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STRUCTURAL AND FUNCTIONAL ABNORMALITIES ASSOCIATED WITH HIGH FRUCTOSE DIET-INDUCED METABOLIC SYNDROME IN WISTAR ALBINO RATS

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ABSTRACT: Purpose of the study: To assess Structural and functional abnormalities associated with High fructose diet-induced Metabolic syndrome in wistar albino rats. **Materials and Methods:** Metabolic syndrome is induced in adult male Wistar albino rats by feeding a combination of High Fructose Diet (55%) and Fructose enriched water (15%) for 75 days and kept as group 2 or HFrD Group. Normal male Wistar albino rats were kept as Normal control. During the entire course of study, weekly weight gain was monitored once a week in both groups. Biochemical investigations such as lipid profile, liver function test, and renal function test was carried out using standard methods. Routine histological studies were done to analyze the microstructural changes. The obtained data were statistically analyzed by students't' tests and the values were considered statistically significant at $p<0.05$. **Results:** Chronic administration of a High fructose diet (HFrD) resulted in obesity, abnormal hepatic and renal functions in wistar rats. The gross and microstructural changes were minimal in the pancreas and heart, whereas significant damages were observed in the liver and kidneys. **Conclusion:** Consumption of a High fructose diet (HFrD) produces structural and functional damages in the liver and kidneys of wistar rats.

INTRODUCTION: Modern lifestyle today has a deleterious effect on our health as it often violates the principles of natural living. Unhealthy food habits and sedentary lifestyles are factors that invite disease rather confronting it.

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These are collectively known as Lifestyle disorders, which is playing a pivotal role in the development of the metabolic syndrome. Metabolic syndrome combines several medical conditions that increase the risk of developing heart diseases, stroke, cancer, non-alcoholic fatty liver and Diabetes Mellitus [1].

It is characterized by the concurrent existence of Obesity, Hypertension, Hyperglycemia, and Dyslipidemia [2, 3]. The risk of developing metabolic syndrome in humans depends on the synergy of both genetic and environmental factors [4].

The worldwide prevalence of metabolic syndrome ranges from 10- 84% depending on the age, gender, race, and ethnicity, and it is 5 to 7% in young adults [5]. Different varieties of animal models have been used for the therapeutic studies of Diabetes, Hyperlipidaemia, and Kidney diseases [6, 7]. Though, studies are still in progress in developing better rodent models. The establishment of appropriate experimental animal models of metabolic syndrome is very important for evaluating the pathophysiology of the disease in humans. The present study is an attempt to explore the influence of the High fructose diet on the metabolism of rats fed with a combination of high fructose diet and water for 75 days.

MATERIALS AND METHODS: This research protocol was approved by the Institutional Animal Ethics Committee, SDM Centre for Research in Ayurveda and Allied Sciences, Udupi (CPCSEA/IAEC/15-16-KT.20). Twelve healthy adult male Wistar albino rats weighing between 180-240 g were selected for the study. They were housed under suitable temperature (22 ± 2 ℃), humidity, and at 12 h of the day-night cycle and received standard pellet diet and purified water *ad libitum*.

The duration of the study was 75 days. Animals were grouped into two, comprising of 6 animals in each. Rats in group I was fed with a normal laboratory diet and kept as the Normal control group. Rats in group II were fed with fructose enriched water (15%) for the initial 30 days, followed by a high fructose diet (55%) for further 45 days. The animals were acclimatized to the experimental conditions two days before the initiation of the study.

Metabolic and Biochemical Assays: After 75 days of treatment, a fasting blood sample was collected from the retro-orbital puncture technique under light ether anesthesia. Biochemical investigations such AS Lipid profile, Liver function test and renal function test were carried out using commercial kits (Erba) with a fully automated clinical analyzer (ERBA-EM-200).

Histological Studies: After the blood collection, the animals were sacrificed by painless cervical dislocation. The kidneys, liver and pancreas were identified and observed for any change in gross appearance and colour. After careful dissection, the organs were transferred into a petri dish containing normal saline. The tissues were carefully wiped using tissue paper and weighed by using a digital weighing machine and immediately transferred to 10% formal saline for histological studies.

Statistical Analysis: Students't' test was used for statistical testing significance between groups. $p < 0.05$ considered significant. All the data are presented as Mean ± SEM.

