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Role of amylin and leptin in diet-induced obesity-associated hepatic and renal dysfunction in mae sprague dawley Rats

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ABSTRACT

This study investigated the effects of amylin (AMN) and leptin (LEP), individually and in combination, on diet-induced obesity (DIO) and its associated hepatic and renal dysfunction in male Sprague Dawley (SD) rats.High-fat diet (HFD) resulted in significant increases in body weight, triglycerides, total cholesterol, and markers of hepatic (AST and ALT) and renal dysfunction (urea, creatinine, and uric acid).Although AMN and LEP administration individually led to moderate improvements, their combined treatment (AMN+LEP) demonstrated superior efficacy, significantly reducing body weight, triglyceride levels, hepatic enzyme activities, and renal dysfunction markers.These findings suggest that the AMN+LEP combination therapy may be a promising strategy for managing obesity-induced metabolic and organ dysfunction.

Figures : 04 References : 55 Table : 00

KEY WORDS : Amylin (AMN), Diet-Induced Obesity (DIO), Hepatic Dysfunction, High-Fat Diet (HFD), Leptin (LEP), Renal Dysfunction.

Introduction

Amylin (AMN) and leptin (LEP) are key regulators of energy balance, hunger, and metabolism. They have been the focus of significant research on their involvement in obesity control. The potential benefits of combining these two hormones in diet-induced obesity (DIO) have been well researched[1]. AMN is a peptide hormone that is co-secreted with insulin from the pancreas and performs numerous key roles in metabolism[2,3]. AMN affects various central nervous system nuclei, such as the area postrema, hypothalamus, and mesolimbic structures, to decrease food intake and body weight[30,37]. AMN also decreases stomach emptying, enhances fullness after meals, and helps regulate blood glucose levels by lowering hepatic glucose production and slowing nutrient absorption[35]. AMN contributes to a negative energy balance through these pathways, which are critical for weight loss[31].

LEP is a hormone that is predominantly generated and secreted by adipose tissue. It plays an important function in the regulation of body weight and energy homeostasis by signaling fat accumulation in the brain[4,13]. LEP lowers food intake by reducing AMP-activated protein kinase 1 (AMPK) activity in the arcuate and paraventricular hypothalamus[33]. It also stimulates hypothalamic mTOR signaling, which directly affects energy intake[10]. LEP enhances energy expenditure by boosting sympathetic nerve activity, activating thermogenesis in brown adipose tissue (BAT), and enhancing fat oxidation through its activities on various

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hypothalamic nuclei, including the dorsomedial, ventromedial, and arcuate nuclei[41]. Low LEP levels suggest low energy stores and encourage appetite, whereas high LEP levels signify satiety[2].

However, with obesity, LEP resistance typically arises, defined by diminished sensitivity to leptin's appetite-suppressing and energy expenditure-enhancing actions despite elevated circulating LEP levels[11]. This resistance has led to increased food intake and weight gain, contributing to the obesity epidemic[26]. In cases of resistance to DIO and LEP, AMN and LEP work synergistically to regulate appetite and metabolism. The combination of these hormones might help prevent obesity by enhancing fullness through delayed stomach emptying while decreasing appetite, leading to better food intake control[39,44,45]. AMN reduces caloric intake, but LEP increases energy expenditure, giving a complementary weight loss effect[18]. AMN may provide an alternative pathway for appetite control and metabolic regulation in individuals with LEP resistance[45]. Research into their combined effects is underway, but preliminary findings suggest improvements for lipid metabolism and triglyceride reduction compared with monotherapies[52].

In DIO, triglycerides and free fatty acids accumulate in the liver[3]. High-calorie meals, particularly those abundant in saturated fats, induce lipid accumulation in hepatocytes, resulting in hepatic steatosis (fatty liver). Obesity-induced insulin resistance is a significant element in developing non-alcoholic fatty liver disease (NAFLD), since it enhances lipogenesis (fat formation) while lowering fatty acid oxidation, encouraging fat storage[46]. Over time, excessive liver fat leads to inflammation, oxidative stress, and hepatocellular damage, advancing to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation, ballooning of liver cells, and fibrosis, potentially leading to cirrhosis[5]. Insulin resistance in the liver also decreases glucose metabolism, increases hepatic glucose synthesis, and exacerbates hyperglycemia[15].

