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Hepatic Safety in Rats Fed on Fructose, Glucose, or Sucrose When Combine with A Moderate Fat Diet

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Consumption of sweets, primarily fructose, and high-fat diets has notably increased in recent years. This food pattern highly associated with the widespread prevalence of obesity and its subsequent health problems, This study aimed to assess the detrimental effects of consuming animal fat plus either fructose, glucose, or sucrose in amounts that matched their realistic proportions in human meals. Sixty male albino rats were divided randomly into four groups (15/group). During 64 weeks, control group was fed a normal diet, every other group was given a moderate-fat diet (MFD) mixed with different fructose (F-MFD group), glucose (G-MFD group) and sucrose (S-MFD group). Compared to normal rats, there was a significant rise in serum triglycerides of F-MFD, up-regulation of expression of lipogenic genes, *ChREBP* and *SREBP-1c* and the proinflammatory gene *TNF-α* with minimal hepatitis. However G-MFD and S-MFD showed similar or lower changes of the same analyzed parameters. Sections of hepatic tissues revealed severe lesions in liver of G-MFD group but normal to mild changes in either F-MFD or S-MFD group. It could be concluded that fructose sugar and fat have minimal morbid effects when consumed with regular concentrations.

Keywords: fructose, glucose, sucrose, *ChREBP*, *SREBP-1c*, *TNF-α*.

Introduction

Since the beginning of the new century, people, particularly young ages, are obsessed with social media and time-consuming gaming through screen devices. Doubtless, social media has hugely provided instant unprecedented communication between not only countries but even individuals regardless their race, age, gender and educational level [1]. Eventually, people spend a long time engaged with screen devices with not only minimal physical activity but also minimal attention to their health and food quality. Alternatively, being very busy, most societies worldwide turned to fast meals and western pattern diet [2] . This pattern of dietary style is recognized by high fat and high sugar levels [3]. It is well known that fructose is not only sweeter than glucose and sucrose but also cheaper in price. Consequently, the consumption of fructose is markedly increasing in the last decade in the form of soft drinks and other beverages [4]. The connection between fructose intake and fatty liver is as old as history of foie gras (fatty liver) by feeding high fructose rich food, geese dates. Later on Justus von Liebig, a German chemist observed that simple monosaccharide enhanced hepatic fat deposition. By the 1960s large number of scientists revealed that the simple sugar was fructose and was clearly differentiated from glucose in its exclusive power to enhance both hepatic fat and plasma TGs [5].

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Accordingly, a strong connection has been discovered linking between consumption of sugar-added beverages, particularly fructose, with non-alcoholic fatty liver disease (NAFLD) [6]. Consequently, fructose potential mechanism, in fatty liver and related metabolic disorders, is now a major research subject [7]. Interestingly, fructose and glucose chemically are isomers; both of them have the same molecular formula of hexose monosaccharide ($C_6H_{12}O_6$) with one group different aldehyde in glucose and ketone in fructose. In addition, both constitute sucrose as a natural disaccharide. Nevertheless, glucose and fructose metabolic pathways are separate.

Fructose is predominantly metabolized in the hepatocytes (50–75%) where it is transformed to lipogenic building blocks including glyceraldehyde 3-P, acetyl CoA and diacylglycerol, which encourage lipid synthesis [8]. Unlike fructose, glucose is less lipogenic; glucose metabolism occur intrahepatic and extra hepatic tissue. Moreover, insulin firmly controls involvement of glucose in the glycolytic processes limiting its contribution in hepatic fat synthesis [9].

Carbohydrate response element-binding protein (*ChREBP*) is triggered in increased glucose intake and binds to carbohydrate response element (ChRE) [10]. *ChREBP* mediates lipogenic genes such as PK [11], FAS [3] , acetyl-CoA carboxylase (ACC)[12] and stearoyl-CoA desaturase 1 (SCD1) [13].

However, *ChREBP* knockout mice demonstrated fatal sucrose/fructose intolerance, suggesting a vital role of *ChREBP* in fructose metabolism [14].

