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Hepatic Damage Induced By Fructose And Aspartame In Carbonated Drinks: Morphological And Histological Analysis In Adult Male Albino Rats

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Abstract

Objective: The study aims to analyze the changes produced by fructose and aspartame in regular and zero-calorie carbonated drinks respectively on the morphology and histology of the liver of adult male albino rats.

Methods: Regular and zero-calorie carbonated drinks in a dosage of 10 ml/kg body weight were administered by oral gavage daily to experimental groups B and C (10 rats in each group) respectively for 21 consecutive days. The weight of animals was noted at the start and end of the experiment. The liver was excised in each animal, weighed, fixed in formalin, and stained with Hematoxylin and Eosin and histological changes such as detachment of capsule, congestion and inflammation of portal triad were observed for comparison between the experimental groups.

Results: Results were recorded and analyzed in the form of photomicrographs. Observations showed a rise in the weight of animals and liver of experimental groups B and C compared to control group A. The shape of the liver was normal. Histological changes including detachment of capsule, inflammation of portal triad, congestion of hepatic sinusoids and portal triad, were observed in both the experimental groups indicating damage to hepatic tissue.

Conclusion: Therefore, it is concluded that consumption of regular and zero-calorie carbonated drinks should be restricted to avoid their harmful effects on the liver leading to hepatotoxicity.

Keywords: Fructose, Aspartame, regular and zero calorie carbonated drinks, liver.

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1. Introduction

For the past three decades, there has been a remarkable increase in the use of carbonated soft drinks because of their taste, and ability to energize and satisfy thirst.[1,2] Soft drinks do not contain alcohol and include carbonated drinks, bottled waters, energy drinks and fruit juices.[2,3] Both regular and zero-calorie carbonated drinks (e.g. coca Coca-Cola and Coke Zero respectively) contain carbonated water, caramel colour, phosphoric acid, natural flavours, citric acid and caffeine.[4-5]

Fructose in regular drinks is replaced by aspartame in zero-calorie carbonated drinks. Fructose, a monosaccharide, the sweetest of all sugars, is naturally present in honey, fruits and vegetables. LD50 of fructose is 4000 mg/kg in rats.[6] Fructose is metabolized primarily in the liver, where it is converted to fructose-1-phosphate, triose-phosphate, glyceraldehyde phosphate and ultimately to acetyl coenzyme by a series of reactions.[7-9] Fructose in regular carbonated drinks is associated with cardiovascular diseases, hypertension, type 2 diabetes, kidney dysfunction; and increased body weight.[10-13] Diets high in fructose are also responsible for causing nonalcoholic fatty liver disease, and oxidative stress along with gross and microscopic changes in hepatocytes.[14,15]

Aspartame, non-nutritive and non-caloric, is 160 times sweeter than regular sugar and is present in zero-calorie carbonated drinks e.g. diet Coke, Coke Zero etc.[16,17] Aspartame is mainly composed of L-aspartic acid and L-phenylalanine.[18] Each 100 ml of Coke Zero contains 52 mg of aspartame.[19] US Food and Drug Administration (FDA) estimated that aspartame can be consumed maximally from 22-34 mg/kg/day but a dosage of 50 mg/kg/day is associated with toxic effects such as headache, mood changes, dizziness, nausea and vomiting.[18]

The acceptable dose of aspartame in rats is 250 mg/kg/day. An oral lethal dose of aspartame in rats and mice is more than 10g/kg/day.[20]Aspartame is metabolized in the liver to 50% aspartic acid, 40% phenylalanine and 10% methanol. All these metabolites are toxic and can cause damage to various organs.[12,17]Aspartame intake is also associated with obesity, insulin resistance, type 2 diabetes mellitus, premature delivery, hepatotoxicity, nephrotoxicity,

increased carcinogenic potential and increased risk of metabolic syndrome, hypertension, heart attack and stroke that could be life-threatening.[21]

Limited research has yet been conducted to study the comparison of changes produced by fructose and aspartame in regular and zero-calorie carbonated drinks related to the histology of the liver. So, the study aims to compare the changes of regular and zero-calorie carbonated drinks on the biochemistry and morphology of the liver of adult male albino rats. These results would be helpful in our lifestyle modifications.

2. Materials & Methods

This randomized control study was conducted at Animal House Postgraduate Medical Institute Lahore for 21 days. Thirty, healthy adult male albino rats weighing 150-200 grams were used in this experimental study and were acclimatized for 7 days.

