kit. Sections from kidney were taken for histopathological study (27). Statistical analysis of data was performed on the basis of Two-Way Analysis of Variance (ANOVA) using a significant level of (P<0.05). Specific group differences were determined using least significant differences (LSD) as described by (28).

Results and Discussion

High density lipoprotein-cholesterol (HDL-C) concentration: Comparing to the control, exposure of rats to 40% fructose in drinking water or given orally ACR for 30 day caused significant (P<0.05) decrease in serum HDL-C concentration (Table, 1). The mean values of this parameter in this period were (44.5±0.07), (37.2±0.04), (31.9±0.03) and (35.3±0.06) for control T1.T2 and T3 group, respectively. Further significant decrease (P<0.05) in serum HDL-C concentration after 60 days of the experiment was observed in groups T1 (27.4±0.04), T2 (21.1±0.02) and T3 (23.7±0.03) when comparing to the value in the control group. The significant decrease in HDL-C concentration is both time and dose dependent

Table, 1: Effect of ACR (o.5mg and 1mg/kg. B.W/orally) and fructose (40% in drinking water) for 60 day on serum High density lipoprotein–cholesterol (HDL-C) concentration (mg/dl) of adult male rats.

Groups / Days	Control	T1	T2	T3
zero	45.8±0.05	44.7±0.03 a	43.3±0.05 a	45.6±0.04 a
30	44.5±0.07 A	37.2±0.04 B b	31.9±0.03 D b	35.3±0.06 C b
60	44.8±0.06 A	27.4±0.04 B c	21.1±0.02 D c	23.7±0.03 C c

Values are expressed as mean ± SE, n = 10 each group. C: control group. T1: Animals received 0.5mg/kg B.W of ACR.T2: Animals received 1mg/kg B.W of ACR. T3: Animals received 40% of Fructose in drinking water. Different horizontally capital letters denote differences between groups, P<0.05 vs. control. Different vertically small letters denote differences within group, P<0.05 vs. pretreated period (zero).

Serum Triacylglycerol concentration (TAG): The results showed that given of 1mg/kg B.W of ACR orally (T2 group) to male rats for 30 days caused a significant (P 0.05) increase in TAG concentration with mean value of (69.5±0.01) comparing to the values in groups T1 (62.8±0.01), fructose (59.5±0.01) and control (56.4±0.01). Further significant increase (P<0.05) in serum TAG concentration was observed at the end of experiment in a ACR (T1,T2) and fructose

treated (T3) groups comparing to the control with mean values of (58.1±0.01), (77.5±0.01) and (83.0±0.02) for control group T1, T2 and T3 group respectively (Table, 2). With exception to control, all experimental groups showed significant increase in TAG concentration after 60 days of different treatment comparing with zero time and 30 day of treatment.

Table, 2: Effect of ACR (o.5mg and 1mg/kg. B.W/orally) and fructose (40% in drinking water) for 60 day on serum Triacylglycerol (mg/dl) concentration of adult male rats in three different times.

Groups / Days	Control	T1	T2	T3
zero	58.7±0.02	58.5±0.01 b	58.o±0.01 c	56.8±0.02 b
30	56.4±0.01 C	62.8±0,01 B b	69.5±0.01 A b	59.7±0.01 BC b
60	58.1±0.01 C	77.5±0.01 B a	83.o±0.02 A a	83.3±0.02 A a

Values are expressed as mean ± SE, n = 10 each group. C: control group. T1: Animals received 0.5mg/kg B.W of ACR.T2: Animals received 1mg/kg B.W of ACR. T3: Animals received 40% of Fructose in drinking water. Different horizontally capital letters denote differences between groups, P<0.05 vs. control. Different vertically small letters denote differences within group, P<0.05 vs. pretreated period (zero).

