

# COMPARATIVE STUDY OF METFORMIN AND CAPTOPRIL ON INSULIN SENSITIVITY IN HIGH-FRUCTOSE FED RATS

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## ABSTRACT

Insulin resistance or compensatory hyperinsulinemia has been associated with dyslipidemia. Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) may be an important circulating cytokine which may provide a potentially reversible mechanism for mediating insulin resistance.

The present study was carried out to compare the beneficial effect of either the oral antidiabetic (metformin) or the angiotensin converting enzyme inhibitor (captopril) on insulin sensitivity in rats fed high-fructose diet for 9 weeks. Other contribution of this work is to find if the improving effect of metformin or captopril on insulin resistance occurs through modulation of TNF- $\alpha$  or not.

108 male albino rats were used throughout this study. The animals were divided into 6 equal groups (n=18). Group (1) served as a control received standard diet for 9 weeks. Group (2) received high fructose diet for 9 weeks. Group (3) received standard diet for 9 weeks and metformin treatment in a dose of 200 mg/kg/day in the last 3 weeks. Group (4) received high fructose diet for 9 weeks and metformin treatment in the last 3 weeks. Group (5) received standard diet for 9 weeks and captopril treatment in a dose of 2 mg/kg/day in the last 3 weeks. Group (6) received high fructose diet for 9 weeks and captopril treatment in the last 3 weeks. Insulin sensitivity test, intravenous glucose tolerance test (IVGTT), fasting serum insulin were all used to determine insulin sensitivity. In addition lipogram

and serum TNF- $\alpha$  were measured. Rats fed high fructose diet developed a significant insulin resistance as evidenced by impaired response to IP injection of insulin in a dose of 1 u/kg body weight. Also these rats showed impaired response to IVGTT. Furthermore these rats showed a significant increase in fasting serum insulin, TNF- $\alpha$ , triglycerides (TG), low density lipoproteins (LDL) with a significant decrease in high density lipoprotein (HDL) and no change in serum glucose and cholesterol levels. Administration of metformin or captopril to rats fed high fructose diet produced a beneficial comparable effect on insulin resistance, dyslipidemia & restored fasting serum insulin & TNF- $\alpha$  to control levels. A fall in TNF- $\alpha$  concentration may contribute to the restoration of insulin sensitivity. Furthermore these results suggest that metformin or captopril treatment could improve insulin resistance & dyslipidemia induced by a diet high in fructose & that these drugs might prove useful in the treatment of non-hyperglycaemic insulin resistant states.

## INTRODUCTION

Insulin resistance is a systemic phenomenon associated with several

diseases including chronic infection (1), cancer (2), obesity and especially non-insulin dependent diabetes mellitus (NIDDM) (3). Insulin resistance or hyperinsulinemia has been consistently associated with dyslipidemia in the form of hypertriglyceridemia and a decreased serum HDL and increased cholesterol level in cross sectional studies (4,5).

Tumour necrosis factor (TNF- $\alpha$ ) is a peptide constitutively expressed and secreted by adipose tissue (6). It has been demonstrated that TNF- $\alpha$  may be a mediator of insulin resistance that is known to occur in obese mice (7). TNF- $\alpha$  interferes with insulin action, probably by inhibiting tyrosine kinase activity of insulin receptors (8). Phosphorylation of the insulin receptor by this tyrosine kinase is known to be a cardinal step in the post receptor events that follow the binding of insulin to its receptor (9). Furthermore, it has been shown that, in adipocytes from obese subjects, the expression of TNF- $\alpha$  message and protein falls markedly after weight loss (10).

Metformin is a biguanide used extensively in type 2 diabetes. It inhibits hepatic glucose production & increases peripheral insulin sensitivity, but

doesn't cause hypoglycaemia (11). The mode of action of metformin is still incompletely understood; however, it appears that its major effects involve decreasing hepatic glucose output and thus lowering the insulin requirement (11). Metformin also may improve insulin sensitivity and decrease insulin levels by decreasing gut absorption of glucose, improving glucose uptake by tissues & increasing the number of insulin receptors (12 & 13).