The random allocation of groups to the animals was done by lottery method and they were equally divided into three groups (10 in each group). Female rats and rats with signs of any illness were not included in the study. The sample size was estimated with an effect size of 0.81 and an error standard deviation of 4.50 by using power and precision 3.0 software. Keeping in view the reference taken from the study, [22] and many histological parameters under study the sample size is raised by 25% to 10 in each group.

Group A (Control) were given distilled water 10 ml/kg body weight orally by gavage for 21 days.

Group B (Experimental) was treated with 10 ml/kg body weight of regular carbonated soft drink (containing 720 mg of fructose) orally by gavage for 21 days.[23]

Group C (Experimental) was treated with 10 ml/kg body weight of zero-calorie carbonated soft drink (containing 5.2 mg of aspartame) orally by gavage for 21 days.[23]

The above dosage given to rats is equivalent to the consumption of 700ml of carbonated drinks daily in an average adult of 70kg. After acclimatization of 1 week, the body weight of the animals was noted at the start of the experiment. A good state of health of all the animals was ensured throughout the experimental period. The weight of the rats was noted at the end of the experiment i.e. at the time of scheduled sacrifice on the 22nd day, 24 hours following the last dose. The rats were euthanized and the liver was taken out by dissecting the falciform ligament and hepatic vessels and the weight of the liver was noted for each animal at the end of the experiment. After washing with saline and fixing in 10% formalin, transverse sections of 5 µm thickness were obtained and stained with haematoxylin and eosin, and slides were examined under a light microscope.

Data was analyzed by using SPSS version 23. Numeric data i.e., initial body weight, final body weight, liver weight and RTWI were presented in mean ± SD. Categorical data i.e. capsule of liver, inflammation in portal triad, congestion in hepatic sinusoids and portal triad, were presented in frequency and percentages. One-way ANOVA and the Kruskal-Wallis test were used to compare the means of numeric data among the groups. Chi-square and Fisher's exact test were used to compare the proportion of categorical data among the groups. A p-value ≤ 0.05 was considered as significant.

3. Results

The mean body weight of animals in all groups was not different significantly at the start of the experiment with a p-value = 0.883 but was significantly increased at the end of the experiment with a p-value < 0.001. However, no significant difference was found in body weight between experimental groups B and C as shown in Table 1.

Table 1: Body weight and weight of liver of rats (g) at the end of the experiment among Control and Experimental groups.

	Group	Mean ± SD	Min	Max	p-value
Body weight of rat after experiment (g)	**A**	162.5 ± 5.3	155.0	173.0	< 0.001*
	B	185.1 ± 8.4	175.0	203.0	
	C	181.1 ± 11.1	167.0	199.0	
Weight of liver (g)	**A**	4.9 ± 0.7	4.0	6.0	0.028*
	B	6.0 ± 1.1	5.0	8.0	
	C	5.8 ± 0.8	5.0	7.0	

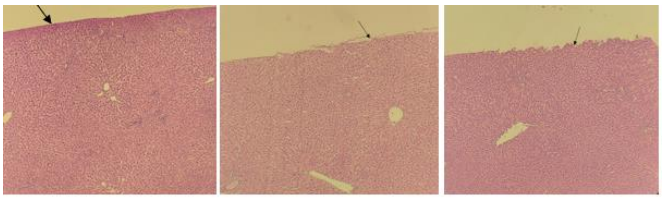
A significant difference in the mean of liver weight was found among the groups with a p-value = 0.028 as shown in Table 1. The weight of the liver of group B was significantly higher as compared to group A. However, no significant difference was found in liver weight between group A vs. C and group B vs. C.

The mean relative tissue weight index among the groups with p-value = 0.599 was not statistically significant.

Histologically, Group B and C (Figure 1) had statistically significant differences in detachment of the capsule of the liver from Group A whereas the difference between experimental groups B and C was not statistically significant as shown in table 2.

Table 2: Capsule of liver of rats in Control and Experimental groups.

Group	CAPSULE OF LIVER (10X)		Total
	Normal	Detached	
A	8 (80.0%)	2 (20.0%)	10 (100.0%)
B	3 (30.0%)	7 (70.0%)	10 (100.0%)
C	2 (20.0%)	8 (80.0%)	10 (100.0%)
Total	**13 (43.3%)**	**17 (56.7%)**	**30 (100.0%)**



1a 1b 1c

Figure 1: Photomicrograph of liver showing normal capsule in control group A (1a) and detachment of capsule in experimental group B and C (1b & 1c)(H&E x 10X) (Black arrow).