RESULTS:

A. Body Weight: From the first week to the end of the study, a gradual increase in body weight was observed in the normal control group. In contrast, the rate of increase in body weight was much higher in the fructose control towards the end of the study. The rate of increase in bodyweight is depicted in **Table 1.**

TABLE 1: THE WEEKLY CHANGES IN BODY WEIGHT EXPRESSED IN GRAMS

Group	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week	9th week
NC	1.66 ± 0.54	3.28 ± 0.73	5.87 ± 0.97	6.96 ± 1.06	9.09 ± 1.13	7.06 ±1.43	9.89 ± 1.26	8.6 ± 1.71	13.83 ± 2.16
HFRD	3.94 ± 0.9*	4.73 ± 1.09*	8.55 ± 2.41*	8.94 ± 4.33*	9.84 ± 4.32*	10.77±4.45*	11.43 ± 3.53*	13.84± 3.64*	22.18 ± 4.48*
% Diff	137.34 ↑	59.45 ↑	45.65 ↑	28.44 ↑	8.25 ↑	52.54 ↑	15.57 ↑	60.93↑	60.37↑

All the values were expressed in Mean ± SD. * represents $p<0.05$.

Weight of Organs: A mild and statistically insignificant increase in the weight of the heart was observed among HFrD rats. In contrast, the Kidneys, Liver and pancreas weight showed a statistically significant increase **Table 2.**

Biochemical Analysis: The lipid profile of the high fructose group showed increased Total cholesterol level, LDL, Triglyceride and Total protein level, whereas serum HDL level was noticeably decreased; these values appeared statistically significant when compared to the normal control group ($p<0.05$). Serum urea levels of the positive control rats showed a minimal and statistically insignificant increase.

Serum uric acid and creatinine levels are significantly increased in HFr D group ($p < 0.01$). In the high fructose diet group, liver function markers like SGPT, SGOT, Alkaline phosphatase and total Bilirubin level were increased ($p<0.05$).

Whereas Total protein, Serum Albumin level and Serum Globulin level showed a mild and statistically insignificant ($p>0.05$) increase in HFrD group. The renal function markers like Serum creatinine and uric acid were elevated in HFrD rats when compared with the normal rats ($p<0.05$) and serum urea levels showed a minimal and statistically insignificant increase.

TABLE 2: WEIGHT OF ORGANS

Organs	Absolute weight (G)	
	Normal control	High fructose diet
Kidneys	1.45± 0.08	1.95 ± 0.12*
Liver	7.11 ± 0.44	8.9 ± 0.32*
Pancreas	0.34 ± 0.03	0.60 ± 0.07*
Heart	0.67 ±0.04	0.70 ± 0.04

All the values were expressed in Mean ± SD. *denotes statistical significance ($p< 0.05$)