Angiotensin converting enzyme inhibitors (ACEIs) have well documented effects in reducing blood pressure and improving other cardiovascular parameters in hypertensive individuals. The influence of ACE inhibitors, such as captopril, on glucose metabolism has also been studied, several clinical studies have shown that short and long term administration of captopril results in an increased insulin stimulated glucose disposal in diabetic or hypertensive individuals (14,15,16). The short term oral administration of captopril at dosages that have no effect on blood pressure has been reported to improve peripheral glucose utilization (17). However, it is currently unclear whether this captopril induced im-

provement in whole body disposal results from an alteration in skeletal muscle insulin signaling pathways, from improved muscle blood flow, or even from the combination of both (18). It has been suggested that ACE inhibitors may exert their effect on insulin sensitivity not only by blocking the renin angiotensin and kinin system but also by inhibiting production and/or release of endothelin (19). Rats fed with high dosages of fructose developed insulin resistance therefore, this study was undertaken to determine whether metformin or captopril could improve insulin resistance and the related abnormalities induced by high fructose diet feeding in normal rats.

## MATERIALS & METHODS

### *Drugs used:*

Metformin: Glucophage tablets, 500mg supplied by Cid Co.

Captopril: Capoten tablets, 25mg supplied by Squip Co.

### *Animals used:*

108 male albino rats were used throughout this study. At the beginning of the experiment, the rats were aged 2 weeks. Food intake was recorded daily & their weight was monitored weekly, they were put under similar



housing condition. They were divided into 6 experimental groups (n=18 per group)..

**Group (1) :** Control group, these animals received standard diet.

**Group (2) :** High fructose-fed rats. Rats received a diet in which fructose composed 33.64% of total carbohydrates (20).

**Group (3) :** Received standard diet & metformin in a dose of 200 mg/kg/day intragastric in water in last 3 weeks of the study (20).

**Group (4) :** Received high-fructose diet for 9 weeks and metformin treatment with the previous dose in the last 3 weeks.

**Group (5) :** Received standard diet for 9 weeks and captopril treatment in a dose of 2 mg/kg/day intragastric in the last 3 weeks (21).

**Group (6) :** Received high-fructose diet for 9 weeks and captopril in the previous dose in the last 3 weeks. The diets composition are described in (Tab.1)

Data are given in grams per 100g of dry weight. The salt mixture is expressed in grams per kilogram: CaH<sub>2</sub>PO<sub>4</sub>, 30g; KCL, 100g; NaCL, 100g; MgO, 10.5g; MgSO<sub>4</sub>, 50g; Fe<sub>2</sub>O<sub>3</sub>, 3g; and FeSO<sub>4</sub> 7H<sub>2</sub>O, 5g. Vitamins

are expressed per kilogram of the vitamin mixture: retinol, 539mg; cholecalciferol, 6.250mg; thiamine, 2,000mg; riboflavin, 1,500mg; niacin, 7,000mg; pyridoxine, 1,000mg; cyanocobalamin, 5mg; menadione, 1,000mg/kg; nicotinic acid, 10,000mg; o-choline, 136,000mg; folic acid, 500mg; p-aminobenzoic acid, 5,000mg; and biotin, 30mg/kg.

#### **Insulin sensitivity assay:**

In 6 animals of each group, insulin sensitivity was performed according to Surwit et al. (22). Rats fed either the standard diet or the high fructose diet fasted for 4 hours & injected intraperitoneally with regular insulin at 1U/kg body wt. Insulin was diluted in sterile saline for a final injected volume of 100  $\mu$ L. Plasma was collected for glucose quantification before injection & at 15,30,90 minutes after insulin injection.

#### **Intravenous glucose tolerance test (IVGTT):**

In 6 animals of each group IVGTT was done according to Rizk et al. (23). Rats were fed standard diet or high-fructose diet, fasted over night (18hs) and injected IV glucose in a dose of 1 gm/kg body wt. Plasma was collected for glucose quantification

before injection & at 0,15,30,60 minutes after glucose injection.