Obesity is associated with low-grade chronic inflammation and oxidative stress, both of which contribute to liver damage. Adipose tissue secretes inflammatory cytokines, such as TNF-á, IL-6, and IL-1â, which promote liver cell death and fibrosis[20]. Excess liver lipids generate reactive oxygen species (ROS)[48], leading to oxidative damage to proteins, lipids, and DNA, driving the progression from basic steatosis to NASH and fibrosis[43,49]. Obesity, particularly a high-fat diet, also causes hepatic lipotoxicity, where excess free fatty acids (FFAs) impair mitochondrial activity, protein synthesis, and membrane integrity, resulting in hepatocyte mortality and fibrosis[24,27]. Lipotoxicity promotes hepatic stellate cells, inducing extracellular matrix deposition and fibrosis, which can lead to cirrhosis[51,55].

DIO changes liver metabolism and increases de novo lipogenesis (DNL), where excess carbs are turned into fatty acids, further leading to NAFLD[9,36]. Obesity also changes lipid profiles, resulting in dyslipidemia, defined by higher triglyceride, low-density lipoprotein (LDL), and lowered high-density lipoprotein (HDL) levels, exacerbating liver damage and NAFLD progression to NASH[38]. Without intervention, liver fibrosis may develop, which is marked by excessive collagen deposition and leads to cirrhosis. Chronic inflammation and oxidative stress activate pathways such as transforming growth factor-beta (TGF-â), promoting hepatic stellate cell activation and fibrosis progression[24]. Advanced fibrosis can proceed to cirrhosis, greatly restricting liver function and potentially necessitating a transplant[29].

DIO is intimately connected to hepatic dysfunction, including NAFLD, insulin resistance, liver fibrosis, and cirrhosis. The liver plays a critical role in metabolic balance, and obesity, especially due to high-fat or high-calorie diets, can radically change its function, leading to both reversible and irreparable damage.

DIO also influences kidney function as obesity is a well-established risk factor for chronic kidney disease (CKD) due to increased metabolic stress, inflammation, and structural abnormalities. The kidney regulates fluid, electrolyte, and acid-base balance; however, obesity impairs these activities. Initially, DIO increases the glomerular filtration rate (GFR) as a compensatory reaction to metabolic demand; however, prolonged obesity and hyperfiltration eventually cause kidney impairment[19]. Increased workload due to elevated blood pressure and glomerular hyperfiltration leads to glomerular damage, glomerulosclerosis, and impaired kidney function.

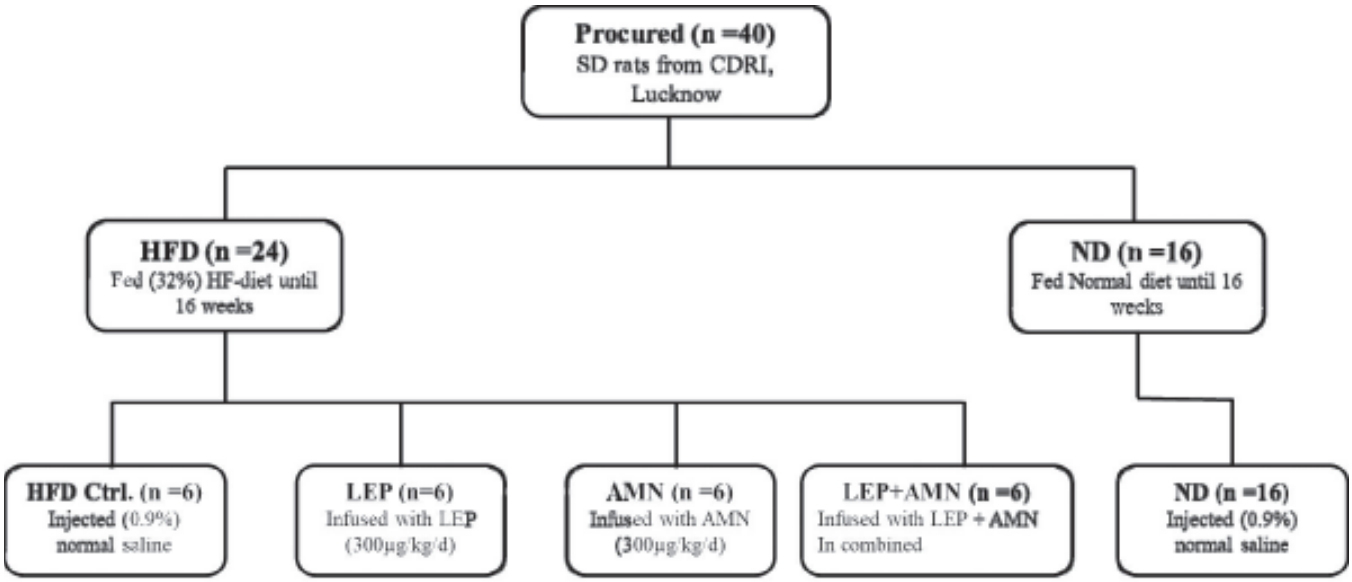
Obesity often promotes hypertension, which is the primary contributor to kidney disease. Increased visceral fat boosts adipokines such as LEP, which heightens sympathetic nervous system activity and blood pressure[16]. Chronic hypertension causes glomerular damage, culminating in glomerulosclerosis and loss of kidney function. Proteinuria (excess protein in the urine) is one of the earliest signs of kidney injury in obesity, indicating glomerular dysfunction[1,37]. High levels of circulating free fatty acids and inflammatory cytokines aggravate glomerular dysfunction, increasing permeability and protein leakage[32,53].

