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Hepatotoxic of Glugophage

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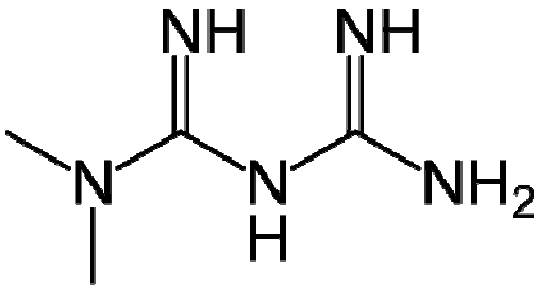
Abstract
Study aim to detection side effects of Glucophage in liver tissue in white albino mice, three doses used in present study, 50, 100, 150 mg\kg for 4 weeks, results of histology studying show that dose 150 mg\kg causes changes in liver of mice, infiltration and congestion, presence of edema fluid and changes in cytoplasm of hepatocyte was occur in liver of mice.
Study concluded that drug must be used in low dose in non-diabeticpation.
Keywords: Glucophage, infiltration, congestion

Introduction
Glucophage is an oral anti diabetic drug in the biguanide class, It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function fig (1) (1-3) Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor. Metformin works by suppressing glucose production by the liver.



Figure(1) chemical structure of Glucophage

Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglyceride levels, and is not associated with weight gain. As of 2010, metformin is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines (the other being glibenclamide)(4).
A review of intentional and accidental metformin overdoses reported to poison control centers over a five-year period found serious adverse events were rare, though the elderly appeared to be at greater risk (5). A similar study where cases were reported to Texas poison control centers between the years 2000 and 2006 found ingested doses of more than 5,000 mg were more likely to involve serious medical outcomes in adults(6).Survival following intentional overdoses with up to 63,000 mg (63 g) of metformin have been reported in the medical literature(7). Fatalities following overdose are rare, but do occur(8-9). In healthy children, unintentional doses of less than 1,700 mg are unlikely to cause any significant toxic effects.(10)
The most common symptoms following overdose appear to include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, rarely, hypoglycemia or hyperglycemia.(4, 6).The major potentially life-threatening complication of metformin overdose is lactic acidosis, which is due to lactate accumulation.(11, 12)
Treatment of metformin overdose is generally supportive, as there is no specific antidote. Lactic acidosis is initially treated with sodium bicarbonate, although high doses are not recommended, as this may increase intracellular acidosis (9). Acidosis that does not respond to administration of sodium bicarbonate may require further management with standard hemodialysis or continuous veno-venous hemofiltration. In addition, due to metformin's low molecular weight and lack of plasma protein binding, these techniques also have the benefit of efficiently removing metformin from blood plasma, preventing further lactate overproduction (13-15)
Metformin may be quantitated in blood, plasma, or serum to monitor therapy, confirm a diagnosis of poisoning, or assist in a medicolegal death investigation. Blood or plasma metformin concentrations are usually in a range of 1–4 mg/L in persons receiving the drug therapeutically, 40–120 mg/L in victims of acute overdosage, and 80–200 mg/L in fatalities. Chromatographic techniques are commonly employed.(16, 17).

