# EVALUATION OF THE EFFECTS OF ALCOHOL AND HIGH-FRUCTOSE CORN SYRUP ON METABOLIC PARAMETERS, SERUM FREE FATTY ACIDS, AND LIVER TISSUE OF RATS

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***ABSTRACT***

***Background and aim****: A number of histopathological and metabolic changes occur worldwide, primarily involving the liver, due to increased consumption of alcohol and high-fructose corn syrup. In our study, we tried to reveal the changes caused in the liver and in serum free fatty acids (FFA) by a diet of alcohol and high-fructose corn syrup (HFCS).*

***Methods****: Twenty-four adult male Sprague-Dawley rats were divided into three groups, with eight of them in each group. All rats were fed ad libitum with normal pellets. The rats in group one received normal drinking water, those in group 2 received a mixture of 10% ethanol and drinking water, and those in group 3 received 55% HFCS dissolved in drinking water. Liver tissue samples were stained with hematoxylin and eosin. Simultaneous analysis of fatty acids was conducted on blood samples using a gas chromatography mass spectrometry device.*

***Results****: Weight gain in the group fed only HFCS was found to be significant (p=0.03). Blood sugar levels were not significantly different between the groups. When the lipid profile was examined, low-density lipoprotein (p=0.038) and high-density lipoprotein (p=0.08) cholesterol levels were found to be significantly higher in the fructose-consuming group. In the comparative evaluation of FFA between groups, C18:2 level was found to be highest in the normal group and lowest in the fructose-consuming group (p=0.07). In the histopathological evaluation of the liver, steatosis and hydropic degeneration in hepatocytes were observed in the two groups fed alcohol and HFCS, and they were more prominent in the alcohol-consuming group than in the fructose group.*

***Conclusion****: Alcohol and fructose caused damage to hepatocytes and sinusoids in the liver, and the levels of C18:2 (long-chain fatty acids) in serum were found to be significantly low, especially in the fructose-consuming group.*

***Keywords:*** *high fructose corn syrup, serum free fatty acids, liver.*

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## Background and aims

Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease, which are two major liver diseases, are the leading causes of chronic liver disease. Today's changing lifestyles and eating habits hold responsibility, especially for NAFLD. It has been stated in recent studies that consumption of food containing high-fructose corn syrup (HFCS) may be associated with NAFLD and non-alcoholic steatohepatitis (NASH)[1,2].

HFCS and sucrose are among the main sweeteners used in desserts and beverages. HFCS consists of 55% fructose and 45% glucose[3,4]). It has been reported that excessive consumption of beverages sweetened with HFSC increases lipogenesis in the liver and is associated with metabolic syndrome and obesity[5,6]. It is known that the basis of the pathogenesis of NAFLD is the accumulation of triacylglycerol (TAG) synthesized from fatty acids in hepatocytes, but the change in serum free fatty acids (FFA) in this process has

been demonstrated with different results in different studies[7]). It is also known that alcohol increases de novo lipogenesis similar to fructose, resulting in dyslipidemia, hepatic steatosis, and insulin resistance[8].

Although it is known that both alcohol and HFCS increase de novo lipogenesis, their relationship with serum FFA has not been adequately evaluated in the literature, and different results have been reported in studies conducted in this area. In our study, we analyzed serum FFA and liver tissue in rats fed HFCS and alcohol, and we aimed to evaluate the effects on metabolic parameters occurring along with itself.

## Materials and methods

### *Rats*

Twenty-four adult male Sprague-Dawley rats were divided into three groups, with eight of them in each group. Rats in the first group were fed ad libitum daily for 8 weeks with pellet mouse feed accompanied by normal drinking water. Rats in group 2 were fed ad libitum daily for 8 weeks with pellet mouse feed supplemented with 10% ethanol dissolved in drinking water, and those in group 3 were fed ad libitum daily for 8 weeks with pellet mouse feed accompanied by 55% HFCS dissolved in drinking water. All animals were kept under standard light for 12 h of daylight and in darkness for 12 h, and were sacrificed by anesthesia with ketamine at the end of 8 weeks.