Obesity-related kidney damage is triggered by persistent inflammation, oxidative stress, and ectopic fat accumulation. Inflammatory cytokines and adipokines from visceral fat increase kidney injury[20], while obesity-

induced oxidative stress alters endothelial function and vascular permeability[21]. Renal lipotoxicity, caused by excess lipids in the kidney cells, further increases inflammation and death [34,40]. Progressive kidney damage eventually leads to fibrosis, reduced renal function, and increased risk of end-stage renal disease (ESRD)[6]. Sprague-Dawley rats were utilized to evaluate the effect of DIO on hepatic and renal functioning.

Materials and Methods

Animals and Diets: Male Sprague Dawley (SD) rats (age = 3 months old, n = 40) were obtained from the Central Drug Research Institute, Lucknow (Uttar Pradesh, India), and were acclimatized for 7 days under



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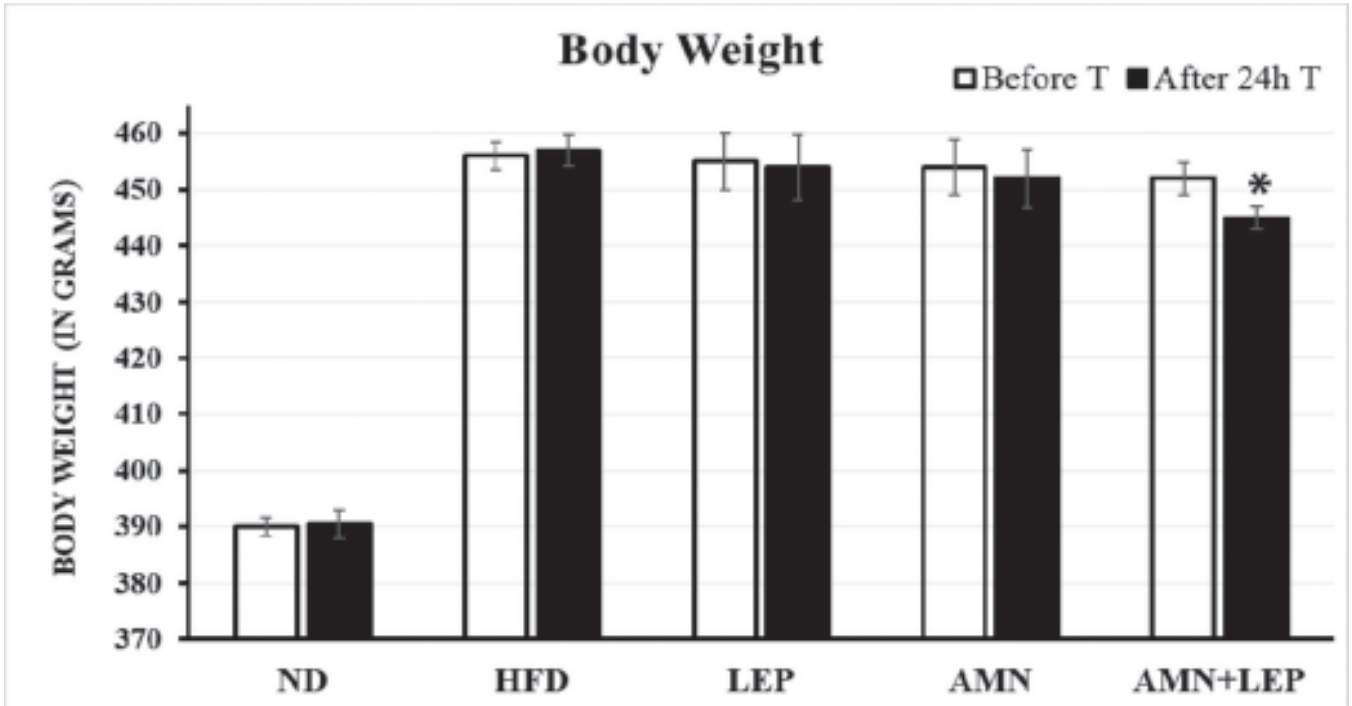