Effect of Acrylamide and fructose on the serum lipid profile (Triacylglycerol and high density lipoprotein-cholesterol (HDL-C): Concerning lipid profile, the present study showed that oral administration of ACR caused case of dyslipidemia manifested by significant increase in TAG and decrease in HDL-C concentration. This finding is in accordance with (29 and 30). Significant elevation in the concentration of serum total cholesterol; TAG, VLDL-C, and LDL-C, with decrease in serum HDL-C concentration was observed in rats received standard diet containing 50-60mg/kg ACR for 35 days (31 and 32). Changes in plasma lipoproteins could serve as sensitive markers for rats liver dysfunction caused by ACR. The elevation in TAG concentration in ACR -treated rats might be explained on the bases of lowered formation of plasma lipoproteins because of liver injury and high mobilization of lipids from the liver (33). The significant increase in serum TAG might be attributed to high level of FFA caused by elevation in cortisol concentration due to ACR induced stress (34), or increase significantly of epinephrine hormone which lead to increase FFA concentration, or probably due to reduced insulin mediated inhibition of lipolysis (35). The fact that fructose was associated with a marked decrease in high density lipoprotein (HDL)-cholesterol and increase in plasma triglyceride and is documented by others (36 and 37). Stimulation of hepatic de novo lipogenesis by fructose and induction of hypertriglyceridemia is observed by *(*38). Besides, acute fructose administration increased the postprandial rise in plasma triglycerides (39) due to an impaired clearance of triglyceride-rich lipoprotein (VLDL) (40). Several recent authors suggested that simple sugars intake, and particularly fructose, is a factor that contributes to hypertriglyceridemia and IR. Fructose is metabolized by the liver into triglycerides, and tends to raise their levels in the blood stream. Therefore, it may contribute to insulin resistance through the same mechanisms as the dietary fat (41).

Serum Glutathione (GSH) concentration: During the treatment period, ACR administration (T1 and T2 groups) or exposure to 40% fructose in drinking water (T3 group) for 30 days, a significant (P<0.05) reduction in serum GSH concentration with mean values of (53.1±0.02), (50.2±0.09) and (52.3±0.02) was observed in groups T1, T2 and T3 respectively comparing to the value in control group. The results have also clarified that ACR treated groups (T1 and T2) and fructose (T3 group) exposure caused a significant (P<0.05) decrease in serum GSH concentration after 60 days of treatment with mean value of (47.8±0.02), (47±0.01) and (48.8±0.01) respectively comparing to the control group. It should be mentioned that depletion of serum GSH is time and dose dependent (Table, 3).

Effect of Acrylamide and fructose on serum Glutathione: The delicate balance between the production and catabolism of oxidants is important for the maintenance of biological function (30). An increase in thiobarbituric acid reactive substance (TARS) - the marker of the extent of lipid peroxidation (LPO) - level in different tissues after ACR exposure has been documented (7). Besides, an

elevation in hepatic malondialdehyde level (42) reduction in GSH level (43 and 44) and other antioxidant enzymes like catalase, glutathione-S-transferees GST and superoxide dismutase (45) has been reported as signs of ACR toxicity. ACR is oxidized to glycidamide, a reactive epoxide and undergoes conjugation with reduced glutathione (GSH) (46). Such conjugation could explain the observed reduction in GSH. Maintenance of glutathione in its reduced form GSH is dependent upon availability of the enzyme glutathione reductase (GR). Accordingly, the reduction in the activity of this enzyme due to the interaction of free radicals and lipid peroxides formed by acrylamide with the sulfhydryl (SH) group present at the active site of the enzyme, will prevents GR enzyme from participating in the formation of reduced GSH, leading to decreased in GSH level (47).

Table, 3: Effect of oral intubation ACR (0.5 mg and 1mg/kg. B.W) and fructose (40% in drinking water) for 60 day on serum Glutathione (GSH) (mg/dl) concentration of adult male rats in three different times.