In addition to initiating a thorough *de novo* lipogenesis pathway, sterol regulatory element-binding protein-1c (*SREBP-1c*) is also thought to be a mediator of insulin effect following carbohydrate consumption [15] Additionally, *SREBP-1c* down regulates phosphoenolpyruvate carboxykinase (*PEPCK*) transcription by displacing Sp1from the *PEPCK* promoter in response to insulin [16]. This stimulation of lipogenic genes and suppression of *PEPCK* leads to the hypothesis that *SREBP-1c* may controle the actions of fructose on gene expression.

Based on substantially published literature, there is a big agreement about the deleterious side effects of increasing fructose consumption; however the molecular mechanism underlying these effects is still unclear. Furthermore, surprisingly, the likely negative health effects of fructose were based on animal studies with difficulties in recording matching results from human similar conditions [17]. Interestingly, in experimental studies, fructose is supplemented in high concentrations equal up to 60 energy percent. On the other hand, 3.7 to 9% of total energy in the human diet is contributed by fructose [2,18]. As previously discussed, sugar consumption contributes to an adult energy range of 13.5-24.6% in 18 industrialised nations [19].

In the same way, most animal studies adapt fat content that is not matching its counterpart in human diet [17]. Additionally, fructose was typically administered through the drinking water in laboratory research, which resulted in excessive fluid intake and decreased consumption of solid foods. This imbalance alters the proportion of calories consumed as fat to carbohydrates and leads to a net increase in the caloric intake of the fructose groups [5]. Therefore, it could be challenging to distinguish between the impact of fructose and the high calorie consumption.

Accordingly, the current study is setup to mimic as identical as possible the condition of the three sugars consumption by human in order to circumvent the false effect of either over sugars intake or fat concentration targeting the actual contribution of any of the three sugars to metabolic disorders.

Material and Methods

The National Science Council's Guide for the Care and Use of Laboratory Animals (Date No. 16/6/2019) and the animal care policies of Kafr-Elsheikh University were both followed during all animal procedures. Sixty male albino rats weighing between 120 and 150 grams were obtained from the Egyptian Association of Biological Products and Vaccines (Agouza, Giza, Egypt). After being acclimated for 14 days, the animals were weighed and divided randomly into three dietary groups and control (n = 15 per group): a moderate fat high-glucose (G-MFD) diet, a moderate fat sucrose (S-MFD), or a moderate fat high-fructose (F-MFD) diet. The only difference between these diets was the composition of the sugar composition. As a control group, the 1th group continued on its normal chow diet. Animals were fed a moderately high-fat semi-synthetic diet (35.9 % fat). Table1 lists the precise dietary components [20]. The (G-MFD) diet contained 32.5 % glucose from (Piochem company, Egypt) while the (S-MFD) diet had 32.5 % sucrose (Piochem company, Egypt), and the (F-MFD) diet

contained 32.5% fructose (Piochem company, Egypt). Every animal's body weight was measured once a week while it was kept in an environment with good ventilation and a 12-hour light cycle. At the start of the experiment and after eight weeks, tail vein postprandial blood samples were taken for blood glucose test to ensure that they are non-diabetic. At the end of the 16th week, 1.9% inhaled diethyl ether was used to anaesthetize all animals before retro orbital blood collection was done in vacutainer tubes. Rats were then decapitated; the liver was immediately removed, and washed with saline. Each liver was split into two pieces, with one of them being frozen in liquid nitrogen for qPCR, while the other portion was kept in 10% formalin for histo-pathological examination.

Biochemical assays of serum lipids

Blood samples collected in plain tubes were left for 15 minutes before centrifugation at 3000 rpm for serum extraction. The extracted serum was used in evaluation of lipid profile using (Spinreact kits, Spain) following the manufacturer instructions.

