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### RESEARCH ARTICLE

## THE EFFECT OF EZETIMIBE ON GLYCEMIC PARAMETER IN IRAQI WOMEN WITH METABOLIC SYNDROME.

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#### Abstract

Metabolic syndrome is multiple clinical component that leads development of Type 2 Diabetes Mellitus, atherosclerosis and various diseases.

The study included 90 female with metabolic syndrome according to International Diabetic Federation (IDF) criteria. They divided into three groups (30 patients in each group)

First group put on diet restriction and physical exercise, the second group put on metformin 750 mg extended release once daily while the third group given ezetimibe 10 mg tab plus diet restriction and physical exercise. The duration of study 12 weeks, samples taken from each patients at zero time to determine baseline level and after 12 weeks including measurements of WC, BMI, FBS, FIHOMA-IR, HbA1c, TG and HDL.

**Results:-** Show significant changes in the measured parameter in the first group while highly significant changes in ezetimibe and metformin group

**Conclusion:-** From these noticeable changes in the patients taken ezetimibe we conclude that ezetimibe have effect in improving glycemic parameter in Iraqi metabolic syndrome women.

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#### Introduction:-

The metabolic syndrome is a clustering of components including hyperglycemia/insulin resistance, obesity and dyslipidemia (Putnam, Shoemaker et al. 2012). Metabolic syndrome also known as syndrome x, Reavansyndrome, insulin resistance syndrome and cardiometabolic syndrome (Ninomiya, L'Italien et al. 2004).

Historically In 1988, Gerald Reaven hypothesized that insulin resistance could be the underlying factor conjugating this constellation of abnormalities, which called "syndrome X (Das 2010).

Metabolic syndrome was defined by different association and organization, firstly The World Health Organization (WHO) first

was updated by the American Heart Association and the National Heart Lung and Blood Institute in 2005 (Villagra 2009). European Group for the Study of Insulin Resistance (EGIR) in 2004 also put diagnostic criteria. In 2005, the International Diabetes Foundation (IDF) developed its definition in 1998 (Kilpatrick, Rigby et al. 2007).

WHO have certain criteria for the definition and diagnosis the patient to have metabolic syndrome.

In 2001, (NCEP) and (ATP III) devised a definition for the metabolic syndrome which published new criteria for metabolic syndrome (Zimmet, Alberti et al. 2005) the focusing on thin in the measurement waist circumference. The criteria illustrated in table (1-1) below

**Table 1-1:-** Definition Of Metabolic Syndrome (Borch-Johnsen 2013).

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia <sup>‡</sup> (plasma insulin >75 <sup>th</sup> percentile)	Central obesity (waist circumference <sup>§</sup> ): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m <sup>2</sup>	Waist circumference: ≥94 cm (M), ≥80 cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria <sup>†</sup>		

\*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.

<sup>†</sup>Urinary albumin excretion of ≥20 µg/min or albumin-to-creatinine ratio of ≥30 mg/g.

<sup>‡</sup>Reliable only in patients without T2D.

<sup>§</sup>Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.

Rx, pharmacologic treatment.

The cut off point of waist circumference for Arab population for men ≥ 94 cm and for women ≥ 80 cm (Alberti, Zimmet et al. 2006)

### Pathophysiology:-

insulin resistance is the link between the different components of metabolic syndrome. It has strong association with obesity especially its central or visceral component (Shankar and Sundarka 2003). Metabolic Syndrome is the consequence of complex interplay between genetic and environmental factors (Thaman and Arora 2013). Central Obesity represent key element of metabolic syndrome the pathophysiology process which involving includes

### Central (visceral) obesity:-

which is in a simple way define as increase the number and size of the adipocyte in the abdomen and can be noticed by an increase in WC in both male and female according to (IDF) measurements. Under normal condition the lipolysis of TG content occurs under the effect of hormone sensitive lipase which is stimulated by sympathetic nervous system (O'Neill and O'Driscoll 2015). Insulin inhibits lipolysis process. In the insulin resistance the rate of lipolysis increases into FFA and glycerol. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle (Laclaustra, Corella et al. 2007). In the liver, FFAs result in an increased production of glucose and triglycerides and secretion of (VLDLs). (Home and Home 2005).

Free fatty acids responsible for insulin resistance in liver, and induce post signaling insulin resistance as mentioned in Randle cycle or glucose-Fatty acid competition cycle (Muoio and Neuffer 2012). Persistent insulin resistance

stimulates the pancreas to secrete additional amount of insulin to compensate the elevation in blood glucose creating what called hyperinsulinemia/euglycemia clamp. Continuous hyperinsulinemia with insulin resistance lead to exhaustion of beta cell in pancreas and development T2DM as shown in figure(1-2) (Jamson and De Groot 2015).

### Inflammation and role of cytokines in insulin resistance

In the state of central obesity (increase in number and size of adipocyte), various inflammatory mediators (cytokines) like Tumor Necrosis Factor -  $\alpha$ , C-reactive protein are produced and involved in the production of insulin resistance (Wisse 2004).

