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Impact of Cilnidipine on Serum Lipid Profile in Alloxan- Induced Diabetic Rats

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Abstract

Diabetes mellitus (DM) emerged as a significant global health crisis in the 20th century and stood as a leading cause of mortality, particularly due to cardiovascular disease (CVD) .Within the diabetic population, a troubling increase was observed in widely recognized microvascular complications, including neuropathy, nephropathy, and retinopathy. Simultaneously, the prevalence of macrovascular complications, such as stroke, carotid artery disease, peripheral artery disease, and coronary artery disease (CAD), also rose among individuals with diabetes.

Hypertension was the most prevalent cardiovascular disease, and its global prevalence continued to increase. Both national and international guidelines advocated for the use of various drug classes, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and beta-blockers, as recommended treatments for hypertension management. Among these options, calcium channel blockers (CCBs) were widely utilized, with Cilnidipine representing a newer dihydropyridine CCB known for its sustained antihypertensive efficacy.

Cilnidipine (CLN) fell within the category of fourth-group dihydropyridine calcium channel blockers (CCBs). This medication possessed a dual mechanism of action, targeting both L and N-type calcium channels. L-type calcium channels were located on vascular smooth muscle, while N-type calcium channels were situated on presynaptic nerve terminals. Cilnidipine exerted its pharmacological influence by eliciting vasodilation, characterized by a sustained and gradual onset of action.

Alloxan, scientifically termed as 5,5-dihydroxyl pyrimidine-2,4,6-trione, was an compound organic type categorized as derivative a urea. This compound possessed carcinogenic properties and was considered a cytotoxic analogue of glucose. It could be represented by the molecular formula $C4H2N2O4$ and had a relative molecular mass of 142.06. Alloxan was frequently employed as a diabetogenic agent in research to evaluate the anti-diabetic properties of both individual compounds and plant extracts in studies focused on diabetes.

Key words: cilnidipine (CLN), calcium channel blockers (CCBs),diabetes mellitus (D.M).

Metabolic disease, characterized by inappropriately elevated blood glucose levels, was encompassed by the term Diabetes mellitus (DM) [Natalia *et al.*, 2020]. Several categories of DM were recognized, containing type 1, type 2 gestational diabetes, maturity-onset diabetes of the young (MODY),neonatal diabetes, and secondary causes attributed to steroid use, and other factors [Pace *et al.*, 2020].

The role of the pancreas in the pathogenesis of diabetes was discovered by Mering and Minkowski in 1889. Distinct clinical phenotypes with varying severity of disturbed metabolism were brought about by the combination(s) of insulin deficiency and sensitivity to its actions. Monitoring these phenotypes was most conveniently accomplished by assessing the degree of

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Corresponding author : Email : shm@uomosul.edu.iq hyperglycemia. Type 1 diabetes mellitus (DM), characterized by absolute insulin deficiency, was linked to autoimmune destruction of insulin-secreting β-cells (referred to as Type 1A DM) as well as various congenital conditions involving genetic defects affecting the formation or function of the endocrine pancreas, along with acquired conditions like relapsing pancreatitis and pancreatectomy [Ritu L., 2013].

Pancreatic beta-cell function could be impaired by hyperglycemia alone, contributing to insulin secretionimpaired. Consequentlyhyperglycemia leading to an impaired metabolic state ensued. Osmotic diuresis occurred in patients due to the saturation of glucose transporters in the nephron at higher blood glucose levels. Although the effect varied, symptoms of polyuria and polydipsia were likely to occur when serum glucose levels exceeded 250 mg/dL [Mabel *et al*., 2021]. Insulin resistance (IR) was attributed to excess fatty acids and pro-inflammatory cytokines, resulting in impaired glucose transport and increased fat breakdown. In response to inadequate insulin production or response, the body inappropriately increased glucagon, further contributing to hyperglycemia [Chang and Chuang., 2010]. Though resistance of insulin was a component of T2DM, the full extent of the disease resulted when the patient had insufficient production of insulin to recompense for their insulin resistance [Chang and Chuang, 2010].