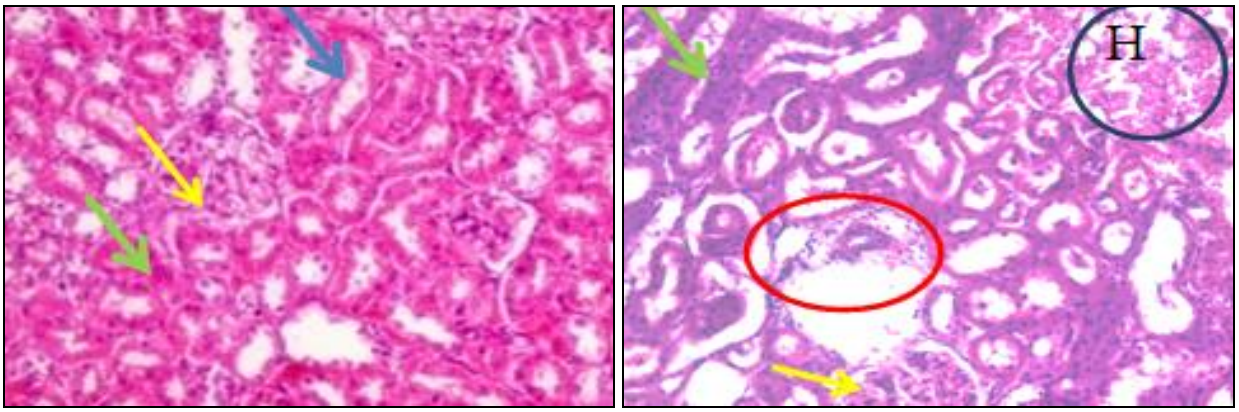
TABLE 3: BIOCHEMICAL ANALYSIS

Parameter	Normal Control	High Fructose Diet
Lipid Profile		
Total cholesterol (mg/dl)	43.16 ± 2.18	64 ± 4.54*
Triglyceride (mg/dl)	100.5±3.59	186.83 ± 13.27*
HDL (mg/dl)	39.66 ± 1.35	21.66 ± 1.08 *
LDL (mg/dl)	13.83 ± 1.37	27.88 ± 3.59 *
Liver Function Markers		
SGOT (U/L	126 ± 3.81	156 ± 26.95*
SGPT (U/L)	66.33± 1.83	108.83± 30.14*
ALP (U/L)	244.83 ± 17.92	320.5 ± 39.94*
Total protein (Gm/dl)	5.71 ± 0.18	5.79 ± 0.13
Albumin (Gm/dl)	2.98 ± 0.05	3.01± 0.07
Globulin (Gm/dl)	2.73 ± 0.2	2.78 ± 0.17
Serum Bilirubin - Total (mg/dl)	0.02 ± 0.0	0.05 ± 0.01 *
Renal Function Markers		
Serum Urea (mg/dl)	24.6 ± 1.5	25.16 ± 2.08*
Serum Uric acid (mg/dl)	1.06 ± 0.04	1.86 ± 0.55*
Serum Creatinine (mg/dl)	0.38 ± 0.01	0.63 ± 0.03*

All the values were expressed in Mean ± SD. * denotes statistical significance ($p< 0.05$)

Histological Studies

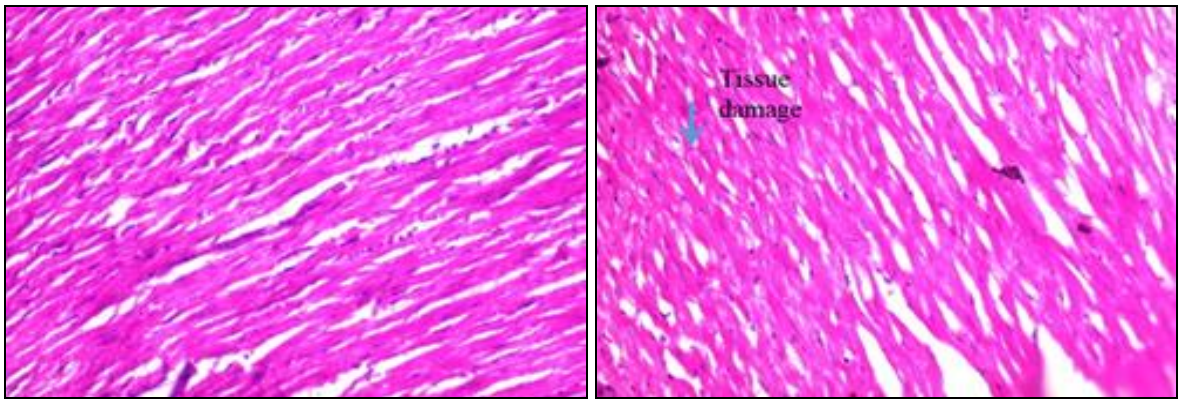
A. Kidneys: Normal control group showed normal histological features in the cortical and medullary regions *i.e.*, normal Glomerulus and tubules. Kidneys showed necrotic changes in the glomerulus, showing the signs of mesangial expansion. Tubules presented with dilatation and an increase in thickness. Localized mononuclear cell infiltrations and hemorrhages were also visible **Fig. 1**.