Inflammation in portal triad was observed and graded from 0 to 3 as Grade 0: no foci, Grade 1: <2 foci /200X field, Grade 2: 2-4 foci/200X field, Grade 3: >4 foci/200x field24 and was found statistically significant in experimental groups B and C in comparison of control group A whereas no statistically significant difference was found between the experimental groups B and C as shown in table 3. (Figure 2 & 3)

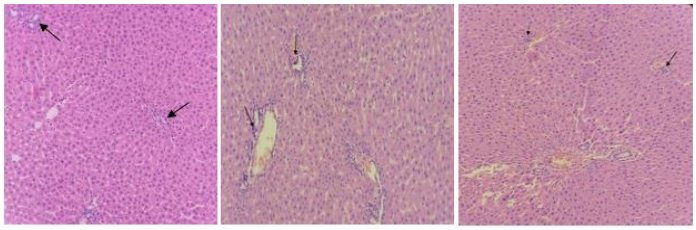
Table 3: Inflammation in the portal triad of Control and Experimental groups

Group	INFLAMMATION IN PORTAL TRIAD			Total
	Grade 0	Grade 1	Grade 2	
A	8 (80.0%)	2 (20.0%)	0 (0.0%)	10 (100.0%)
B	0 (0.0%)	4 (40.0%)	6 (60.0%)	10 (100.0%)
C	0 (0.0%)	2 (20.0%)	8 (80.0%)	10 (100.0%)
Total	**8 (26.7%)**	**8 (26.7%)**	**14 (46.6%)**	**30 (100.0%)**

Congestion of portal triad (20X) and hepatic sinusoids (40X) graded from 0 to 3 as Grade 0: No congestion, Grade 1: Mild congestion, Grade 2: Moderate congestion, Grade 3: Severe congestion[25]were observed in both the experimental groups and was statistically significant in comparison to control group A whereas difference between group B and C was insignificant as shown in table 4. (Figure 4)

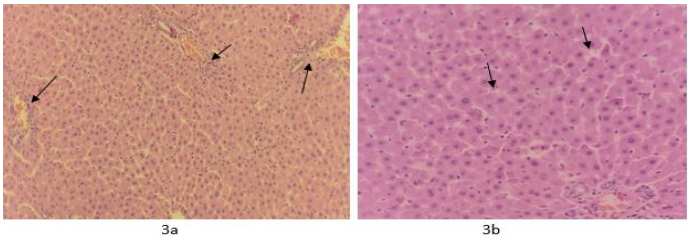
Table 4: Congestion in hepatic sinusoids and portal triad of Control and Experimental groups

Group	Congestion In Hepatic Sinusoids And Portal Triad				Total
	Grade 0 (Normal)	Grade 1	Grade 2	Grade 3	
A	7 (70.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	10 (100.0%)
B	0 (0.0%)	2 (20.0%)	3 (30.0%)	5 (50.0%)	10 (100.0%)
C	0 (0.0%)	1 (10.0%)	3 (30.0%)	6 (60.0%)	10 (100.0%)
Total	**7 (23.3%)**	**6 (20.0%)**	**6 (20.0%)**	**11 (36.7%)**	**30 (100.0%)**



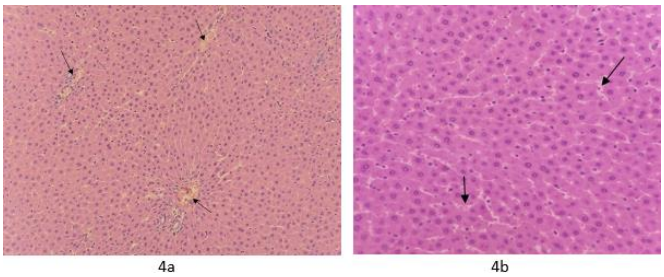
2a 2b 2c

Figure 2: Photomicrograph of liver of control group A (2a) showing no inflammation and group B and C (2b & 2c) showing Grade 2 inflammation in the portal triad (H&Ex20X) (Black arrows).