### *Liver pathology*

Liver tissue samples were extracted by a necropsy conducted at the end of the 8th week for histopathological evaluation and fixed in 10% formalin solution for 48 h. They were embedded in paraffin blocks for routine tissue processing. Sections with a thickness of 4 μm were taken from each block. Preparations arranged for histopathological examination were stained with hematoxylin-eosin (HE) and examined under a light microscope (Leica DM 1000, Germany). The sections were evaluated according to histopathological findings as none (-), mild (+), moderate (++), or severe (+++).

### *Blood samples for FFA*

Serum samples of 200 $\mu$L were precipitated with 1 mL of 0.05% H2SO4, and fatty acids were extracted by vortexing for 60 s with 3 mL of ethyl acetate. Blood was collected from the heart of rats for biochemical measurements, fatty acid evaluation, and liver analysis.

Simultaneous analysis was performed with FID and MS detectors by using an SGE brand BPX90 (100 × 0.25 ID) column in an Agilent 7890A/5970C model gas chromatography mass spectrometry (GC-MS) device. The chromatographic conditions were as follows: the furnace temperature was started from 1200C and reached 2500C at 50C/min, followed by a waiting period of 3 min, and then reached 2600C at 20C/min, followed by a waiting period of 8 min, with a total time of 40 min. The injection volume was 1 $\mu$L, and the split ratio was 1/10. The solvent delay time was selected as 12 min, carrier gas was selected as He, and when the constant gas flow was set as 1 mL/min, the H2 flow was automatically adjusted by the program at 35 mL/min, dry air flow at 350 mL/min, and N2 at 20.227 mL/min. Before and after each injection, the injector washed itself five times with solvent (hexane), then drew the sample twice and left it in the waste bottle, giving the sample to the column at the third pull. Thus, the possibility of contamination from the previous sample was minimized.

### *Statistical Analysis*

In calculating the sample width of our study, the power of the test for each variable was determined by taking at least 0.80, and Type-1 error ($\alpha$) as 0.05. Descriptive statistics for continuous (quantitative) variables were expressed as median, mean, standard deviation, minimum, and maximum. The Shapiro-Wilk test ($n<50$) was used to examine whether the continuous measurement averages in the study were normally distributed, and non-parametric tests were applied because the variables were not normally distributed. The Kruskal-Wallis H test was used to compare the measurements according to the groups, and Bonferroni correction was used as post hoc (multiple comparison) to determine the different groups that were found to be significant. Spearman correlation coefficients were calculated to determine the relationship between the measurements, as well as separately in the groups. The level of statistical significance in the calculations was set at $\alpha$ 5% and SPSS (IBM SPSS for Windows, Ver. 24) package program was used.

## Results

The weights of the rats at the beginning and at the end of the 8th week were noted as following:

181.7±10.8 g and 187.5±10.2 g in the normal group; 188.2±16.6 g and 188.3±15.5 g in the alcohol-consuming group; and 196.7±10.8 g and 203.3±10.3 g in the HFCS consuming group, respectively. Weight gain in the group fed only HFCS was found to be significant (p=0.03). When the rats were evaluated in terms of feed consumption, the average was detected as 727.5±123.7 g, 532±87.6 g, and 538.1±170.9 g in the normal, alcohol, and HFCS groups, respectively (p=0.09). Feed consumption was found to be significantly lower in the alcohol and HFCS groups than in the group with the normal rats (Fig 1).