Fig. 1: Effects of a high-fat diet (HFD) on body weight in Sprague Dawley (SD) rats after 24 hours of infusion with LEP (300 µg/kg/day), AMN (100 µg/kg/day), and AMN+LEP in HFD-induced obese SD rats. * Represents statistical significance at p d" 0.05 when compared between HFD vs. AMN+LEP. (ND-Normal Diet, HFD-High fat diet, LEP- leptin, AMN-Amylin)

laboratory conditions (T = 23–25°C, 12-hour light/dark cycle) in polypropylene cages. All protocols and animal handling procedures were approved by the Institutional Animal Ethics Committee (994/GO/Re/S/06/CPCSEA) of Guru Ghasidas Vishwavidyalaya, Bilaspur, India (Reference No. 288/IAEC/Pharmacy/2021).

After acclimatization, SD rats were assigned to the LEAN and OBESE groups (rats fed a 32% fat diet, VRK Nutritions, Pune). All the rats had *ad libitum* access to food and water. Food and water consumption was monitored daily at 7 AM, and body weight was recorded weekly.

Experimental Design: The leptin (LEP) and amylin (AMN) doses administered to rats were based on previously published studies[44]. Male Sprague-Dawley rats received recombinant rat LEP (R&D Systems), rat

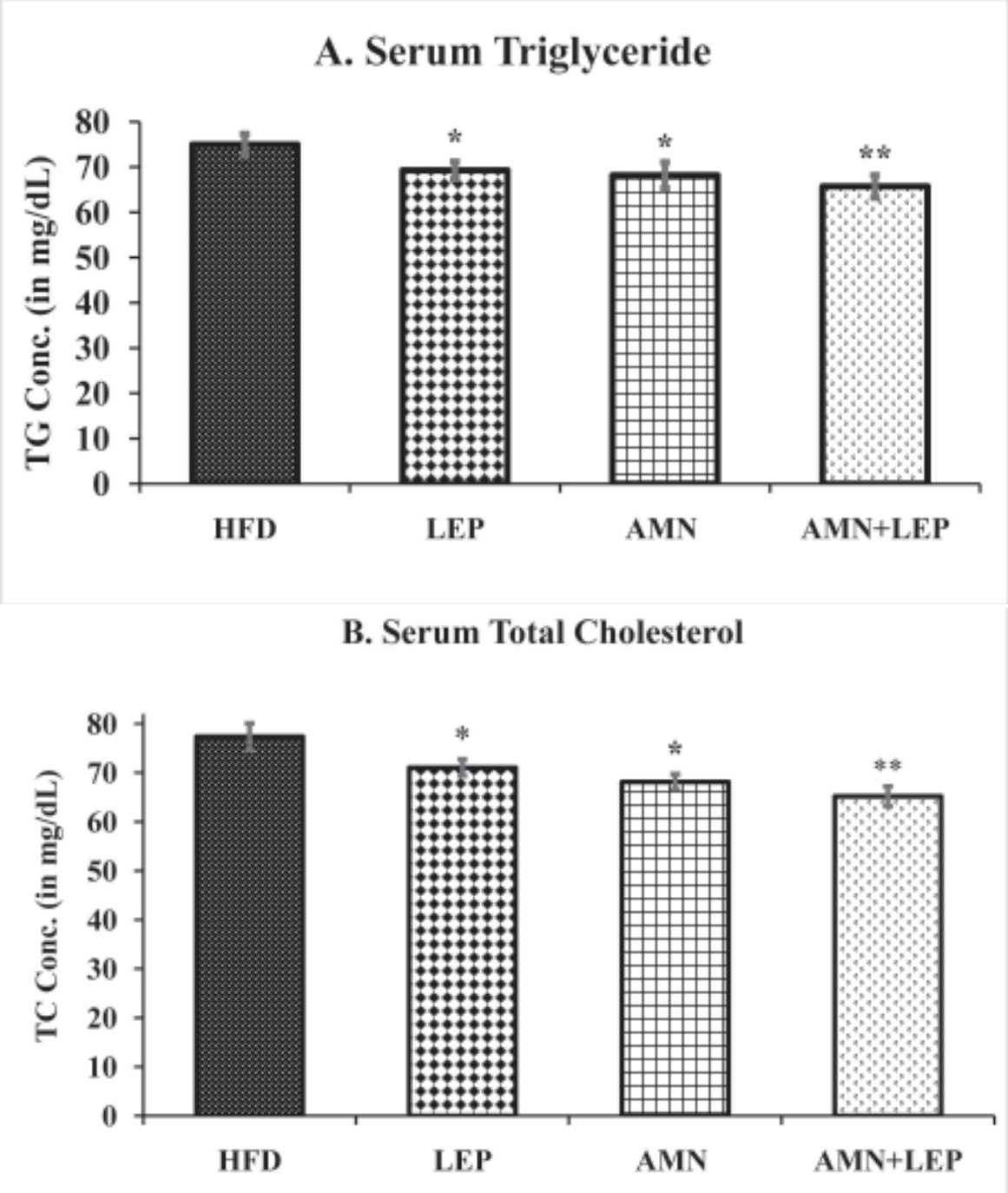