Group / Day	Control	T1	T2	T3
zero	59.8±0.01 a	58.2±0.02 a	59.3±0.02 a	57.2±0.02 a
30	59.5±0.02 A a	53.1±0.02 B ab	50.2±0.09 B ab	52.3±0.02 B ab
60	59.3±0.02 A b	47.8±0.02 B b	47±0.01 B b	48.8±0.01 B b

Values are expressed as mean ± SE, n = 10 each group. C: control group. T1: Animals received 0.5mg/kg B.W of ACR.T2: Animals received 1mg/kg B.W of ACR. T3: Animals received 40% of Fructose in drinking water. Different horizontally capital letters denote differences between groups, P<0.05 vs. control. Different vertically small letters denote differences within group, P<0.05 vs. pretreated period (zero).

Significant decrease in GSH concentration was observed following fructose exposure indicating a cause of oxidative stress. Several investigations reported that feeding high fructose diet in rats increased the rate of ROS production which might be responsible for oxidative damage of cellular constituent and diminished anti-oxidative capacity (48). In fructose fed rats free radical production could be enhanced during hyperinsulinemia and hyperglycemia which might be due to enhanced glycation and autoxidation of glucose. Besides, fructose itself could create oxidative stress (49). Feeding fructose will cause depletion in ATP due to increase its concentration in the formation of sugar phosphate. Such depletion will lead to decrease in denovo synthesis of GSH (a process required ATP) with consequent depression in its concentration (50).

Uric acid was shown to stimulate the local renin–angiotensin system, induce oxidative stress manifested by a rise in hydrogen peroxide -an important ROS in the body (51), leading to GSH depletion. Accordingly, hyperuricemia detected in the present study could be claimed as a possible cause of depletion in GSH concentration after fructose exposure. Besides, sorbitol could be converted to fructose in the proximal tubule, which is then metabolized by fructokinase, leading to ATP depletion, proinflammatory cytokine expression and oxidative stress (52). In addition to producing clear changes in glucose and lipid metabolism, fructose feeding creates an oxidant-antioxidant imbalance in cells and tissues (53) which might lead to depletion in the antioxidant defense system like GSH.

Serum Uric acid concentration: After 30 days of ACR administration in groups (T1 and T2) or exposure to 40% fructose (T3), a significant (P<0.05) increase in uric acid concentration was observed with mean values of (4.00±0.06), (5.70±0.03) and (5.46±0.02) for group T1, T1 and T3 respectively comparing to control group. Further significant (P<0.05) increase in this parameter at the end of experiment was observed respectively after treatments with two concentration of ACR groups (6.75±0.01), (9.15±0.01) or fructose group (8.51±0.02) comparing with the value in control group (Table, 4).

In conjunction with the result of (29 and 54), the present study showed that administration of ACR caused hyperuricaemia compared to untreated groups which might indicate renal dysfunction as the kidneys are the way of excretion of ACR and its metabolites. Hyperuricaemia could occur either due to decrease excretion or over production of uric acid or both (55). Obesity or lipid abnormalities might also contribute to the development of hyperuricaemia (56).

Table, 4: Effect of ACR (0.5 mg and 1mg/kg. B.W/ orally) and fructose (40% in drinking water) for 60 day on serum Uric acid (mg/dl) concentration of adult male rats in three different times.

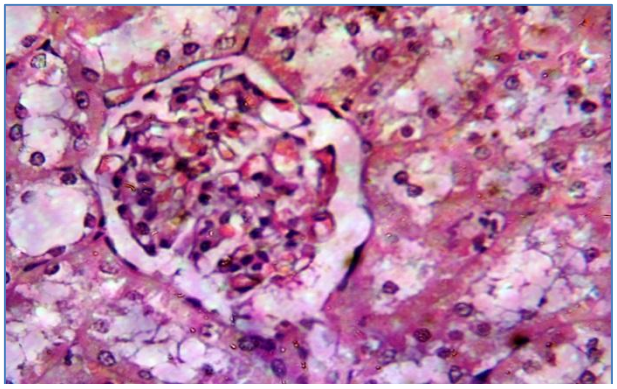
Group / Day	Control	T1	T2	T3
zero	2.36±0.07	2.34±0.07 c	2.23±0.06 c	2.37±0.06 c
30	2.23±0.07 C	4.00±0.06 B b	5.70±0.03 A b	5.46±0.02 A b
60	2.34±0.07 D	6.75±0.01 C a	9.15±0.01 A a	8.51±0.02 B a