Quantitative Real-Time Polymerase Chain Reaction (RT-PCR):

Using the QIAzol reagent, total RNA was extracted from the liver samples (Hilden, Germany, cat# 74536 QIAGEN Inc.). After that, RNA purity and concentration were measured spectrophotometrically at 260/280 nm. We use RNA for reverse transcriptase in cDNA synthesis using QuantiTect reverse transcription kit (Cat. No. 205311, Qiagen, USA) in accordance with the manufacturer's instructions. The Macrogen Company (Macrogen Company, GAsa-dong, Geumcheon-gu, Korea) manufactured the primers s (Table 2) after using the primer 3 software. SYBR green qRT-PCR (easy-REDTM total RNA Extraction Kit) was utilised with the real-time PCR technique. The conditions were as follows: 40 cycles of 15 s at 95°C, 30 s at 60°C, and 30 s at 72°C were performed preceded by 10 minutes of initial denaturation at 94/95C. Data collection was done with a Rotor-Gene Q (Qiagen), which assessed the threshold cycle value (Ct). The gene expression difference between experimental groups was evaluated using the method ΔΔ CT, normalized to β-actin, and expressed as relative mRNA levels compared with control.

Histopathological Examination

Fixed liver tissue underwent dehydration through repeated submersion in progressively higher alcohol concentrations, followed by washing in xylene before being embedded in paraffin blocks. Hematoxylin and eosin (H&E) was used to stain the paraffin blocks after they had been sectioned into 5 µm thick sections. Under a light microscope, the stained sections were viewed, photographed, and described for any hepatic abnormalities using a super-resolution digital camera computer interface (Nikon digital camera, Shinagawa-ku, Tokyo, Japan).

Statistical Analysis

One-way variance analysis (ANOVA) followed by Bonferroni's as a post-hoc test was used to check variances among different experimental groups (GraphPad Software Inc., San Diego, CA, USA). The significance of $p < 0.05$ is considered statistically significant. All data were expressed as means ± SE.

Results

Biochemical assays

Serum lipid profile assessment revealed highly significant at ($p < 0.0001$) increase in TG and LDL levels in F-MFD (figure 1) compared to not only normal diet fed animals but also to G-MFD and S-MFD groups. However, the three diets showed nearly the same effect on serum cholesterol and HDL.

Lipogenesis supporting genes SREBP-1c , ChREBP and Pro-inflammatory cytokine tumor necrosis factor (TNF-α) gene expression by qRT-PCR

The contribution of F-MFD, G-MFD and S-MFD feeding to hepatic lipid metabolism was investigated in comparison to control group via measuring the level of *SREBP-1c* and *ChREBP* expression in liver tissue. Generally, the three diets showed significant (P> 0.0001 for F-MFD or S-MFD and P> 0.001 for G-MFD) up-regulation of SREBP-1c expression (Fig.2). However, clear variation was observed between the effects of every diet on the level of ChREBP expression. In comparison with the control group, the level *ChREBP* expression displayed highly significant up regulation (P<0.0001) in F-MFD animals but less significant (P<0.001) up regulation in G-MFD and significant (P< 0.01) up regulation in S-MFD (Fig.2 right). Figure (2, C) depicts histograms demonstrating the level of TNF-α expression in hepatic samples of various groups of animals under investigation. Compared to control group, it has reported a highly significant (p< 0.0001) up regulation in F-MFD. In contrast, lower significant upregulation was recorded by either G-MFD or S-MFD.

Histopathological findings

The light microscopic examination of hepatic tissues sections obtained from every animal group and stained by H&E revealed according to Fig. (3), (A) liver of control rats showed normal hepatic architecture represented by cords of healthy hepatocytes organized around the central vein, while (B) of liver sections obtained from G-MFD revealed advanced and severe hepatic vacuolation and focal area of necrosis accompanied with mononuclear inflammatory cells infiltration mostly lymphocytes. In contrast, (C) represents hepatic tissues of S-MFD rats and showing moderate degree of hepatic vacuolation of granular cytoplasm consistent with glycogen storage. However, liver sections of F-MFD demonstrated mild degree of hepatic glycogen storage as seen in (D).

The figure shows (A) Represent the control group with normal liver lobule architecture. (B) displays liver tissue gained from G-MFD with intense lymphocytic infiltration in foci of necrosis and severe vacuolation of hepatocytes. (C) in which hepatic tissues of S-MFD rats with moderate degree of hepatic vacuolation of granular cytoplasm consistent with glycogen storage. (D) Demonstrates liver sections of F-MFD demonstrated mild degree of hepatic glycogen storage.

