Contents

Title	Page
1. INTRODUCTION AND AIM OF WORK	1-3
1.1. Aim of the work	2
1.2. Plan of work	3
2. REVIEW OF LITERATURE	4-31
2.1. The potent existence of fructose in our recent life	4
2.2. Absorption and metabolism of fructose	6
2.3. Hepatic uptake of glucose and fructose	8
Unique regulation of hepatic glucose uptake by fructose	10
2. 4. Characteristic features of fructose metabolism	11
2.5. Pathophysiology of Non-alcoholic fatty liver disease (NAFLD)	12
2.5.1.The 'first hit hypothesis' ,hepatic triglyceride accumulation, or steatosis	13
2.5.2. The '2-hit hypothesis' Steatohepatitis	14
2.5.2.1.Oxidative stress and mitochondrial dysfunction of hepatocytes	15
2.5.2.2. endoplasmic reticulum (ER) stress of hepatocytes	
2.5.3. The '3rd-hit hypothesis' (Hepatocyte death)	
2.6. Role of fructose in the pathophysiology of NAFLD	
2.6.1. Fructose mediated lipogenesis	18
2.6.2. Fructose mediated hepatic ATP depletion and hyperuricemia	20
2.6.3. Fructose mediated bacterial overgrowth in the small intestine	21
2.6.4 Fructose mediated insulin resistance	22
2.7. Fructose and metabolic syndrome	24
2.8. Adipose tissue as an endocrine organ: a key target for NAFLD	26

Title	Page
2.8.1. Adiponectin	27
2.8.2. Leptin and Ghrelin	28
2.8.3. Resistin	28
2.8.4. Tumer necrosis factor alpha (TNFα) and Interleukin-6 (IL-6)	
2.9. Probiotics as recent treatment of NAFLD	31
3. MATERIALS AND METHODE	32-46
3.1 Materials	32
3.1.1. Diets	32
3.1.2. Pure fructose	32
3.1.3. Lactobacilli probiotic treatment (Lacteol fort)	32
3.1.4. Experimental animals	33
3.2. Methods	33
3.2.1. Experimental design and animal grouping:	34
3.2.2. Sampling and tissue preparation:	34
3.2.2.1. Blood samples	34
3.2.2.2. Sacrifice of rats	35
3.2.2.3. Liver tissue samples	35
3.2.3. Blood biochemical analysis	36
3.2.3.1. Quantitative determination of fasting serum glucose level	36
3.2.3.2. Quantitative determination of triacylglycerols levels of serum	37

Title	Page
3.2.3.3. Quantitative determination of total cholesterol levels of serum	38
3.2.3.4. Quantitative determination of HDL levels of serum	38
3.2.3.5. Quantitative determination of serum Alanine aminotransferase enzyme activity	39
3.2.3.6. Quantitative determination of serum Aspartate aminotransferase enzyme activity	40
3.2.3.7. Quantitative determination of serum Albumin	41
3.2.3.8. Quantitative determination of serum insulin and TNFα by Enzyme- Linked ImmunoSorbent Assay method	
3.2.3.8.1. Quantitative determination of fasted serum insulin level:	
3.2.4. Liver tissue analysis:	43
3.2.4.1. Liver hemogenization:	43
3.2.4.2.Liver Hemogenate analysis:	43
3.2.4.2.1. Quantitative determination of reduced glutathione (GSH) level:	43
3.2.4.2.2. Quantitative determination of lipid peroxidase (Malondialdehyde) (MDA) level	
3.2.4.2.3. Quantitative determination of nitric oxide level	45
3.2.4.2.4. Quantitative determination of TNF-α level	45
3.2.5. Statistical analysis:	46
3.2.6. Calculation of percentage (%) of improvement	46

Title	Page
4. RESULTS	47-65
5. DISCUSSION	66-77
5.1. Effect of high fructose and supportive treatment on body weight and body weight gain	66
5.2. Effect of high fructose and supportive treatment on fasted serum glucose, insulin and insulin resistance	69
5.3. Effect of high fructose and supportive treatment on fasted serum TAG and TC	72
5.4. Effect of high fructose and supportive treatment on TC of serum lipoprotein fractions	73
5.5. Effect of high fructose and supportive treatment on the enzymes activity related to liver function and Albumin	74
5.6. Effect of high fructose and supportive treatment on liver MDA, GSH and NO	75
5.7. Effect of high fructose and supportive treatment on liver TNF-α	76
6. SUMMARY	78-80
Recommendation	80
7. REFERANCES	81-107
Arabic Summary	108-110