At the end of the experiment the remaining 6 rats of each group were decapitated after 14 hours of starvation and blood collected. Blood samples were allowed to clot & were centrifuged. Serum was separated & frozen at  $-70^{\circ}\text{C}$  until time of the assay of the following parameters:

Serum glucose: according to the enzymatic glucose oxidase method of Trinder (24).

Fasting serum insulin: according to Morgan & Lazarow (25) by radioimmunoassay using iodinated kit, manufactured by diagnostic production corporation.

Total serum cholesterol: using kits of biomerieux Co. according to Richmond (26), HDL & LDL according to Burstein (27) using kits of Biomerieux Co. and TG according to Fassati & Prencipe (28) using TG kits of Biomerieux.

Serum tumour necrosis factor alpha ( $\text{TNF-}\alpha$ ): according to Carti et al. (29) using a kit from immuno-tech (A Cloulter Co.) by enzyme

linked immunosorbent assay method.

### **Statistics:**

Statistical analysis of the result were carried out according to Pipkin (30) using students "t" test. P is significant at  $< 0.05$ .

## **RESULTS**

*Food consumption and weight of the rats:* Throughout the experiment, all groups had similar food intake. After 6 weeks, the body weight of the rats was similar in all groups.

*Insulin sensitivity (Tab. 2):* Rats received high fructose diet developed a significant insulin resistance as evidenced by impaired response to IP. insulin dose of  $1\text{u/kg BW}$ . On the other hand rats fed standard diet showed a significant reduction in plasma glucose in response to IP. injection of insulin in a dose of  $1\text{u/kg BW}$ .

*IVGTT (Tab. 3):* Rats fed high fructose diet showed a significant impairment in response to IV glucose administration compared to rats fed standard diet. Administration of either metformin or captopril for 3 weeks to rats fed high fructose diet significantly improved the IVGTT.

*Effect of either metformin or captopril on fasting serum glucose, insulin, cholesterol, HDL, LDL, & TG in rats fed either standard diet or high fructose diet (Tab. 4):* Rats fed high fructose diet for 9 weeks showed a significant increase in fasting serum TG, LDL & fasting serum insulin. On the other hand there was a significant decrease in HDL and no change in fasting serum glucose and cholesterol level.

Administration of metformin to rats fed high fructose diet in a daily dose of 200 mg/kg BW intragastric in the last 3 weeks produced a significant

decrease in serum fasting TG, LDL & insulin & TNF- $\alpha$  (but it produced a significant increase in HDL & no change in fasting serum glucose and cholesterol level (Tab.4).

Administration of captopril in daily dose of 2mg/kg body wt. intragastric in the last 3 weeks to rats fed high fructose diet induced a significant decrease in fasting, LDL, TG insulin & TNF- $\alpha$  but it induced no change in serum cholesterol and glucose levels. On the other hand captopril in the previous dose & duration induced a significant increase in serum HDL (Tab.4).

**Table (1): Diet composition of standard and high fructose diet (20).**

	Standard diet	High fructose diet
Glucose	38	15.96
Fructose	-	33.64
Wheat starch	20	8.40
Casein	23	23
Cellulose	6	6
Corn oil	5	5
Salt mixture	7	7
Vitamins	1	1



**Tab. (2):** Insulin sensitivity assay in rats fed either standard or high fructose diet for 9 weeks & fasted for 4 hours before intraperitoneal insulin injection in a dose of 1 u/kg body weight (n=6). M±SE.

Time (minutes)	Glucose (mg/dl)				
	Standard diet	High fructose diet	Standard diet + Metformin	High fructose diet+Metformin	Standard diet + Captopril
0	90±0.5	91±0.7 P1 NS	88±0.4 P2 NS	90±0.4 P3 NS	92±0.6 P5 NS P6 NS
15	70±0.3	85±0.4 P1< 0.05	72±0.3 P2< 0.05	75±0.4 P3< 0.05	71±0.2 P5< 0.05 P6< 0.05
30	60±0.5	75±0.6 P1< 0.05	61±0.4 P2< 0.05	66±0.5 P3< 0.05	62±0.6 P5< 0.05 P6< 0.05
90	55±0.6	70±0.7 P1< 0.05	57±0.6 P2< 0.05	56±0.5 P3< 0.05	57±0.3 P5< 0.05 P6< 0.05