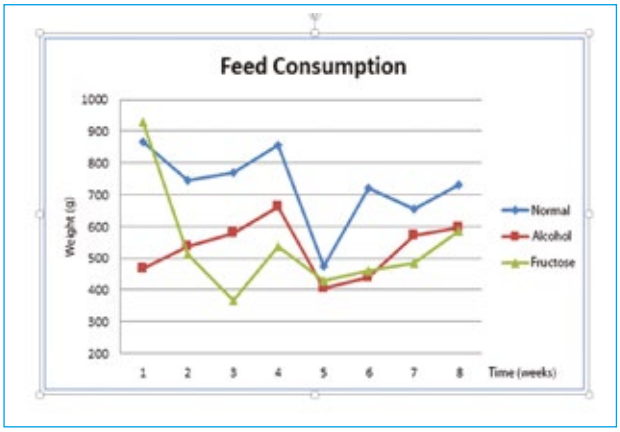


**Fig. 1**: Feed consumpition according to groups.

When the rats were evaluated in terms of their fluid consumption, we found a mean of 642.5±108.9 mL, 562.5±226.3 mL, 893.7±114.7 mL in the normal, alcohol and HFCS groups, respectively (p=0.08). We found that fluid consumption decreased significantly in the alcohol group and increased significantly in the HFCS group (Fig 2).

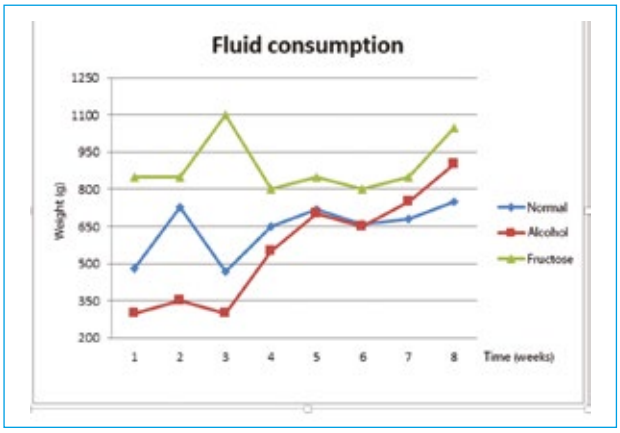


**Fig. 2**: Fluid consumption according to groups.

Blood sugar levels were 142±6.6 mg/dL in the normal group, 144.5±9.3 mg/dL in the alcoholic group, and 163±26.31 mg/dL in the fructose-consuming group (p=0.121). When the lipid profile was examined, low density lipoprotein (LDL) (p=0.038) and high density lipoprotein (HDL) (p=0.08) cholesterol levels were found to be significantly higher in the fructose-consuming group (Table 1).