Discussion

To find chronic effects, the study was run for 16 weeks. Our hypothesis was that if there was any detectable difference between the three diets, it would most likely be noted in liver tissue, as this is where majority of fructose metabolism is reflected by changes in metabolic biomarkers, including serum lipids profile and genes that control sugar metabolism. Animals fed an experimentally westernized moderate fat diet did not show any change in body weight or fat-induced adiposity compared with the group fed the low-fat diet eat normally. However, plasma TG concentrations were increased by fructose content, as F-MFD rats had higher TG concentrations than both G-MFD rats and S-MFD animals.

These findings are backed by a meta-analysis in human that revealed that fructose adds to body weight in a manner similar to that of other carbohydrates [21,22]. Then, Sievenpiper et al. demonstrated that fructose consumption in comparison to glucose consumption, could elevate serum levels of uric acid and TG, but did not deteriorate insulin levels, fatty liver features or fibrotic markers mortar of lipid profiles [23]. Surprisingly, fructose may induce healthy changes on body weight and blood pressure in human related investigations [23,24].

It is still unclear what causes fructose to cause hypertriglyceridemia. On one hand [25], the exchange of fructose carbons into fatty acids by de novo lipogenesis may be attributable to both the increase in hepatic TG synthesis and VLDL-TG secretion, while also improving the levels of circulating TG [26]. On the other hand, fructose was proposed to hamper plasma clearance of TG-rich lipoproteins, since co-ingested fructose enhanced the TG response to a mixed food [27]. Consequently, both processes could differ depending on the population, the amount of fructose consumed, and additional nutrients.

Dietary components can affect plasma cholesterol levels. However, the findings were found to be consistent with other research in which rats fed a high-energy diet for 90 days had plasma cholesterol levels that did not significantly alter throughout the duration of the study [14,11]. The plasma HDL and LDL findings were consistent with the pertinent literature [28,12]. According to research, fat level in the diet has a greater impact on how HDL and LDL are regulated than carbohydrate content.

However, energy source intake can influence these parameters and insulin resistance, diabetes and other metabolic disorders begin with hyperlipidemia [13,29].

De novo lipogenesis is actually the primary aberration in NAFLD [30]. Although both monosaccharides increase lipogenesis, it is unknown if the composition or quantity of lipid changes as a result of glucose or fructose supplementation. The activation of the transcription factor SREBP1c by fructose has been shown to increase lipogenesis, either directly by increasing ER stress [31] or indirectly by causing insulin resistance and hyperinsulinemia because insulin promotes transcription and proteolysis of SREBP1c [14]. Contrarily, it has been observed that glucose activates ChREBP by increasing its expression, promoting nuclear entry, and binding to its downstream targets [15]. A new study in response to this paradigm, however, reveals that fructose also activates ChREBP, namely via triggering a second promoter in the ChREBP gene and an alternative splicing event to create the ChREBP- isoform [16].

Accordingly, our findings on gene expression showed strong agreement with previously published research. Human investigations have also revealed similar results, with raised SREBP1 levels in

individuals with fatty liver disease [32], while an increase in total expression ChREBP has been reported in insulin-resistant steatosis states [33]. In addition, knockout studies reported that exclusion of SREBP1c [13] or ChREBP [34] resulted in only a partial reduction in adipogenesis. Furthermore, while fructose and glucose regulate different subsets of lipid synthesis and storage enzymes, HFD alone does not regulate any lipid transcription factors and, in fact, the effects of fructose and glucose are impaired on HFD compared with the chow diet.

According to a large body of research, sugar consumption is one of the factors that triggers subclinical inflammation [35,36] . It is actually well-known that sugar boosts de novo synthesis of free fatty acids (FFA) in the liver [37,38]. The FFA derivatives may initiate inflammatory paths and produce free radicals, according to the lipo-toxicity theory [39,40].