P1: Test of significance between rats that fed high fructose diet & fed standard diet

P2: Test of significance between rats fed standard diet & treated with metformin versus rats fed standard diet

P3: Test of significance between metformin treated rats & fed standard diet versus metformin treated rats and fed standard diet

P4: Test of significance between rats received captopril & standard diet versus rats fed standard diet

P5: Test of significance between rats treated with captopril & fed high-fructose diet versus rats fed high-fructose diet.

P6: Test of significance between rats fed high-fructose diet & treated with captopril versus that fed high-fructose diet + metformin

\* NS = non significant

\*SE = Standard error

Tab. (3): Intravenous glucose tolerance test for rats. Rats were fasted over night (18 hours) before IV glucose injection at dose of 1 gm/kg BW.

Time (minutes)	Glucose (mg/dl)				
	Standard diet	High fructose diet	Standard diet + Metformin	High fructose diet+Metformin	Standard diet + Captopril
0	83.1±0.3	85.6±0.2 P1 NS	84.3±0.4 P2 NS	83.8±0.1 P3 NS	81.1±0.20 P5 NS P6 NS
15	100.6±0.1	146.8±0.3 P1 < 0.05	118±0.9 P2 < 0.05	129.2±0.3 P3 < 0.05	120.2±0.9 P4 NS P5 < 0.05 P6 < 0.05
30	137.5±0.2	177.4±0.5 P1 < 0.05	134.2±0.7 P2 < 0.05	161.2±0.5 P3 < 0.05	150.3±0.7 P4 NS P5 < 0.05 P6 < 0.05
60	97.3±0.4	134.2±0.4 P1 < 0.05	101.8±0.6 P2 < 0.05	114.4±0.6 P3 < 0.05	100.6±0.5 P4 < 0.05 P5 < 0.05 P6 < 0.05

P1: Test of significance between rats that fed high fructose diet & fed standard diet.

P2: Test of significance between rats fed standard diet & treated with metformin versus rats fed standard diet

P3: Test of significance between metformin treated rats & fed standard diet versus metformin treated rats and fed standard diet

P4: Test of significance between rats received captopril & standard diet versus rats fed standard diet.

P5: Test of significance between rats treated with captopril & fed high-fructose diet versus rats fed high-fructose diet

P6: Test of significance between rats fed high-fructose diet & treated with captopril versus that fed high-fructose diet + metformin

\*S.E. = Standard error

\* NS = non significant



Tab. (4): Effect of either metformin or captopril on fasting serum glucose, insulin, cholesterol, HDL, LDL, TG & TNF- $\alpha$  in rats fed either standard diet or high fructose diet (M $\pm$ SE).