3a 3b

Figure 3: Photomicrograph of the liver of experimental group B showing congestion of portal triad (3a) (H&Ex20X) and hepatic sinusoids (3b) (H&Ex40X)



4a 4b

Figure 4: Photomicrograph of the liver of experimental group C showing congestion of portal triad (4a) (H&Ex20X) and hepatic sinusoids (4b) (H&Ex40X)

4. Discussion

The increase in weight of animals and liver associated with the consumption of fructose-containing carbonated drinks is due to its primary metabolism in the liver and its metabolites responsible for lipogenesis, gluconeogenesis, dyslipidemia and insulin resistance leading to obesity and nonalcoholic fatty liver disease.[26] Sadowska and Rygielska also observed weight gain in male Wistar rats after giving a fructose-rich diet for 7 weeks.[27] A noteworthy increase in the weight of the liver of rats was also observed by Suzuki et al. after giving a fructose-rich diet for 4 weeks.[28]

Aspartame is also responsible for the increase in the weight of animals and livers. Adaramoye and Akanni also concluded that administration of aspartame in a dosage of 35mg/kg and 70mg/kg daily orally for consecutive 9 weeks resulted in a significant increase in the weight of the brain and liver in rats.[29] However, in contrast to the results of the present study, Alkafafy et al., 2015 concluded that the rats who received high doses of aspartame (1000 mg/Kg BW) showed a significantly lower body weight gain in comparison to those who received the low doses of aspartame i.e. (250 mg/Kg BW) for 8 weeks.[30] Weight gain caused by aspartame is because the metabolites of aspartame are more harmful than aspartame itself.[18] Intake of aspartame unveils several essential factors leading to obesity such as decreased inflammatory response, imbalance of gut microbes, increased release of inflammatory cytokines and infiltration of macrophages in adipose tissue.[31]

Histological changes including a detachment of the capsule, inflammation in the portal triad, and congestion in hepatic sinusoids and portal triad were seen in both the experimental groups with statistically significant p-values < 0.001. The results are similar to Lu et al.who observed oxidative stress in the liver and the release of inflammatory cytokines in mice after giving high fructose water for consecutive 8 weeks.[32] Kashif also observed changes similar to the results of the present study and noticed lymphocytic infiltration and congestion of hepatic sinusoids with aspartame when given in a dosage of 200 mg/kg for 3 weeks.[33]

Fructose causes damage to hepatic tissue because the liver is the primary site for its metabolism. Increased intake of fructose is responsible for the activation of enzymes (aldolase B and triokinase) responsible for the breakdown of fructose to pyruvate and acetyl-CoA, leading to lipid dysregulation. Fat accumulation and oxidative stress play a significant role in the pathogenesis of liver damage. Fructose is also responsible for causing hepatic damage by altering calcium homeostasis.[34] In contrast to fructose, aspartame caused hepatic damage by reducing the action of antioxidant enzymes and augmenting lipid peroxidation leading to inflammation and cell necrosis via activation of p53. p53 in turn causes inhibition of transcriptional factors (principal regulators of glucose and lipid metabolism) as a result of which there is a change in lipid serum levels leading to lipid accumulation. The process of gluconeogenesis is also impaired leading to hypoglycemia.[35]

At the root of all discussion arguments, there is a uniformity in the pattern of results where almost all parameters had statistically significant differences between control and treated groups, but no statistically significant difference amongst treated groups was observed.

The duration of the study was short and the sample size was small. More research work needed to be done in a large group of the study population to establish statistically significant differences between the harmful effects of fructose and aspartame-containing carbonated drinks. This may be helpful in aware the general population about the hazardous effects of carbonated drinks on vital organs.

5. Conclusion

The findings of this study suggest that fructose and aspartame in regular and zero-calorie carbonated drinks respectively have the potential to alter the body weight of albino rats, the weight of the liver and the histological architecture of the liver after consumption for a short period. The changes were statistically significant in comparison to the control group but statistically insignificant between the experimental groups, so it is concluded that consumption of regular and zero-calorie carbonated drinks should be restricted by the general population to avoid their harmful effects on the liver leading to hepatotoxicity.

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Contributions:

F.S, M.S, H.N, S.I - Conception of study
- Experimentation/Study Conduction
F.S, A.A, S.M - Analysis/Interpretation/Discussion
F.S, A.A, H.N - Manuscript Writing
F.S, M.S, S.I, S.M - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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