Fig. 2: Serum triglyceride and cholesterol levels in male SD rats fed a 32% HFD for 16 weeks and infused with LEP (300 µg/kg/day), AMN (100 µg/kg/day), and AMN+LEP for 24 hours.Notes: (A) Triglycerides (B) Total Cholesterol. * Represents statistical significance at p d" 0.05 when compared between HFD vs. LEP and HFD vs. AMN. ** Represents significance at p d" 0.01 when compared between HFD vs. AMN+LEP

AMN (Tocris), or a combination of AMN and LEP in a single injection (LEP: 300 µg/kg; AMN: 100 µg/kg) or saline (SAL; 0.9% NaCl, 10 µL/h).

Serum Analysis : The rats were anesthetized using a cocktail of ketamine (87 mg/kg) and xylazine (13 mg/kg) to ensure a painless procedure. Subsequently, the rats were euthanized by rapid decapitation and blood samples were collected from the neck. Blood was placed into EDTA-treated tubes, centrifuged (3,500 rpm for 30 min at -4°C), and plasma was separated and aliquoted. Aliquots were stored at -80°C for subsequent serum analysis.

The concentrations of triglycerides (TG), total cholesterol (TC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, uric acid, and creatinine were measured using commercial assay kits and analyzed using a semi-automated biochemistry analyzer.

Statistical Analysis : All statistical analyses were performed using Microsoft Excel (2019).Data are presented as the mean ± standard deviation