GROUP I **GROUP II**

FIG. 1: H&E STAINED SECTIONS OF KIDNEYS, GROUP I NORMAL CONTROL GROUP II FRUCTOSE GROUP. G-GLOMERULUS (YELLOW). PCT (GREEN) DCT (BLUE) FIG. B: HAEMORRHAGE (BLUE CIRCLE), CELL INFILTRATION (RED CIRCLE), TUBULAR THICKENING (GREEN ARROW) AND MESANGIAL EXPANSION (YELLOW ARROW)

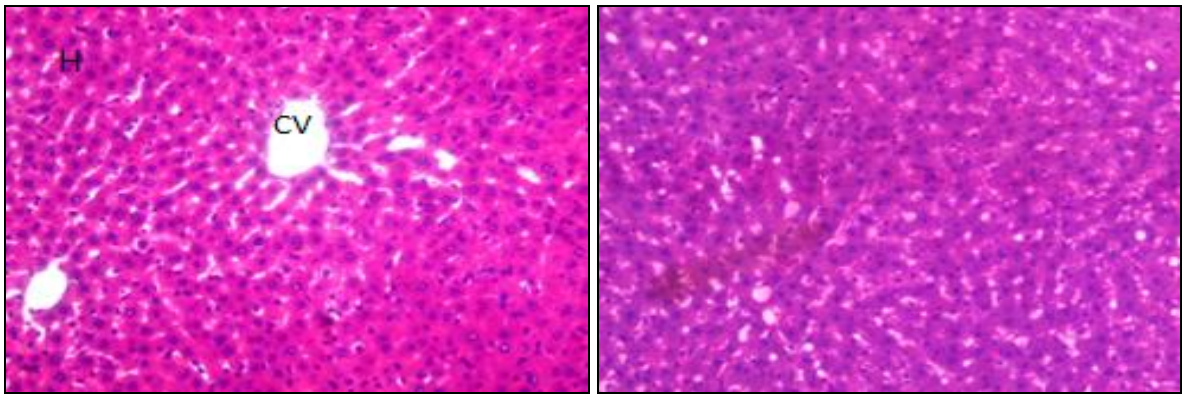
B. Cardiac Muscle: Normal control showed normal histological features. No significant changes were observed in fructose control rats except mild tissue damage & hyaline degeneration **Fig.2**.



GROUP I **GROUP II**

FIG. 2: H&E STAINED SECTIONS OF CARDIAC MUSCLE, GROUP I - NORMAL CONTROL, GROUP II - FRUCTOSE GROUP

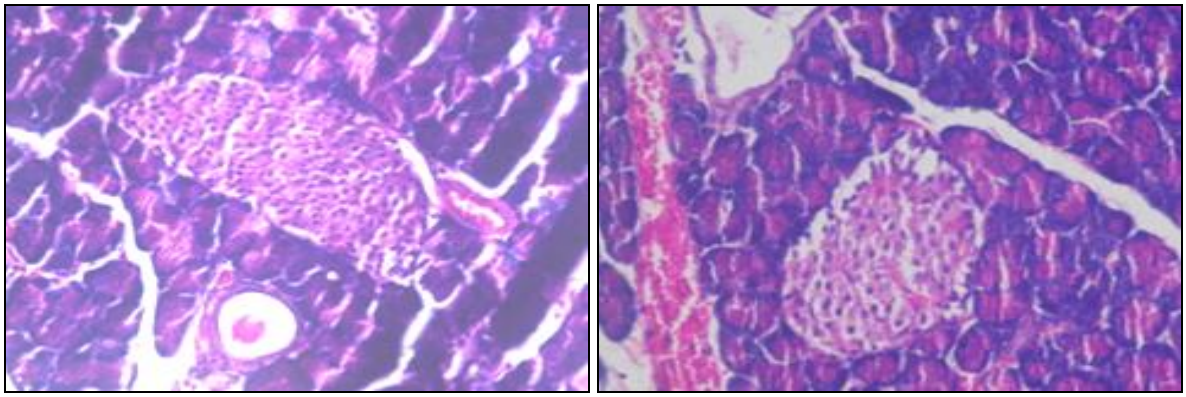
C. Liver: Microstructure of HFrD rat liver showed fatty and necrotic changes with lymphatic infiltrations, dilated Sinusoidal space and periportal inflammations **Fig. 3**.



GROUP I **GROUP II**

FIG 3: H&E STAINED SECTIONS OF LIVER, GROUP I -NORMAL CONTROL GROUP II - FRUCTOSE GROUP

D. Pancreas: Tissue sections from normal control showed normal pancreatic structure (Normal islets of Langerhans and normal exocrine part); no marked changes were visible in the pancreatic Islets of the high fructose diet group. But exocrine part, *i.e.*, acini showed moderate fibrosis **Fig. 4**.