### Ezetimibe:-

Ezetimibe inhibits intestinal and excreted in bile absorption of cholesterol also phytosterol (Sudhop, 2002). A transport protein, Niemann-Pick C1-like 1 (NPC1L1) which found in the apical of enterocyte of intestine also liver, is the target of the drug. It is effective in the absence of dietary cholesterol because it also inhibits reabsorption of cholesterol excreted in the bile (Katzung, Masters et al. 2009).

In animal study EZM decrease fatty liver and improve insulin signaling (Jenkins, Toth et al. 2014). Also ezetimibe used to treat NAFL by decrease hepatic fat content (Ahmed, 2010)

### Patients and Method:-

In this study 90 patients with metabolic syndrome included in the study according to (IDF) criteria, for each group 30 patients enrolled:-

1. control group, patients put only on diet restriction and physical exercise.
2. metformin group, patients received metformin 750 mg extended release (gluophage XR)<sup>R</sup> formulation diet orally once daily at night in addition to diet restriction and physical exercise.
3. Ezetimibe group, in which patients receive ezetimibe 10mg tab orally 1hr before breakfast in addition to diet restriction and physical exercise. The following parameters measured for all participant starting from zero time (baseline level) and continued for 12 weeks, 10 ml venous blood sampling and they should be fasting overnight for 12 hr. waist, Body Mass Index (BMI), FBS, FI, HOM-IR, HbA1c, TG and HDL.

### Results:-

Using paired t-test statistically for results analysis

**Table (1-1):-** The Effects of Ezetimibe on Obesity and lipid Parameters

Parameters	Control group		Metformin group		Ezetimibe group	
	Base line	after 12 weeks	Base line	After 12 weeks	Base line	after 12 weeks
WC	115.2±74	110.62±0.66	117.1±5.7	93.68±0.72	118.83±5.76	103.51±0.72**
BMI	35.59±41	30.61±0.35*	36.98±1.17	27.73±0.88**	38.16±1.18	26±1.18**
TG	271.4±6.51	216.9±8.02*	277.33±70.5	148.5±4.6**	289.20±9.21	144.60±4.6**
HDL	33.4±0.16	41.75±0.67*	37.16±1.34	52.03±1.88	35.761±1.37	53.65±2.06**

**Table(1-2):-** The Effects of Ezetimibe on Glycemic Parameters of Studying Groups

Parameters	Control group		Metformin group		Ezetimibe group	
	Base line	after 12 weeks	Base line	after 12 weeks	Base line	after 12 weeks
FBS(mg/dl)	115.2±5.74	110.62±0.66*	117.1±5.7	93.68±0.72	118.83±5.76	93.68±0.72**
FI( $\mu$ l)	48.36±1.08	38.77±0.95*	49.26±1.51	24.63±0.75**	49.56±1.18	27.26±0.81**
HOMA-IR	13.8±0.35	10.58±0.2*	12.62±0.47	5.7±0.18**	14.54±0.44	6.59±0.17**
HbA1c(%)	6.43±0.12	5.82±0.09*	6.13±0.05	5.21±0.04	6.1±0.05	5.43±0.04**

### Discussion:-

In this study ezetimibe cause highly significant reduction in waist circumference and body weight which can explained by the ability of ezetimibe inhibit absorption of dietary cholesterol absorption.(Chan, Watts et al. 2010)also approved **Both weight loss and ezetimibe plus weight loss significantly reduced body weight, visceral and subcutaneous adipose tissues**. the results lead to decrease of lipoprotein contentcholesterol decrease. in addition ezetimibe will directly inhibit apo protein B100 of Very Low Density Lipoprotein (VLDL) leading to reduction of VLDL level .these overall effects lead to reduce fat contents in the body and especially visceral fat. (Takase, Dohi et al. 2012)ezetimibe, reduces visceral fat in patients with metabolic syndrome through significantly improved lipid profile.(Ohbu-Murayama, Adachi et al. 2015)C and biliary cholesterol. The effect of ezetimibe on insulin resistance recognized by changes in fasting insulin and fasting blood sugar ,this effect produce changing in HOMA-IR and HbA1c, and this related to incese free fatty acid and TG elevation which lead to insulin resistance and hyperinsulinemia which vicious cycle, so treatment with ezetimibe lead to reduction in insulin level and fasting blood sugar .(Deushi, Nomura et al. 2007)hypothesized that ezetimibe could directly affect insulin signaling in liver, and showed that ezetimibe dramatically enhanced insulin signaling (i.e., phosphorylation of IR, IRS-1, and Akt-1) in hepatocyte in vitro on in obese rat model of metabolic syndrome.

### Conclusion:-

From this study,the obvious improving effect of ezetimibe on both lipid and hyperglycemic parameters of patient with metabolic syndrom.

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