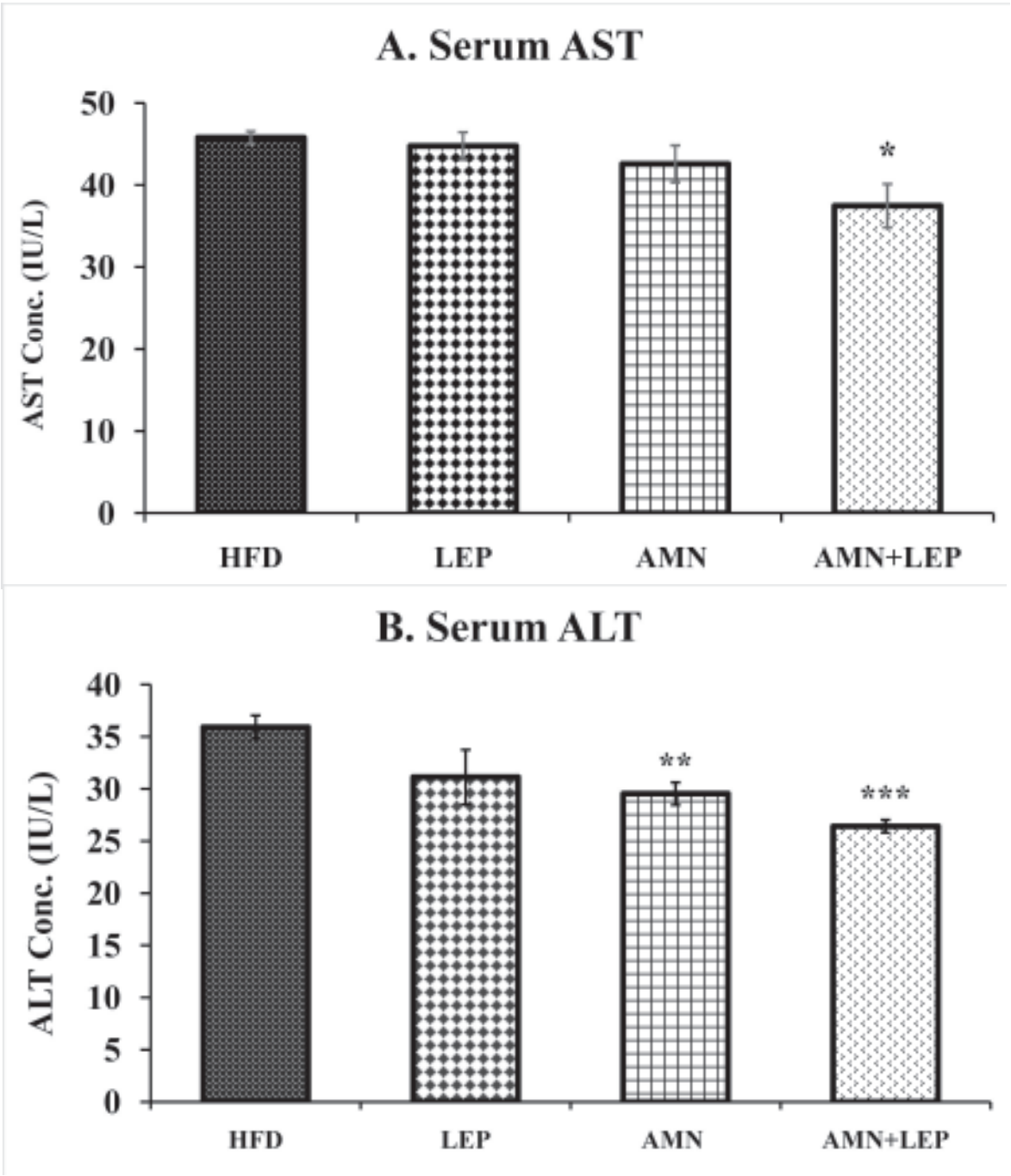

Fig. 3: Effects of LEP (300 µg/kg/day), AMN (100 µg/kg/day), and AMN+LEP on hepatic function in HFD-induced obese SD rats. *Represents statistical significance at p d" 0.05, **p d" 0.01 and, ***p d" 0.001