Values are expressed as mean ± SE, n = 10 each group. C: control group. T1: Animals received 0.5 mg/kg B.W of ACR.T2: Animals received 1 mg/kg B.W of ACR. T3: Animals received 40% of Fructose in drinking water. Different horizontally capital letters denote differences between groups, P<0.05 vs. control. Different vertically small letters denote differences within group, P<0.05 vs. pretreated period (zero).

TAG level were significantly higher and HDL-C level was significantly lower in subject with hyperuricaemia (57). The previous parameters were similarly affected by ACR administration in this study which may explain the mechanism of ACR-induced hyperuricaemia. Decreased excretion of uric acid by cytogenetic agents (58) like ACR might also lead to hyperuricaemia. Besides, ACR is able to increase the release of ROS, LPO, inducing oxidative stress (59), accompanied by significant decrease in antioxidant level of kidney (60 and 61) and thus impaired its function leading to hyperuricaemia. However, the underlying cause of hyperuricaemia could be duo to malignancy, lymph proliferative disease, stone or tumor lysis syndrome (62). High dietary intake of fructose are documental contributed to hyperuricemia and MS (63). Increase in uric acid production was observed following intravenous fructose administration (64 and 65). Meanwhile, in fructose-fed rats, administration of allopurinol lowered uric acid levels and significantly reduced blood pressure (66). As well, impaired renal function in high fructose diet-induced metabolic syndrome was observed in rodents (67 and 68). The increase production of uric acid due to fructose metabolism might be related to the activity of ketohexokinase because it rapidly phosphorylates fructose to fructose-1 phosphate leading to marked ATP depletion (69).

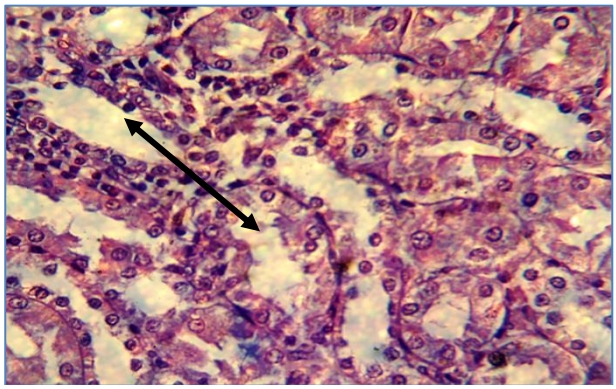
Such depletion in ATP and inorganic phosphate, important inhibitors of 5_nucleotidase and AMP-deaminase, will lead to elevation in uric acid formation by AMP degradation (70). Furthermore, it appears that the fructose- uric acid mediated effects might be explained on the fact that metabolism of fructose by fructoskinase would lead to generation of oxidants and the induction of leukocyte adhesion proteins (ICAM-1) and chemokine's (MCP-1) that act with result in combination with oxidative stress in local tubular injury, inflammation and accelerate the renal lesion (21 and 71), which might affect uric acid excretion.

Histological Examination: Comparing to the kidney section in the control rats which showed no observable histopathological lesion (Fig. 1).

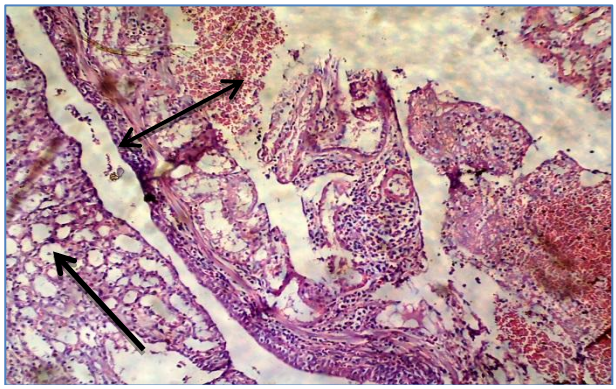


Figure, 1: Histological section in kidney of adult male rat(control) at day 60, showed normal structure of kidney. (H and E 40X).