Animal group (n=6)	Fasting serum glucose (mg/dl)	Fasting serum insulin (mu/ml)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)	TNF- $\alpha$ (pg/ml)
Standard diet (9 weeks)	75.2 $\pm$ 0.5	14.1 $\pm$ 1	80.5 $\pm$ 0.8	49.3 $\pm$ 0.4	37.8 $\pm$ 0.8	94.6 $\pm$ 0.7	0.91 $\pm$ 0.1
High fructose diet (9 weeks)	76.4 $\pm$ 0.3 P1: NS	24.3 $\pm$ 0.9 P1< 0.05	81.2 $\pm$ 0.9 P1: NS	25 $\pm$ 0.3 P1< 0.05	50.7 $\pm$ 0.9 P1< 0.05	135.2 $\pm$ 1 P1< 0.001	3.84 $\pm$ 0.25 P1< 0.001
Standard diet + metformin treatment 20 mg/kg BW for 3 weeks	74.5 $\pm$ 0.4 P2: NS	13.8 $\pm$ 0.6 P2< 0.05	80.5 $\pm$ 0.7 P2: NS	47.9 $\pm$ 0.6 P2< 0.05	36.9 $\pm$ 0.5 P2: NS	94.5 $\pm$ 0.8 P2< 0.05	0.95 $\pm$ 0.23 P2: NS
High fructose diet + metformin treatment 200 mg/kg BW for 3 weeks	73.9 $\pm$ 0.2 P3: NS	18.6 $\pm$ 0.8 P3< 0.05	79.9 $\pm$ 0.9 P3: NS	46.9 $\pm$ 0.7 P3: NS	35.9 $\pm$ 0.7 P3< 0.05	96.9 $\pm$ 0.6 P3< 0.05	0.98 $\pm$ 0.3 P3< 0.001
Standard diet + captopril treatment 2mg/kg BW for 3 weeks	74.8 $\pm$ 0.7 P4: NS	13.6 $\pm$ 0.5 P4: NS	81.1 $\pm$ 0.8 P4: NS	48.2 $\pm$ 0.3 P4: NS	37.3 $\pm$ 0.5 P4: NS	93.8 $\pm$ 0.9 P4: NS	0.96 $\pm$ 0.21 P4: NS
High fructose diet + captopril treatment 2mg/kg BW for 3 weeks	74.2 $\pm$ 0.2 P5: NS P6: NS	16.1 $\pm$ 0.3 P5< 0.05 P6< 0.05	80.5 $\pm$ 0.6 P5: NS P6: NS	49.1 $\pm$ 0.5 P5< 0.05 P6< 0.05	36.8 $\pm$ 0.2 P5< 0.05 P6: NS	95.1 $\pm$ 0.5 P5< 0.05 P6: NS	0.97 $\pm$ 0.24 P5< 0.001 P6: NS

P1: Test of significance between rats that fed high fructose diet & fed standard diet.

P2: Test of significance between rats fed standard diet & treated with metformin versus rats fed standard diet.

P3: Test of significance between metformin treated rats & fed standard diet versus metformin treated rats and fed standard diet.

P4: Test of significance between rats received captopril & standard diet versus rats fed standard diet.

P5: Test of significance between rats treated with captopril & fed high-fructose diet versus rats fed high-fructose diet.

P6: Test of significance between rats fed high-fructose diet & treated with captopril versus that fed high-fructose diet + metformin.

\* NS = non significant

\* SE = Standard error

## DISCUSSION

In the present work, the effect of either metformin or captopril on high fructose diet induced insulin resistance was studied. Insulin sensitivity is based on intravenous glucose tolerance and insulin sensitivity test (31,22). Furthermore fasting serum insulin has been used as an index of insulin sensitivity in several epidemiological studies, assuming that hyperinsulinaemia is a proxy of insulin resistance (32).

### *Effect of high fructose diet on fasting serum glucose, insulin, lipids and TNF- $\alpha$ :*

In the present study rats fed high-fructose diet showed significant increase in fasting serum insulin, TNF- $\alpha$ , TG & LDL. On the other hand there was a significant decrease in HDL and no change in fasting serum glucose & cholesterol levels as compared with rats fed standard diet. Insulin resistance has been proposed to: [1] elevated serum TG through increasing the production of very low density lipoprotein (VLDL) & reducing the catabolism of (VLDL) due to low lipoprotein lipase activity and to [2] lower serum HDL through decreasing the synthesis of HDL-cholesterol from LDL-triglycerides due to low lipopro-

tein lipase activity elevating fractional catabolic rate of apolipoprotein A-1 (the major apolipoprotein for HDL-cholesterol) elevating hepatic lipase concentration and increasing cholesteryl ester transfer protein activity. The results are in agreement with previous studies (5,6,35) which concluded that high-fructose diet produced insulin resistance in rats within 6 weeks due to decrease insulin receptor binding and post-receptor defects which are the most underlying explanation (36,37).

Furthermore, high-fructose fed rats showed a significant increase in TNF- $\alpha$  which may mediate insulin resistance (7). TNF- $\alpha$  induces an effect antagonistic to insulin, through the inhibition of insulin receptor tyrosine kinase (9). In addition, TNF- $\alpha$  may cause insulin resistance in vivo by raising free fatty acid concentration, which in turn impairs muscle glucose metabolism (38).