| | Group | Median | Mean | Std. Dev. | Min. | Max. | *p. |
|---|---|---|---|---|---|---|---|
| Glucose (mg/dl) | Normal | 142,00 | 140,86 | 6,67 | 127,00 | 148,00 | ,120 |
| | Alcohol | 144,50 | 145,63 | 9,53 | 130,00 | 161,00 | |
| | Fructose | 163,00 | 163,63 | 26,31 | 127,00 | 211,00 | |
| AST (U/L) | **Normal** | **109,00 a** | **162,14** | **29,69** | **109,00** | **195,00** | ,039 |
| | **Alcohol** | **170,00 a** | **167,13** | **51,89** | **108,00** | **280,00** | |
| | **Fructose** | **162,00 b** | **133,13** | **75,87** | **93,00** | **320,00** | |
| ALT (U/L) | **Alcohol** | **66,00 a** | **67,57** | **15,97** | **50,00** | **97,00** | ,002 |
| | **Fructose** | **46,00 b** | **50,00** | **10,70** | **36,00** | **68,00** | |
| | **Normal** | **41,50 b** | **41,88** | **4,91** | **35,00** | **50,00** | |
| GGT (U/L) | Normal | ,40 | ,46 | ,29 | ,00 | ,80 | ,310 |
| | Alcohol | ,70 | 1,40 | 1,50 | ,00 | 4,50 | |
| | Fructose | ,60 | ,80 | 1,03 | ,00 | 3,20 | |
| ALP (U/L) | Normal | 158,00 | 185,14 | 97,17 | 95,00 | 387,00 | ,101 |
| | Alcohol | 91,50 | 112,38 | 56,61 | 64,00 | 242,00 | |
| | Fructose | 99,00 | 124,38 | 60,47 | 54,00 | 209,00 | |
| HDL (U/L) | **Normal** | **46,00 ab** | **44,29** | **5,06** | **36,00** | **50,00** | ,008 |
| | **Alcohol** | **38,50 b** | **38,25** | **5,80** | **32,00** | **48,00** | |
| | **Fructose** | **47,50 a** | **50,13** | **6,17** | **45,00** | **64,00** | |
| LDL (U/L) | **Normal** | **9,00 b** | **9,24** | **2,03** | **8,00** | **13,70** | ,038 |
| | **Alcohol** | **8,10 b** | **8,19** | **1,87** | **5,60** | **11,00** | |
| | **Fructose** | **12,50 a** | **11,83** | **2,33** | **7,80** | **14,40** | |
| TG (U/L) | Normal | 70,00 | 84,29 | 51,86 | 43,00 | 194,00 | ,124 |
| | Alcohol | 112,50 | 105,13 | 32,09 | 49,00 | 147,00 | |
| | Fructose | 60,50 | 74,88 | 48,99 | 34,00 | 187,00 | |
| İnsulin | Normal | ,07 | ,15 | ,23 | ,03 | ,68 | ,500 |
| | Alcohol | ,07 | ,14 | ,21 | ,05 | ,67 | |
| | Fructose | ,06 | ,06 | ,02 | ,02 | ,09 | |
| C:16 | Normal | 53,59 | 50,91 | 6,12 | 42,68 | 57,33 | ,238 |
| | Alcohol | 54,31 | 55,13 | 5,31 | 50,31 | 64,40 | |
| | Fructose | 56,06 | 55,88 | 2,16 | 53,13 | 59,53 | |
| C:18.0 | Normal | 34,98 | 34,57 | 5,70 | 27,73 | 41,70 | ,479 |
| | Alcohol | 31,88 | 30,57 | 4,37 | 24,71 | 36,49 | |
| | Fructose | 32,35 | 31,17 | 4,79 | 21,87 | 36,37 | |
| C:18.1 | Normal | 2,84 | 3,50 | 2,67 | ,00 | 8,42 | ,840 |
| | Alcohol | 5,01 | 4,22 | 3,16 | ,00 | 8,46 | |
| | Fructose | ,37 | 4,06 | 5,58 | ,00 | 12,37 | |
| C:18.2 | **Normal** | **4,85 a** | **5,13** | **4,00** | **,00** | **10,47** | ,007 |
| | **Alcohol** | **2,91 a** | **3,51** | **3,71** | **,00** | **8,81** | |
| | **Fructose** | **,03 b** | **,02** | **,01** | **,00** | **,03** | |
| C:20.4 | Normal | 4,71 | 5,88 | 6,24 | ,00 | 14,77 | ,255 |
| | Alcohol | 5,05 | 6,58 | 3,58 | 2,03 | 11,26 | |
| | Fructose | 8,18 | 8,89 | 2,93 | 5,49 | 12,98 | |

**Table 1**: Comparison of biochemical values and serum FFAs between groups.

In the comparative evaluation of fatty acids between groups, C18:2 fatty acid levels were found to be highest in the normal group and lowest in the fructose-consuming group (p=0.07) (Fig 3).

In the histopathological evaluation of the liver, steatosis and hydropic degeneration in hepatocytes were observed in the two groups fed alcohol and HFCS, and they were more prominent in the alcohol-

consuming group than in the fructose group (Table 2 and Fig 4).

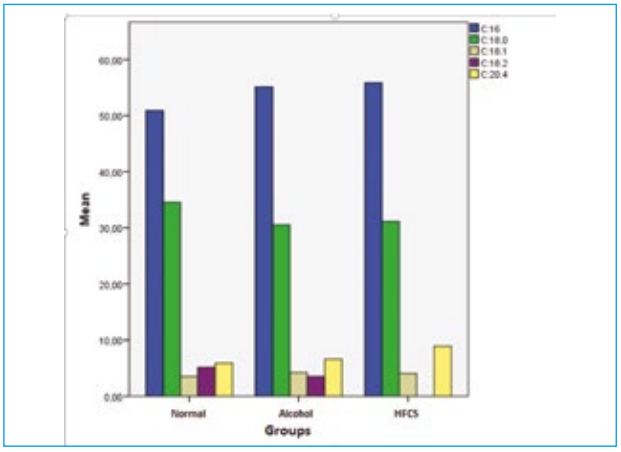


**Fig. 3**: FFA levels between groups.

| | Normal group | Alcohol group | HFCS group |
|---|---|---|---|
| Hydropic degeneration of hepatocytes | - | +++ | ++ |
| Coagulation necrosis of hepatocytes | - | +++ | - |
| Steatosis | - | +++ | + |
| Sinusoidal dilatation and hypermia | - | +++ | ++ |