Alloxan, chemically known as 5,5-dihydroxyl pyrimidine-2,4,6-trione, was categorized as an organic compound, specifically as a urea derivative. This compound was recognized for its carcinogenic properties and its role as a cytotoxic glucose analog [Szkudelski T., 2001]. It could be represented by the formula molecular $C_4H_2N_2O_4$ and had a comparative molecular mass of 142.06. Alloxan was commonly employed as a diabetogenic agent in research to evaluate the anti-diabetic promising of both compound spure and plant extracts in findings connecting diabetes. The induction of diabetes by alloxan principal described by Dunn and McLetchie in their research , where diabetes was efficaciously provoked in rabbits experimental [Szkudelski T., 2001].

The mechanism of action of alloxan involved two distinct pathological effects, including the inhibition selective for glucose-encouraged insulin secretion and the induction of reactive oxygen species (ROS) formation, which promoted the selective necrosis of beta cells in the pancreas. Both effects cooperatively resulted in the development of a pathophysiological state of insulin-dependent diabetes or type 1-like diabetes mellitus [Federiuk *et al*., 2004] [Lenzen S., 2008].

Blood pressure (BP) regulation, both in the quick-term and long-term, was influenced by the combined actions of multiple cardiovascular, renal, neural, endocrine, and local tissue control systems [Paul *et al*., 2021].

In primary (essential) hypertension, the precise causes of impaired renal function were not completely understood, although excessive weight gain and dietary factors appeared to play a major role, as hypertension was rare in non-obese hunter-gatherer populations living in non-industrialized societies [Rahimi *et al*., 2021]. Current developments in genetics offered occasions to discover gene-environment interactions that might also contribute to hypertension, although success in this regard had been inadequate mainly to the identification of rare monogenic forms of hypertension [Sondra *et al*., 2018].

Calcium-channel blockers (CCB), particularly dihydropyridines, were considered important first-line treatment choices in hypertension [Sondra *et al*., 2018]. CCBs were the only principal-stroke drug class that could be originated deprived of the need for information and timely follow-up of electrolyte status and kidney meaning, creating them a adjacent optimal as soon as keep on preparation was challenging. The vasodilating effects of CCBs could lead to adverse effects such as, flushing, dizziness, headache, and tibial edema, with female being additional possible to knowledge these special effects. Calcium-channel blockers, particularly nifedipine, were reflected safe for use during pregnancy and were also appropriate for considering Raynaud's phenomenon, which was extrapredominant in females[Williams *et al*., 2018]. Thiazide and thiazide-like diuretics were also considered principal-line treatments for hypertension [Rirash *et al*., 2017]. Thiazide groups was associated with a reduced risk of osteoporotic fractures, which predominantly affected females. Though, observational findings recommended that this consequence might be more clinically discernible in males, which was somewhat surprising [McDonagh *et al*., 2021].

Cilnidipine was a newer dihydropyridine calcium antagonist known for its prolonged antihypertensive properties. Cilnidipine was a diesterified 1,4-dihydropyridine-3,5-dicarboxylic acid, categorized as a calcium channel blocker [McDonagh *et al*., 2021]. Cilnidipine was first approved in Japan in 1995 and subsequently received approval from other countries, becoming one of the primary anti-hypertensive drugs in use [Soeki *et al*., 2012].

Cilnidipine was an L/N-type calcium channel blocker, and its blood pressure-lowering effects were achieved, in part, by the inhibition of sympathetic nerve activity at peripheral sympathetic nerve endings in vivo [Oladayo., 2016]. It was shown to reduce both systolic blood pressure (SBP) and diastolic blood pressure (DBP) without increasing pulse rates (PR) or plasma catecholamines. Additionally, it was found to be effective in hypertensive patients with morning hypertension, where sympathetic nerve over activity was potentially involved [Chakraborty *et al*., 2021].