GROUP I **GROUP II**

FIG. 4: H&E STAINED SECTIONS OF PANCREAS, GROUP I - NORMAL CONTROL GROUP II - FRUCTOSE GROUP

DISCUSSION: Fructose is a major component in a variety of soft drinks, sauces, ready-made fruit juices, fresh and dried fruits which is consumed by a majority of the population. Its excessive consumption may increase [1]. The risk of abnormal blood clotting ailments and hypertension [2]. The risk of type 2 Diabetes [3]. Total blood cholesterol levels serve in part as the raw material for the synthesis of cholesterol within the body [4]. LDL cholesterol levels and blood triglyceride levels [5]. Obesity due to enhanced deposition adipose tissue. As fructose has a greater susceptibility to increase serum triglycerides than glucose, fructose consumption is in fact, more destructive [8, 9]. Over the past few decades, epidemiological studies have shown that increased fructose consumption is an etiological element of metabolic syndrome (Met S) [10].

Met S is a cluster of conditions that include increased blood pressure, high blood sugar, excess body fat and abnormal cholesterol or triglyceride levels. It affects almost all systems of the body organs, especially the heart, liver, pancreas and kidneys [11]. The goal of the present study was to develop an effective animal model which mimics the structural and functional abnormalities associated with Metabolic syndrome in humans. In order to draw a parallel between obesity and fructose consumption, weekly assessment of body weight changes were recorded during the entire period of study. A progressive increase in the percentage of weight in the High Fructose fed rats indicated the direct relationship between high fructose consumption and obesity.

In concordance with our results, Miriam E. Bocarsly *et al.* reported that overconsumption of HFCS could very well be a major factor in the development of obesity [12]. The obesity-associated with high fructose diet may be attributed to the postprandial hypertriglyceridemia that enhances visceral adipose deposition [13]. Equilibrium among synthesis and degradation of biological tissues is maintained by Lipid metabolism [14]. Abnormalities in this metabolism cause dyslipidemia produced by excessive and regular consumption of HFrD that augments lipid peroxidation, leads to delayed gastric emptying, and affects the digestion process [15]. The present study also exhibited altered lipid levels in HFrD fed rats. An abnormally increased Serum LDL, Serum triglyceride and Total cholesterol levels and increased Serum HDL levels, signs of the dyslipidemia associated with metabolic syndrome were observed. Dyslipidaemia is a major risk factor of cardiovascular and kidney diseases [16]. Mild tissue damage in the myocardium of the heart seen in the histological study may be an indicator of this abnormal lipid metabolism. A characteristic feature of the metabolic syndrome is the irregularities in hepatic and renal enzyme production [17]. To evaluate the functional abnormalities in Liver and kidney, assessment of Serum SGOT, SGPT, ALP, Total Protein, Serum Creatinine, Serum urea and serum uric acid levels were done in both groups. The high fructose diet significantly increased SGOT, SGPT, ALP and serum urea and uric acid levels, whereas a minimal and statistically insignificant increase in Total protein level, serum albumin and globulin level. The present findings are in concordance with previous reports [18]. It is obvious that alterations of functions are due to the structural changes in the organ system concerned. To substantiate this, we have conducted histological studies in liver, Pancreas, Kidneys and heart. Increased consumption of fructose increases the triglyceride accumulation in the liver that may lead to non-alcoholic fatty liver.

The typical sign of Non-Alcoholic Fatty Liver Disease (NAFLD) is vacuolations and inflammations [19], which was obvious in the current study. Kidneys showed structural changes in the PCT and the Glomerulus with mononuclear infiltrations. These changes illustrate the metabolic disturbances in the body due to overconsumption of high fructose for a long period.

Unlike the chemically induced diabetes such as streptozotocin, where the metabolic derangements are due to the direct damage to the beta cells of the pancreatic islets [20], here there were no marked changes observed in the heart and pancreas, except few mild hyaline degenerations in the myocardium and mild fibrosis in the exocrine part of the pancreas. Our findings were appeared similar to the previous reports on high fructose-induced metabolic syndrome in rats [21, 22]. On the basis of the present investigation, overconsumption of high fructose for a prolonged period may imbalance the metabolism by accentuating obesity and inducing structural and functional changes in the liver and

kidneys. This fructose-fed rat model may be useful to define potential treatments for Type 2 Diabetes or metabolic syndrome.

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CONFLICTS OF INTEREST: No conflicts of interest.

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