**Table 2**: Histopathological evaluation of liver.

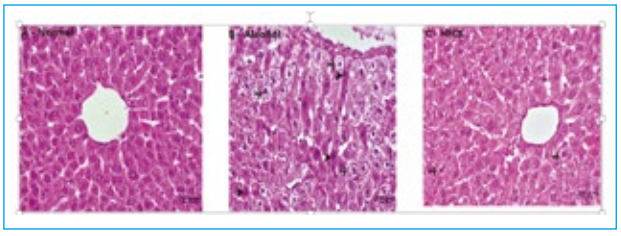

**Fig. 4**: Histopathologic evaluation of the liver H&E, Bar: 200 pixel. **A**- Normal histological appearance in normally fed rats, **B**- Hydropic degeneration of hepatocytes in liver tissue (arrows), coagulation necrosis (arrowheads), dilatation and hyperemia in the sinusoids, **C**- Hydropic degeneration of hepatocytes (arrows), mild dilatation and hyperemia in the sinusoids

A summary of the FFA and liver histopathological findings of rats by group is summarized in Fig 5.

## Discussion

As a result of our changing lifestyles, diseases such as obesity, fatty liver disease, and lipid profile deterioration constitute main health problems of our age. Studies have indicated that sweeteners such as HFCS and alcohol in beverages consumed may be important causes of these health problems[1,2,8,9].

In our study, when the feed consumption of rats in the alcohol, HFCS, and normal groups was evaluated, we found that the amount of feed intake was significantly reduced in the HFCS and alcohol groups.

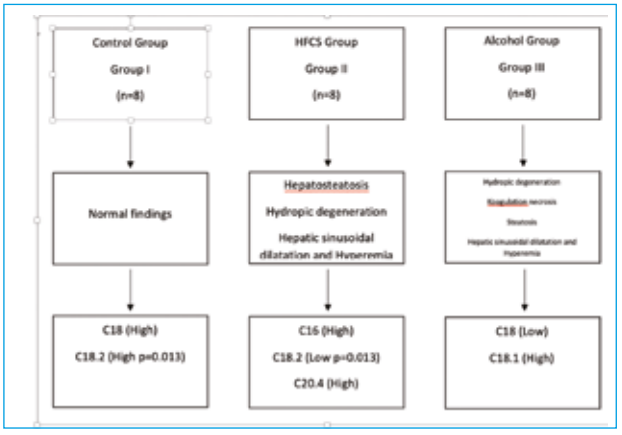


**Fig. 5**: Summary of FFA and histopathological changes according to groups of rats.

In a study conducted by Ramos VW et al., 10 rats in the control group and 10 Wistar rats were fed 20% fructose syrup. Similar to our study, they found no difference in feed consumption in the first 30 days, but a significant decrease in the feed consumption of the fructose-consuming group was noted on days 60 and 90[10]. Similar to our study, A. Richardson et al. found that for 12 rats, the feed intake of the control group after 9 days remained unchanged, while that of the group with 9 days of 10% alcohol consumption had significantly decreased at 9 days[11]. It has been stated that one of the main reasons for this may be related to the fact that fructose and alcohol themselves are sufficient to provide sufficient calories per day[10,11].