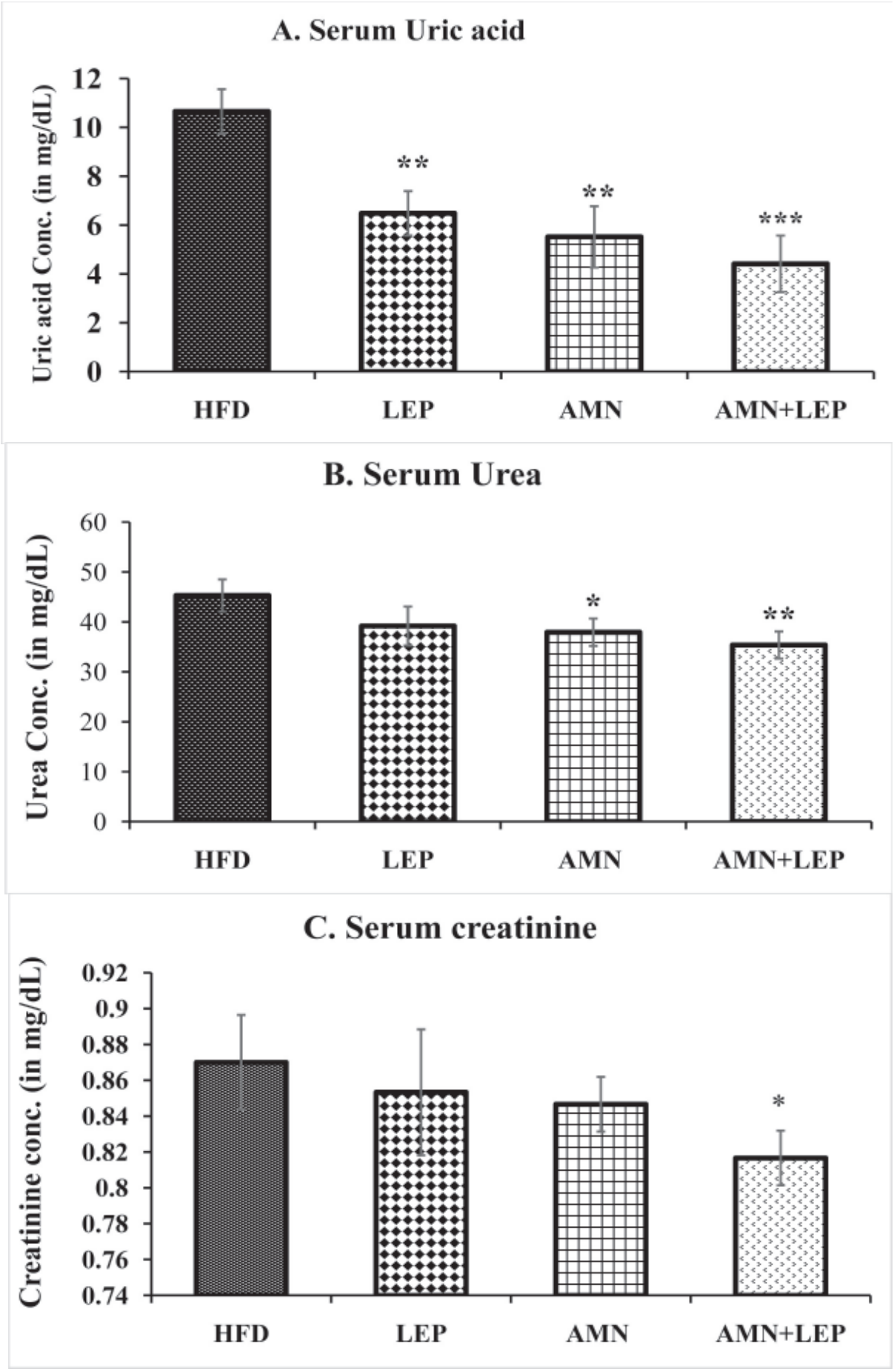

Fig. 4: Effects of LEP (300 µg/kg/day), AMN (100 µg/kg/day), and AMN+LEP infusion for 24 hours on renal function in HFD-induced obese SD rats, measured as: (A) Uric acid (B) Urea (C) Creatinine clearance. Rats were fed an HFD (32%) for 16 weeks before receiving LEP, AMN, or AMN+LEP injections. * Represents statistical significance at p d" 0.05. ** p d" 0.01 and, ***p d" 0.001

(SD).Student's t-test was used to compare differences between groups, with statistical significance set at P d" 0.05.

Results

Body Mass Index : Analysis of body weight across different time points revealed significant differences between the groups.The AMN+LEP group exhibited a significantly lower body weight than the HFD, LEP, and AMN groups after 24 h of treatment.No significant differences were observed between the HFD, LEP, and AMN groups.However, the AMN+LEP group showed a significant decrease in body weight compared with the HFD group (p d" 0.05) (Fig. 1).