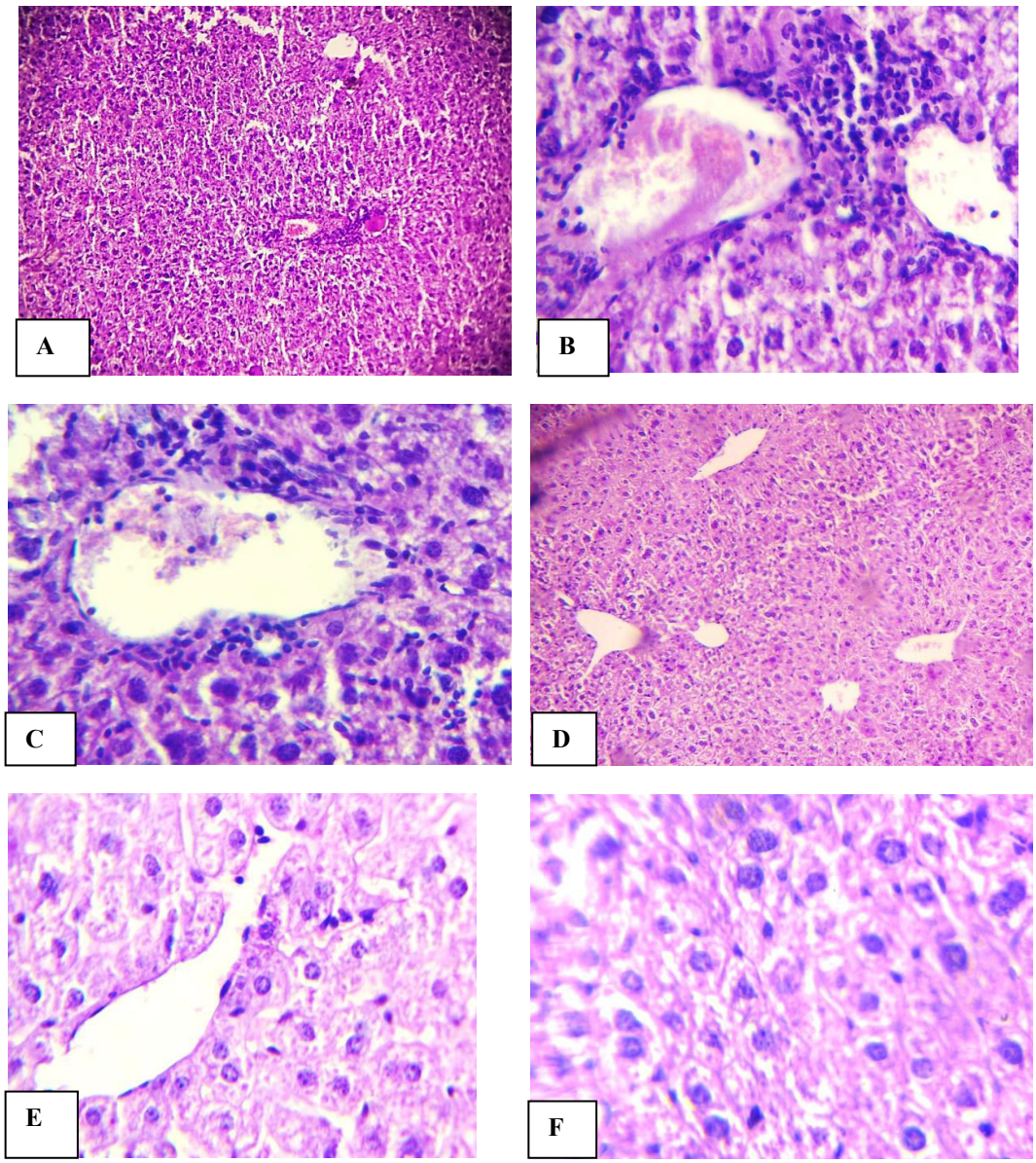
Material and methods

1- Animal lab. 30 whitealbino mice, have 25±5 gm weight were used in this study, animals divided into 3 group.Group A. animals treated by 50 mg\kg.Group B Animal treated by 100 mg\kg.Group C. treated by 150 mg\kg of glucophage (merck,santeSAS.) for 4 weeks then animal was victimized for histopathological changes in liver according to (21).

Results and discussion

Results of present study show that Glucophage (150 mg\kg) causes different effects on liver of mice. Hepatocytes losing normal architechere and presence of vascular congestion ,Leukocyte infiltration and presence of edam fluid in (figure 2-A), Leukocyte infiltration in central vein of liver in (figure 2-B) also absence of vascular congestion of central veins of hepatic lobules

Normal central vein in liver, losing nuclei of hepatocyte and vacuolization of cytoplasm in (figure 2-C and D), most hepatocyte losing their normal cytoplasm which have vacuoles (E).Presence of vascular congestion with few infiltration and vacuolization of cytoplasm (F) and Normal central vein in liver, losing nuclei of hepatocyte and vacuolization of cytoplasm in (figure 2-G).