APPRIVIATIONS

ACC	Acetyl CoA carboxylase
ALT	Alanine amino transferase
AMP	Adenosine monophosphate
ANOVA	Analysis of variance
apoB	apolipoprotein B
AST	Aspartate amino transaminase
ATP	Adenosine triphosphate
DAG	Diacylglycerol
ER	Endoplasmic reticulum
FAS	fatty acid synthase
FFA	Free fatty acid
G-6-PD	glucose-6-phosphate dehydrogenase
GLUT 4	Glucose transported protein 4
GLUT 5	Glucose transported protein 5
GSH	Reduced glutathione
H ₂ 0 ₂	Hydrogen peroxide
НСС	Hepatocellular carcinoma
HDL	High density lipoprotein
H&E	Hematoxyline and eosin stain
HMP-Shunt	Hexose monophosphate shunt
HSCs	Hepatic stellate cells
KCs	Kupffer cells
IL	Interlukine
ICAM-1	Intercellular adhesion molecule 1
IR	Insulin resistance
IRS	Insulin resistance syndrome
LDL	Low density lipoprotein
LPL	Lipoprotein lipase
MDA	Malonyldialdehyde
NEFA	Non-esterified fatty acid

NF	Necular factor
NO	Nitric oxide
PDH	Pyruvate dehydrogenase
РКС	protein kinase C
rpm	Revolution per minute
ROS	Reactive oxygen species
SCD-1	stearoyl CoA destaturase-1
TAG	Triacylglycerols
ΤΝΓ-α	Tumor necrosis factor-alpha
VLDL	Very low density lipoprotein

6. SUMMARY

Nonalcoholic fatty liver disease is emerging as a common medical problem. It is usually associated with one or more of these conditions which are insulin resistance, type 2 diabetes, dyslipidemia and obesity. Recently they collectively termed as the metabolic syndrome. It is generally accepted that high fat diets can be used to generate a valid rodent model for NAFLD.

The present study aimed to experimental induction of NAFLD by using of high fructose in water (15%) in male Albino rats and to evaluate the biochemical and hormonal changes that occur in plasma and tissue which related to charbohydrate and lipid metabolism.

In addition, an attempt was made to clarify the role of some new probiotics represented by Lactobacilli as a supportive treatment of NAFLD.

The experiment was carried out on male Albino rats for a period of 13 weeks. Rats were divided into four main groups (C, F, FL and L groups) according to the type of the consumed drinking water. Control group fed with the normal tap drinking water, F group fed with tap drinking water with high fructose, FL group fed with tap water with high fructose and lactobacilli and finally L group fed with tap water with lactobacilli.

The effect of added fructose and treatment on body weight of rats was determined.

The effect of added fructose and treatment on serum glucose, insulin, HOMA-IR index, TAG, TC, LDL-TC, HDL-TC, ALT, AST, AST/ALT ratio and albumin were studied. In addition, MDA, NO, GSH and TNF α were measured in liver homogenate. Histopathological examination of liver tissue is carried out.

78

Results recorded in (7) tables (12) figures have been obtained statistical data and analysis showed the following:

1) Add fructose to drinking water to Albino rats for 13 weeks showed an increase in body weight of rats in all groups of rats compared to C group and also the treated groups showed a significant increase in body weight compared to F group.

2) A significant increase in the level of serum glucose in F and FL group compared to control group but serum insulin level stayed within normal level in the fasting state as well as insulin resistance in all groups of rats except (F) group which showed a moderate insulin resistance.

3) A significant increase in the concentrations of triglycerides and when there is not significant changes in total cholesterol there was a significant increase in total cholesterol of lipoproteins, low-density and very low-density, but highdensity showed no changing and that in the second group (F) compared to the control group and the third group (FL) showed significant decrease in the level of triglycerides and cholesterol lipoproteins, low-density and very low-density, compared to the F group.

4) There were no significant changes in the activity of the enzyme ALT and AST as well as the ratio of AST to ALT in groups, as well as the level of albumin in serum did not indicate any significant change in all groups.

5) A significant increase in the level of nitric oxide in the three groups compared to the control group, whereas the level LPO showed a significant increase in the F group compared to the control group and the significant decrease in the FL group compared to F group. Level of reduced glutathione did not show any change observed in any of the groups.

6) Liver TNF α level showed no significant deviation in all groups of rats.

Recommendation

Avoid the consumption of high fructose as it causes hyperglycemia, hyperinsulinemia, insulin resistance and hypertriglyceridemia and we advise giving probiotic to patients suffer from hepatic metabolic changes.