Materials and Methods

The current study obtained approval from the medical research ethics committee at the College of Medicine, University of Mosul, Nineveh, Iraq. The comparative interventional study was conducted in the Animal House of the College of Veterinary Medicine, University of Mosul, Iraq, and spanned from October 2022 to the end of February 2023.

Seventy (70) adult male albino rats, weighing between 180 and 250 grams, were examined by a veterinary physician to assess their general health and condition. They underwent a one-week adaptation period before the experiments, within the facilities of the Animal House at the College of Veterinary Medicine, University of Mosul, Iraq. The rats were housed in rodent plastic cages measuring 30×20×17 cm with wire mesh covers. Homogenized wood shavings were used as bedding material, and the rats preserved at a temp. of (22 ±2)°C under a 12-hour light/12-hour dark cycle. They were provided with standard laboratory chow and had access to water ad libitum. This study adhered to the rules of the recognized animal research ethics group.

General laboratory chemicals utilized in this study met standard grades, and standard kits were employed to measure certain biochemical parameters as suggested in this study. Test procedures were performed and interpreted following the instructions provided with each kit.

Alloxan was administered intraperitoneally (I.P.) at a dose of 100 mg/kg using a freshly prepared alloxan solution. Alloxan was dissolved in (5% D.W, pH 7 at room temperature). Following alloxan injection, an oral solution of 5% glucose in tap water was prepared and provided via a water bottle immediately for the next 24 hours to prevent hypoglycemic shock and mortalities during the hypoglycemic phase. Prior to alloxan administration, the animals fasted for 12 hours while having free access to drinking water. The higher dose of alloxan typically led to death before severe diabetes could develop. To confirm the effect of alloxan and establish the diabetic state, blood samples were obtained from the tip of the rat's tail at 48 and 72 hours after injection. These blood samples were collected on a reagent strip to determine the blood glucose level using a portable glucometer (Joycoo, Hamburg, Germany). Rats with blood glucose levels above 10 mmol/L were considered diabetic. Following the stabilization of diabetes for one week, the diabetic group was divided into five subgroups, with ten rats in each subgroup, and they were treated by oral gavage for four weeks as follows:

Group I: Diabetic control group (D.C); received just 5%D.W.

Group II: Diabetic control group+ methyl cellulose (D.C+M.C); received daily 50 – 2000 mg/kg methyl cellulose only.

Group III: diabetic rats ; received a daily cilnidipine in dose (1 mg/kg) with methyl cellulose (1%).

Group IV: diabetic rats; received a daily cilnidipine in dose (5 mg/kg) with methyl cellulose (1%).

Group V: diabetic rats; received a daily cilnidipine in dose (10 mg/kg) with methyl cellulose (1%).

The normal control groups (20 rats) were subdivided in to:

① Normal controls (N.C) (10 rats) ; received just 5% D.W.

②Normal controls+Methyl cellulose (N.C+M.C) (10 rats) received Methyl cellulose 1% as vehicle in a dose of 50-2000 mg/kg daily.

The collection of blood samples was initiated after the rats had undergone a 12-hour fasting period. Blood sampling was conducted by withdrawing blood from the retro-orbital venous plexus under light ether anesthesia. Micro hematocrit capillary tubes were employed for this purpose, and the blood was collected in gel activator tubes. Blood collection occurred at the commencement of the study (following diabetes induction) and subsequently on the 14th and 28th days of the study. The collected blood was allowed to coagulate, and serum separation was achieved by subjecting it to centrifugation at a speed of 4000 revolutions per minute for 15 minutes. The resulting serum was then stored at (-20)° C until biochemical analyses of Fasting plasma glucose (FPG), Fasting serum insulin, Fasting serum c-peptide, and serum lipid profile were conducted.