In the current study, analysis of the liver tissue slides revealed that both diets induced liver tissue inflammation, which was particularly evident in the periportal regions, although without fibrosis. There is evidence for a special role for glucose in oxidative stress, which, in turn, may result in elevated biomarkers of inflammation chronicity, taking into account the influence of glucose, exhibiting larger and more visible lesions. Due to recurring hyperglycemia in the early postprandial phase and higher free fatty acid levels in the late postprandial phase, glucose has a high dietary glycemic index (GI), which is concomitant to augmented inflammation. Both are thought to trigger inflammatory cytokine release and excessive free radical renewal, which can both result in inflammation and vascular damage [10]. Because fructose has a low glycemic index, it is clear that eating foods with lower dietary GL/GI has anti-inflammatory effects. Therefore, because fructose consumption prevents glycemic spikes, it may help to reduce chronic inflammation [41]. This could be one explanation for why there haven't been any recurring warning signs or negative effects related to fructose consumption.

The manifestation of elevated hepatic TNF-α level, however, allowed us to identify the emergence of indirect inflammation. In this regard, information from laboratory and clinical investigations suggests that TNF-α not only activates the first stages of fatty liver disease but also changes the liver damage into more advanced stages [1].

Additionally, it has been noted that rats fed fructose can activate signalling pathways linked to liver inflammation [30]. Other mechanistic animal studies also demonstrate that fructose alters lipopolysaccharide endotoxin levels, promotes intestinal flora overgrowth with increased intestinal permeability, and activates Toll-like receptor 4 in hepatic Kupffer cells [22], whose activation leads to the release of several cytokines, including mainly TNF-α [30].

According to the overall results of the current study and previous investigations on either human or animal subjects, controlled fructose consumption is not more harmful to the liver with respect to subclinical inflammation than glucose or sucrose, as all of the aforementioned points have shown. Do not concur that managed fructose consumption is more harmful to the liver in terms of subclinical inflammation than glucose or sucrose, as was previously mentioned [42].

However, as reviewed before [42] the animal research was heterogeneous and certain comparisons had only a small number of trials, which provided scanty and untrustworthy evidence. As a result, all comparisons had poor meta-evidence ratings. Indeed, larger studies are needed to reach more conclusive findings about the pro-inflammatory and perhaps harmful effects of free fructose alone or fructose containing substance.

Conclusion

The data of this study concluded that consumption of a diet with regular concentration of sucrose or fructose combined with moderate fat content is hepatic-safe but glucose should be used with caution. Also, the data published in previous studies are not reliable being carried out using exaggerated concentrations of either or both of sugars and fat.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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TABLE 1. Composition of diet for all groups of rats

Normal chow diet		Moderate fat diet			
Component	**Percentage (by weight)**	**Component**	**Percentage (by weight)**		
Water	9.7%		F-MFD	G-MFD	S-MFD
Crude protein	20.5%	Normal chow diet			
Crude fat	4.6%	Fructose	32.5	-------	-------
Ash content	6.2%	Glucose	-------	32.5	-------
Nitrogen free extract	52.5%	Sucrose	--------	-------	32.5
Calcium	1.2%	Lipids*	18	18	18
Phosphorous	0.9%				
Lysine	1.3%				
Methionine + cysteine	0.7%				

*The lipid fraction contained 12.6 g sunflower oil, 2.16 g flaxseed oil and 3.24 g coconut (v/wt) [20].

TABLE 2. Primers sequence for qPCR.

Oligo Name	Sense 5` - Oligo Seq - 3`	Antisense 5` - Oligo Seq - 3`
TNFa	ACTGAACTTCGGGGTGATTG	GCTTGGTGGTTTGCTACGAC
SREBP-1c	CAGAGGGACTACAGGCTGAGAAAG	CACGTAGATCTCTGCCAGTGTTG
ChREBP	GAAGACGGCGGAGTACATCCT	TGGCAGCATTGAGCTCCTCTA
β-actin	TGTTGTCCCTGTATGCCTCT	TAATGTCACGCACGATTTCC