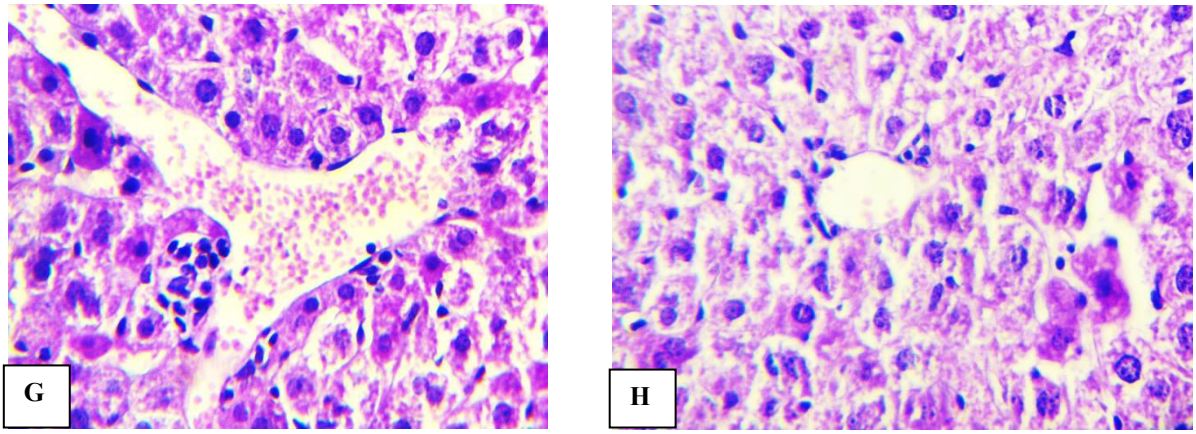


Figure (2) Histopathological changes in liver of mice treated by Glucophage
A- Hepatocytes losing normal architechereand presence of vascular congestion (200X).
B- Leukocyte infiltration and presence of odam fluid (400X).
C- Leukocytes infiltration in central vein of liver (400X).
D- Absence of vascular congestion of central veins of hepatic lobules (100X).
E- Normal central vein in liver, losing nuclei of hepatocyte and vacuolization of cytoplasm (400X).
F- Most hepatocyte losing their normal cytoplasm which have vacuoles(400X)..
G- Presence of vascular congestion with few infiltration and vacuolization of cytoplasm(400X).
H- Normal central vein in liver, losing nuclei of hepatocyte and vacuolization of cytoplasm(400X).

As a result of increasingused Glucophage in treated diabetic patients and non-diabetic patients, obese used this drug to decreased unfavorable weight especially obese women,Although of benefit of this drug in decreasing glucose level in blood it causes hypoglycemia in healthy persons used this drug in other uses in over dose , hypoglycemia causes lowering in pour level in cells thus cell began to uses pour storage in body then cells will die which causes different disease .

Metformin is a biguanide commonly used in type 2 diabetes and is considered to be a safe drug with minimalside effects. The antihyperglycemic effect of metformin iscaused by a decrease in hepatic glucose production, areduction in intestinal glucose absorption, an increase ininsulin sensitivity and an elevation in peripheral glucoseuptake and utilization. The results of the UK ProspectiveDiabetes Study indicated that metformin treatment wasassociated with a reduction in total mortality compared toother anti-hyperglycemic treatments and the Recommended treatment of choice for overweight type 2diabetic patients (22).Metformin-associated hepatotoxicity is very rare andfew cases have been reported in the literature (23-25).

These patients are presented with nausea, vomiting,weakness, jaundice with marked elevations in serum livertransaminases and intrahepatic cholestasis after initiationof metformin therapy. Pathophysiology of metformin-induced hepatotoxicity is unclear. However, it seems that acutehepatitis is caused by an idiosyncratic adversereaction to metformin. These cases suggest thatmetformin can induce acute portal and parenchymal inflammation. There has been no reported specifictreatment of metformin-associated hepatotoxicity. Afterdiscontinuation of metformin, the liver enzymes return tonormal values within a few weeks. Our case demonstrated the clinical and laboratoryfindings of metformin-induced hepatotoxicity and MALA.It is highly likelythat MALA and hepatotoxicity bothcontributed to clinical deterioration. In our institution, thelevel of metformin could not be measured, but otherpotential causes of wide anion gap metabolic acidosiswere not considered in our patient since acute onsetsymptoms developed immediately after initiation ofmetformin.

Overdose of acetylsalicylic acid might havecaused wide anion gap metabolic acidosis, but bloodsalicylate level was found within therapeutic range in ourpatient. Although the mechanism causing MALA is notclear, we believe that idiosyncratic hepatotoxicitytriggered MALA (26).

Present studyconclude that used metformin In over dose caused changes in liver.

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