In our study, we found that the greatest fluid consumption was in the fructose group. In a study conducted by Miranda CA et al. on 11 rats, they showed that 7% fructose consumption and daily fluid consumption in rats in the control group increased significantly in the group consuming fructose[12]. At the end of eight weeks of feeding in our study, significant weight gain was observed in the group fed only HFCS. Bocarsly et al. found that rats fed 10% HFCS for 12-h and 24-h periods gained more weight than rats in the group fed 10% sucrose and a normal diet[13]. One of the reasons for the higher weight gain in rats fed with fructose is that while circulating glucose causes insulin secretion from the pancreas, fructose cannot stimulate the secretion of insulin due to the lack of receptors for fructose transport in the pancreas. Because of low insulin levels, the secretion of leptin is reduced, resulting in an inability to suppress appetite[14,16]. In our study, we found that rats in the fructose group consumed

more feed and gained more weight. In a study conducted by Nelson et al., in which they evaluated the relationship of alcohol with appetite and weight gain in rats, it was found that daily 3 g/kg alcohol injection increased blood ethanol concentration, suppressed appetite, and prevented weight gain[17,18]. When we looked at the lipid profiles of the rats in our study, we found that HDL and LDL cholesterol levels were highest in the group consuming fructose. Although triglyceride (TG) levels were higher in the group consuming fructose, the difference was not statistically significant. In a study conducted by Botezelli et al., they found that TG was higher in the group fed with beverages with high fructose content, similar to our study, but LDL and HDL values were not higher than those in the other groups. One reason for this was the high amount of fructose used in our study whereas in this study, fructose was administered to rats in carbonated beverages[19]. Morales-Gonzalez et al. found that there was at least a 10-fold increase in AST levels below 5% and 40% alcohol at the 12-week follow-up in Wistar rats, which correlated with histopathological findings[20].

In our study, aspartate aminotransferase (AST) levels were found to be highest in the group consuming alcohol, and histopathological findings such as hydropic degeneration of hepatocytes, coagulation necrosis, dilatation and hyperemia in the sinusoids were found to be highest and most severe in the group consuming alcohol in correlation with AST levels at the same time. When Köseler et al. evaluated liver histopathology in rats to which they administered 10% and 20% fructose and glucose, respectively, they found that inflammation and ballooning in hepatocytes were higher in the fructose-consuming group than in the glucose-consuming group[21].

In our study, it was found that hydropic degeneration in hepatocytes, steatosis, sinusoidal dilatation, and hyperemia were observed in rats in the HFCS group, but these pathological changes were observed to be less severe than in the alcohol-consuming group. Song et al. evaluated the histopathological changes in the liver of rats that received HFCS, alcohol, and alcohol and HFCS together. They stated that while hepatic steatosis was observed in rats that received alcohol and HFCS alone, the most significant histopathological changes were observed in rats that received alcohol together with HFCS[22]. Although it is known that FFA are theoretically important in liver diseases, especially in NAFLD, previous research studies have not sufficiently assessed and discussed this. In a study conducted by Feng R. et al. comparing FFA in underweight, overweight, and obese NAFLD patients, they reported that C 14 and C 16:1 fatty acid levels could be used in the early diagnosis of NAFLD[23].

In a study conducted by Tranchida et al., in which they evaluated the difference in fatty acids between rats fed with high fructose and saturated fatty acids (HFS) and rats fed with normal feed, they found that the plasma FFA profile of the HFS group had higher proportions of monounsaturated fatty acids such as palmitoleic acid [16: 1 (n-7)] and oleic acid [18: 1 (n-9)], while some polyunsaturated fatty acids such as linoleic acid [18: 2 (n-6)] and arachidonic acid [20: 4 (n). -6)] were lower than those in the control group[24]. They stated that the HFS diet may lead to an adaptive response in the plasma FFA profile over time, in connection with the development of metabolic syndrome[24]. In our study, we found that the level of C 18: 2 (linoleic acid) was significantly lower in rats fed HFCS. Although C18: 2 was determined to be low in alcohol-consuming rats, it was not as remarkable as in the HFCS group. Since there are no studies in the literature that directly evaluate the effect of alcohol consumption and HFCS consumption on FFA, we believe that this study will be a significant contribution to the literature.

In conclusion, in our study, we found that weight gain and feed intake increased, and C 18: 2 level was lower in rats fed HFCS. However, we found that histopathological findings such as hydropic degeneration of hepatocytes, coagulation necrosis, dilatation, and hyperemia in the sinusoids in the liver were more pronounced in rats fed alcohol.

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