### *Effect of metformin administration in rats fed high-fructose diet:*

The results of the present study showed that metformin therapy improved insulin sensitivity, decreased serum insulin, TG and produced no change in serum cholesterol in high

fructose fed rats. These findings were in accord with Tobey et al. (39) and Faure et al. (20) who reported that the improvement of insulin sensitivity produced by metformin may be due to its potential antioxidant effect.

Furthermore metformin improved glucose uptake by the peripheral tissues which could result from increased insulin binding to its membrane receptors, from the activation of post-receptor metabolic pathways as well as from a beneficial effect on lipid metabolism (40,41,42).

Metformin administration in rats fed high fructose diet induced a significant increase in HDL and a significant decrease in LDL. These findings were in agreement with Perrillo et al. (43). This could be explained on the basis that metformin improved insulin resistance. In addition, metformin induced a significant decrease in  $\text{TNF-}\alpha$  in high fructose-fed rats which may explain the improving of insulin sensitivity. The finding of Dan Don et al. (7) supports this result as they reported that a fall in  $\text{TNF-}\alpha$  concentration contributes to the restoration of insulin sensitivity.

#### *Effect of captopril administration in*

#### *rats fed high-fructose diet:*

Administration of captopril to high fructose fed-rats induced improvement in insulin sensitivity associated with a significant decrease in serum TG, insulin and produced no change in serum cholesterol levels. These findings are in accordance with previous studies (14,15,16). They reported that in human & animal models of insulin resistance, ACE inhibitors increase sensitivity to insulin. Most previous investigations have attributed the influence of ACE inhibitors on glucose disposal to improved capillary blood flow & an accompanying increased delivery of insulin & glucose to muscle (44,45). Other investigators indicated that the improvement of insulin sensitivity following treatment with ACE inhibitors was due to increase in insulin-induced insulin receptors and insulin receptor substrate-1 phosphorylation (IRS-1) as well as IRS-1 phosphatidylinositol (PI-3) kinase association. Furthermore in the liver and muscle (21) it has been suggested that captopril induced improvement of insulin sensitivity via endothelin-1 inhibition(19). Endothelin-1 has potent glucogenolytic effect on hepatocytes & may cause insulin resistance in rat adipocyte.



Furthermae, captopril induced a significant decrease in TNF- $\alpha$  in high fructose fed rats as compared to rats fed standard diet treated with captopril. As TNF- $\alpha$  induced an effect antagonistic to insulin through the inhibition of insulin receptor tyrosine kinase (9), so the normalization of TNF- $\alpha$  levels can explain the improvement of insulin sensitivity with captopril treatment.

### Conclusions:

The present results provided additional evidence that feeding rats with high dosage of fructose leads to insulin resistance. On the light of this study, it could be concluded that captopril and metformin treatment has a comparable beneficial effect in the reversal of insulin resistance and its accompanying metabolic changes. TNF- $\alpha$  may be an important circulating cytokine which may provide a potentially reversible mechanism for mediating insulin resistance. Furthermore both captopril and metformin might prove useful in the treatment and/or preventing non-hyperglycaemic insulin resistance states such as obesity and impaired glucose tolerance as well as in the treatment of established NIDDM.

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## دراسة مقارنة لكل من دوائى الميتفورمين والكابتوبريل على حساسية الأنسولين فى الفئران البيضاء التي تغذت على كمية كبيرة من سكر الفركتوز

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قسم الفارماكولوجى الإكلينيكى - طب المنصورة

أجرى هذا البحث لدراسة ومقارنة التأثير الإيجابى لكل من الميتفورمين أو الكابتوبريل على حساسية الأنسولين فى الفئران البيضاء التي غذيت بكمية كبيرة من سكر الفركتوز لمدة ٩ أسابيع لإحداث مقاومة لمفعول الأنسولين بها وكان من أحد أهداف هذا البحث معرفة ما إذا كان التأثير المحسن لمفعول الأنسولين المحدث بهذه الأدوية من خلال استرجاع معامل تحليل الأورام ألفاً فى المصل إلى المستوى العادى أم لا .