Section in the kidney of rats administered 0.5 mg/kg. B.W of ACR for 60 days (T1) showed mononuclear cells aggregation particularly lymphocytes between renal tubules with moderated cellular degeneration of renal tubules (Fig. 2), while the microscopic examination of renal tissue of rat treated with 1 mg/kg B.W of ACR showed neutrophils in congested blood vessels and in the interstitial tissue with acute cellular degeneration of epithelial cells of renal tubules (Fig. 3). Another section from the same group showed marked vacuolar degeneration, desquamation of epithelial cells of renal tubes lead to occlude their lumen (Fig. 4).

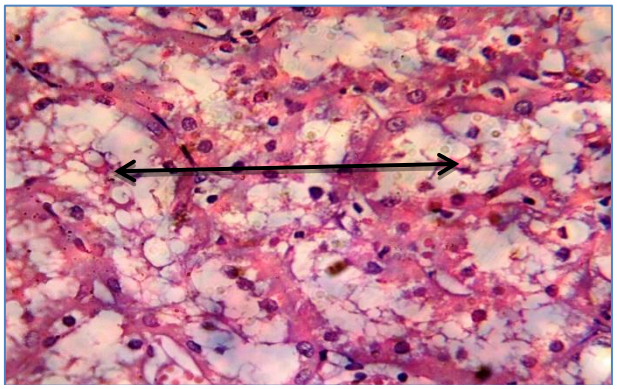


Figure, 2: Kidney of animal treated with 0.5mg/kg B.W of acrylamide for 60 days, showed mononuclear cells particularly lymphocytes aggregation between renal tubules with moderated cellular degeneration of renal tubules ⟷ (H and E stain 40X).

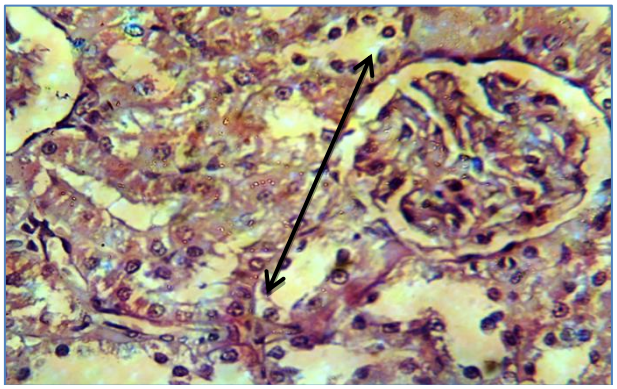


Figure, 3: Histopathological section in the kidney of adult male rat at day 60 post treated with 1mg/kg B.W acrylamide, showed neutrophils in congested blood vessels ⟺ and in the interstitial tissue with acute cellular degeneration of epithelial cells of renal tubules ⟶ (H and E stain 10X).

Acute cellular degeneration is characterized by enlargement of epithelial cells of renal tubules that leading to narrowing their lumen, in addition basophilic nuclei of epithelial lining cells of this tubules was showed in the kidney of adult male rat that received 40% fructose in drinking water for 60 day (Fig. 5). Orally consumed acrylamide is absorbed into the circulation, then distributed to various organs, and reacts with DNA, neurons, hemoglobin, and essential enzymes causing several toxic effects (30 and 31). Renal injury with swelling in the epithelial cells of the tubules with focal fibrosis between tubules (29) and mononuclear inflammatory cells, as well as, vacuolar degenerative changes of some cells lining the renal tubules and necrosis (54) was observed after ACR exposure in rats.



Figure, 4: kidney of animal treated with 1mg/kg B.W of acrylamide for 60 days, showed marked vacuolar degeneration, desquamation of epithelial cells of renal tubes lead to occluded their lumen ⟷ (H and E stain 40X).