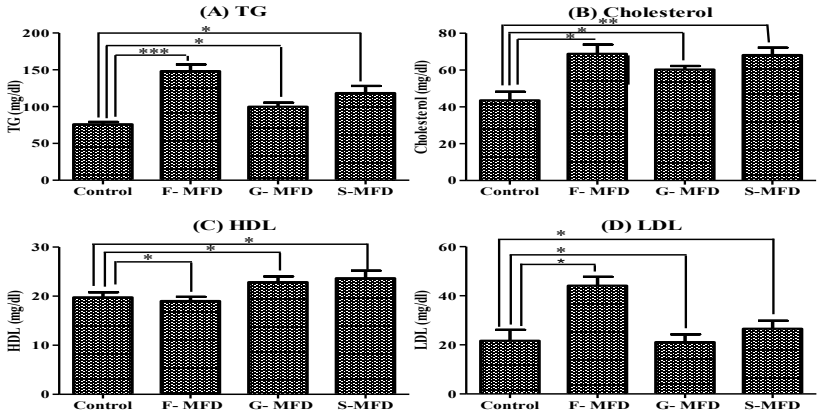

Fig. 1. The serum level of (A) Triglycerides (TG), (B) Cholesterol, (C) High density lipoproteins (HDL), and (D) Low density lipoproteins (LDL). Data were presented as mean ± SE. * significantly different at $p < 0.05$ using ANOVA followed by Bonferroni's as a post-hoc test, ** significantly different at $p < 0.01$, * significantly different at $p < 0.001$, ≠ no significantly difference.**

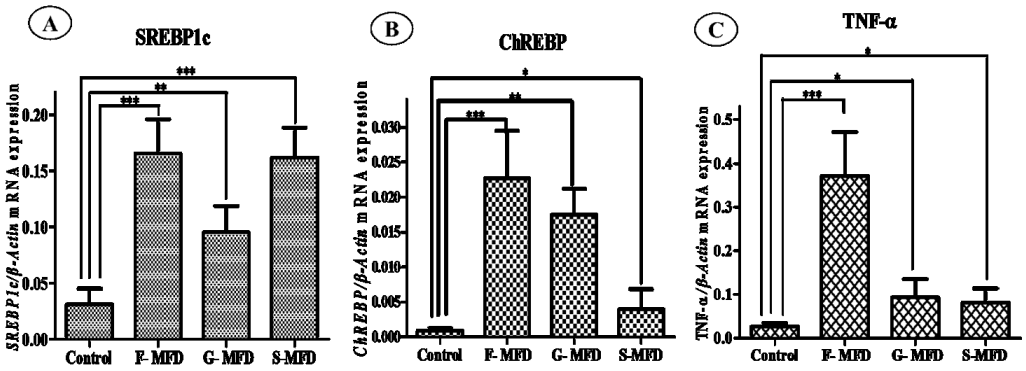

Fig. 2. Expression of genes *SREBP-1c, ChREBP* and *TNF-α*

(A) *SREBP-1c* and (B) *ChREBP,* The mRNA levels were assessed by qRT-PCR and adjusted to β-actin. Data Were the mean ±SE. (*) significantly different at $p < 0.05$ using ANOVA test, (**) significantly different at $p < 0.001$, (***) significantly different at $p < 0.0001$, using ANOVA test. (C) mRNA expression of tumor necrosis factor (*TNF-α*) gene. The mRNA expression levels were determined by qRT-PCR and adjusted to β-actin. Data are the mean ±SE (*) significantly different at $p < 0.05$ using ANOVA, (**) significantly different at $p < 0.001$, (***) significantly different at $p < 0.0001$.