استخدم فى إجراء هذا البحث عدد ١٠٨ فأر أبيض، وقسمت إلى ٦ مجموعات متساوية، كل منها يتكون من ١٨ فزر كالتالى :

**المجموعة الأولى :** ضابطة غذية بطعام لا يحتوى على نسبة عالية من سكر الفركتوز (غذاء قياسى) لمدة ٩ أسابيع .

**المجموعة الثانية :** غذيت بطعام يحتوى على نسبة عالية من سكر الفركتوز لنفس المدة السابقة.

**المجموعة الثالثة :** تكونت من فئران غذيت بطعام قياسى لمدة ٩ أسابيع وأعطيت دواء الميتفورمين بالفم بجرعة ٢٠٠ مجم/كجم يومياً خلال الثلاثة أسابيع الأخيرة.

**المجموعة الرابعة :** تغذت على طعام يحتوى على كمية عالية من سكر الفركتوز لمدة ٩ أسابيع وأعطيت دواء الميتفورمين بالفم بنفس الجرعة السابقة خلال الثلاثة أسابيع الأخيرة .

**المجموعة الخامسة :** تغذت على الطعام القياسى لمدة ٩ أسابيع وأعطيت دواء الكابتوبريل بالفم بجرعة ٢ مجم/كجم يومياً خلال الثلاثة أسابيع الأخيرة .

**المجموعة السادسة :** تكونت من فئران غذيت بطعام يحتوى على نسبة عالية من سكر الفركتوز لمدة ٩ أسابيع وأعطيت دواء الكابتوبريل بالفم بنفس الجرعة السابقة خلال الثلاثة أسابيع الأخيرة .

وتم قياس حساسية الأنسولين عن طريق إختبار تأثير حقن وحدة واحدة من الأنسولين لكل كجم من وزن الجسم فى الغشاء البريتونى للفئران وتم قياس مستوى الجلوكوز فى البلازما. وأيضاً دراسة تغير مستوى الجلوكوز فى المصل الناتج عن حقن سكر الجلوكوز بالوريد بجرعة ١ جم/كجم من وزن الجسم كدلالة على الحساسية لمفعول الأنسولين وكذلك لنفس الغرض تم قياس مستوى الأنسولين الصائم فى المصل. كما تم أيضاً عمل صورة للدهون فى المصل وكذلك قياس معامل تحليل الأورام - ألفا فى المصل.

#### ويمكن تلخيص نتائج هذا البحث كما يلى :-

تغذية الفئران بطعام يحتوى على نسبة عالية من سكر الفركتوز لمدة ٩ أسابيع أدى إلى إحداث مقاومة لمفعول الأنسولين التى ظهرت فى صورة خلل للاستجابة لحقن الأنسولين فى الغشاء البريتونى وأيضاً لحقن سكر الجلوكوز فى الوريد. كما أحدث هذا الغذاء زيادة ذات دلالة إحصائية فى مستوى الأنسولين الصائم فى المصل، وأدى كذلك إلى خلل فى مستوى الدهون بالمصل وإرتفاع مستوى معامل تحليل الورم - ألفا فى المصل، وعند إعطاء أى من الميتفورمين أو الكابتوبريل للفئران التى تغذت على طعام يحتوى على نسبة عالية من سكر الفركتوز حدث تأثير إيجابى ومفيد على المفعول المقاوم لعمل الأنسولين الصائم ومعامل تحليل الأورام - ألفا فى المصل أيضاً .

وعلى ضوء هذه الدراسة يمكن إستخلاص أن كل من دوائى الميتفورمين والكابتوبريل لهما تأثير متقارب على معالجة التأثير المقاوم لمفعول الأنسولين ومعالجة خلل مستوى الدهون فى المصل، وذلك عن طريق إنقاص تركيز معامل تحليل الأورام - ألفا فى المصل ولهذا فان هذين الدوائين قد تثبت فائدتهما فى الحالات التى تعاني من مقاومة مفعول الأنسولين .