Figure, 5: Histopathological section in kidney of animal at day 60 post-treated with 40% fructose, showed basophilic nuclei of epithelial cells of renal tubules with ⟷ acute cellular degeneration (H and E stain 40X).

The present study concluded that enhanced lipid peroxidation and deterioration of the antioxidant defense system that resulted from acrylamide exposure may play a significant role in the pathogenesis and deleterious histological changes (72). Concerning the effect of fructose on renal histology, high fructose consumption was associated with induction of MS accompanied with renal disturbances characterized by renal hypertrophy, glomerular hypertension and cortical vasoconstriction (73). The possibility that fructose might accelerate renal damage through its proinflammatory effects were recently investigated. The administration of a high fructose diet caused rapid worsening of proteinuria, renal function and more severe glomerulosclerosis (74) and tubulointerstitial disease in rats (75). Such renal damage may be attributed to poor excretion of fructose from the kidney and long period of dosing (76).

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تاثير الاكريلامايد والفركتوز في بعض المعايير ذات العلاقة بمتلازمة الأيض في ذكور الجرذان البالغة

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الخلاصة

صُمّمت هذه الدراسة للتحقق في إمكانية استحداث متلازمة الأيض باستعمال الأكريلاميد مقارنة مع الفركتوز في ذكور الجرذان البالغة. أُخِذَ أربعون من ذكور الجرذان البالغة وقسمت عشوائيا على اربع مجاميع كل مجموعة تحتوي على 10 جرذان، جرعت لمدة 60 يوم: مجموعة السيطرة، المجموعة الأولى والثانية جرعت الأكريلمايد (بجرعة 0.5 و1 ملغ/كلغ من وزن الجسم على التوالي، في حين أعطيت حيوانات المجموعة الثالثة الفركتوز بتركيز 40% في ماء الشرب. جُمِعَتْ عينات الدم بوساطة تقنية ثقب القلب (سحب الدم مباشرة من القلب) في ثلاث حقب من زمن التجربة (اليوم الاول قبل التجريع، يوم 30 و 60) لغرض

قياس تركيز مصل الدم للمعاير المرتبطة بمتلازمة الايض وكالآتي: الكولسترول في البروتين الدهني عالي الكثافة، الدهون الثلاثية، حامض اليوريك والجلوتاثيون. أظهرت النتائج أن التجريع الفموي لتركيزين من مادة الاكريلمايد و تعرض الفئران إلى٪ 40من الفركتوز في مياه الشرب تسبب في حدوث حالة متلازمة الأيض تجلت في حدوث ارتفاع في تركيز الدهون الثلاثية، انخفاض تركيز الكوليسترول في البروتين الدهني عالي الكثافة في مصل الدم وفرط حمض يوريك الدم. وقد رافق هذه التغييرات الوظيفية التغيرات نسجية في الكلية. حيث أظهر الفحص النسجي لبنكرياس الجرذان المعالجة بلفركتوز شق المتوسعة بين خلايا وجزر لانكرهانز وتنخر العنيبات. اظهرالفحص النسجي لكلية الجرذان المعاملة بالأكريلمايد الى حدوث تلف كلوي تمثل بتقشر وإنحطاط في الخلايا الطلائية للنبيبات الكلوية فضلاً عن ارتشاح الخلايا الالتهابية (اللمفاوية) بين النبيبات الكلوية، كما لوحظ حدوث تلف كلوي في الجرذان المعاملة بالفركتوز. يمكن الاستنتاج بأن الأكريلمايد قد تسبب في استحداث متلازمة الأيض في الجرذان كما هو الحال مع الفركتوز (المعروف بامكانية استخدامة في استحداث متلازمة الأيض). وفقا للمراجع المتوفرة ويبدو أن هذه الدراسة هي الأولى التي أظهرت تأثير مادة الأكريلاميد في بعض المعايير المتعلقة بمتلازمة الأيض.

الكلمات المفتاحية: الأكريلامايد، الفركتوز، متلازمة الأيض، الجرذان.