Serum Triglyceride and Total Cholesterol: Serum triglyceride levels were significantly upregulated in maleSprague-Dawley rats fed a 32% HFD for 16 weeks.Animals treated with LEP (300 µg/kg/day) and AMN (100 µg/kg/day) showed a slight decrease in serum triglyceride levels compared with the HFD group.However, AMN+LEP treatment significantly lowered serum triglyceride levels compared withthe other groups.Total serum cholesterol followed a similar pattern of regulation to that of serum triglycerides (Fig. 2).

Hepatic Function : Excessive lipid accumulation in the livers of DIO rats generates reactive oxygen species (ROS), leading to oxidative damage to cellular proteins, lipids, and DNA.This process contributes to liver inflammation and fibrosis.Accumulation of free fatty acids (FFAs) in hepatocytes disrupts cellular functions, including mitochondrial activity, protein synthesis, and membrane integrity.

In our study, the HFD group showed a significant increase in the AST concentration.This increase was not reversed in the AMN or LEP treatment groups individually; however, combination therapy (AMN + LEP) significantly lowered AST levels.Similarly, serum ALT levels increased in the HFD group but remained elevated in the LEP group. However, both AMN and AMN+LEP treatments significantly reduced ALT levels (Fig. 3).

Renal Function : DIO has profound effects on the kidney function.Obesity is a well-established risk factor for the development and progression of chronic kidney disease (CKD). The kidney plays a critical role in regulating fluid, electrolyte, and acid-base balance as well as in the detoxification of metabolic waste. Obesity-induced metabolic alterations can impair these functions, leading to kidney dysfunction.

In our study, HFD-fed SD rats exhibited elevated serum levels of uric acid, urea, and creatinine, indicating renal dysfunction.However, uric acid levels showed a significant decline in all treatment groups compared with the HFD group.Serum urea levels were significantly reduced in the AMN and AMN+LEP groups, whereas serum creatinine levels were significantly lower only in the AMN+LEP group than in the HFD group (Fig. 4).

Discussion

Our investigation reveals that AMN, LEP, and their combination (AMN+LEP) may alter hepatic and renal functions in HFD-fed Sprague Dawley (SD) rats. AMN enhances fat oxidation and improves insulin sensitivity, both of which contribute to reducing triglyceride (TG) levels. Insulin resistance is a critical component that contributes to high triglyceride levels in the bloodstream; consequently, enhancing insulin sensitivity might have favorable effects on triglyceride levels[12,16]. Through its impact on decreasing insulin levels and modifying lipid metabolism, AMN might possibly decrease hepatic triglyceride formation[28]. In clinical studies, pramlintide, a synthetic AMN analog, was demonstrated to lower TG levels in persons with diabetes and obesity[50].

LEP, which is generated by adipose tissue, plays a critical function in lipid metabolism and energy balance. It can minimize fat accumulation by boosting energy expenditure and enhancing fat oxidation. LEP operates on the hypothalamus to reduce appetite while improving the breakdown and clearance of triglycerides by boosting lipoprotein lipase (LPL), an enzyme that hydrolyzes triglycerides into lipoproteins[18,41]. Additionally, LEP reduces hepatic triglyceride production by decreasing hepatic lipogenesis, hence lowering circulating TG levels[24]. Animal research and human trials have showed that LEP treatment decreases TG levels, notably in obese and insulin-resistant people[7,22]. This observation is also verified by our investigation.

Combined AMN+LEP treatment has the ability to reduce food intake and boost energy expenditure, resulting to reduced triglyceride production and accumulation in adipose tissue[44,49]. Both AMN and LEP enhance insulin sensitivity, which can further lower the generation of triglycerides, as insulin resistance is a key factor to high triglyceride levels in obesity[24,44].

Conclusion

DIO severely impairs hepatic and renal function through numerous pathways, including elevated blood pressure, inflammation, oxidative stress, and insulin resistance. These variables lead to the development of renal damage and increasing dysfunction. Early intervention and weight control are critical to prevent or reduce the course of obesity-related hepatic and renal failure. Our work confirms the prior evidence and is more focused on hepatic and renal functions being affected by the injection of HFD in Sprague Dawley rats. We conclude that the AMN+LEP combination treatment has promise as a viable strategy for controlling DIO.

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