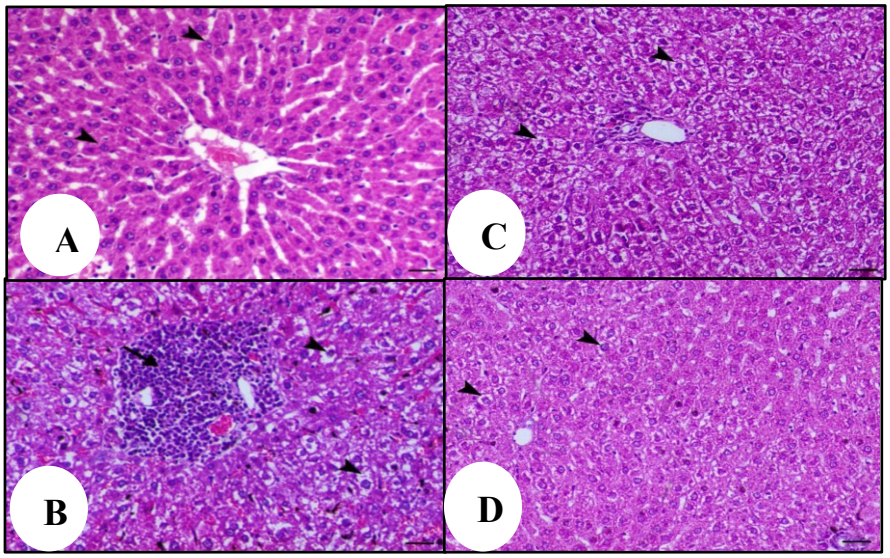

Fig. 3. Histopathological examination of hepatic tissue obtained from rats of tested groups

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مقارنة السلامة الكبدية في الفئران التي تتغذى على الفركتوز أو الجلوكوز أو السكروز عند دمجه مع نظام غذائي معتدل الدهون .

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في السنوات الأخيرة زاد استهلاك السكريات، وخاصتا سكر الفركتوز، مع الوجبات الغذائية الغنية بالدهون (الوجبات السريعة) بشكل كبير. وهذا النمط الغذائي له ارتباط كبير بانتشار السمنة على نطاق واسع ومشاكلها الصحية اللاحقة، وفقًا للأبحاث المنشورة على نطاق واسع. ومع ذلك، بالمقارنة مع الكميات التجارية المستخدمة فعليا، استخدمت غالبية الأبحاث محتوى أعلي من الدهون والسكريات.

لذلك فقد سعت الدراسة الحالية إلى تقييم واختبار الآثار الضارة للاستهلاك الدهون الحيوانية بالإضافة إلى السكربأنواعة المختلفة ،الفركتوز و الجلوكوز و السكروز بكميات تتناسب مع الواقع الملموس في وجبات الإنسان الطبيعية .

وبناء علية تم عمل الأتي.

تم تقسيم 60 فأرمن ذكور جرذ ألبينو إلى أربع مجموعات للدراسة (15 حيوانًا لكل مجموعة) خلال 64 أسبوعًا .

تم تغذية المجموعة الأولى بنظام غذائي طبيعي ، وتم إعطاء كل مجموعة الأخرى نظامًا غذائيًا معتدلًا من الدهون ممزوجًا بنوع سكر مختلف على النحو التالي:

المجموعة الثانية : أعطيت نظام غذائي معتدل الدهون مع سكر الفركتوز المجموعة الثالثة :أعطيت نظام غذائي معتدل الدهون مع سكر الجلوكوز وتم تغذية المجموعة الرابعة والأخيرة بنظام غذائي معتدل الدهون مع سكر السكروز.

ومقارنة بالفئران العادية ، أظهرت النتائج المكتسبة ارتفاعًا كبيرًا في نسبة الدهون الثلاثية في الدم بالمجموعة الثانية، وأرتفاع التعبير الجيني للجينات المولدة للدهون ، ChREBP و SREBP-1c والجين المسبّب للالتهاب TNF-α مع الحد الأدنى من التهاب أنسجة الكبد .

كما أظهرت مجموعات السكر الأخرى الثالثة و الرابعة تغيرات مماثلة أو أقل لنفس المعلمات التي تم تحليلها.

يمكن أستنتاج أن السكريات والدهون لها تأثيرات مرضية قليلة عند تناولها بتركيزات منتظمة (تناسب السعرات الحرارية اليومية) .

الكلمات الدالة : جلكوز ، فركتوز ، سكروز، .*ChREBP*, *SREBP-1c*, *TNF-α*.