Results

After 28 day of treatment with cilnidipine, there was a significant differences in serum cholesterol level between NC groups and CLN1+D.C, CLN5+D.C, CLN10+D.C, (*p*= 0.0031,0.0012,0.0401) respectively. In compar-

Table I: Impact of different doses of Cilnidipine (CLN) on serum cholesterol levels (mg/dl) after 28-day treatment period.

Groups **Parameter**	**Control (n=10)**	**Control+ M.C (n=10)**	**D.M (n=10)**	**D.M+ M.C (n=10)**	**CLN1+D.M (n=10)**	**CLN5+D.M (n=10)**	**CLN10+D.M (n=10)**
Serum Cholesterol Level	44.07	43.63	73.415	74.32	73.94	59.93	51.50
(mg\dl)	a	a	c	c	c	b	b
Mean							
SEM	1.146	2.098	2.682	5.652	1.136	1. 1.34	0.6683
***P*- Value**				0.000***			
Control vs. Control M.C		0.998					
Control vs. D.M			0.000***				
Control vs.D.M+M.C				0.000***			
Control vs. CLN1+D.M					0.0031**		
Control vs. CLN5+D.M						0.0012**	
Control vs. CLN10+D.M							0.0401*
D.M vs. D.M+M.C				0.999			
D.M vs. CLN1+D.M					0.0589		
D.M vs. CLN5+D.M						0.0001**	
D.M vs. CLN10+D.M							0.001**
CLN1+D.M vs. CLN5+D.M						0.0031*	
CLN1+D.M vs. CLN10+D.M							0.00107**
CLN5+D.M vs. CLN10+D.M							0.729

In the present study, normality tests (Kolmogorov-Smirnov, Shapiro-Wilk) were conducted on all groups to assess data distribution.

Subsequently, the data underwent one-way ANOVA, shadowedby the Post Hoc Tukey test, to examine differences between the groups. In the results, small superscript letters (a, b) indicate that the groups with the same letter exhibited no significant differences, while different letters signify distinctions between groups. Furthermore, significance levels were denoted as follows: * for a significant difference at $p < 0.05$ and ** for highly significant differences at $p < 0.01$.

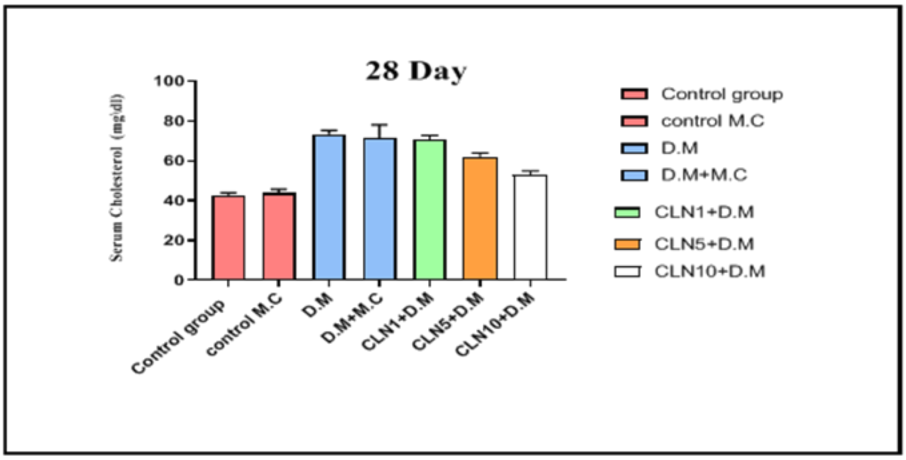

Fig 1 : Impact of cilnidipine (CLN) on serum cholesterol level (mg\dl) after 28 treatment period.

ing the diabetic control groups with CLN5+D.C and CLN10+D.C, there were a significant reduction in serum cholesterol level especially with CLN10+D.C (*p*= 0.0001,0.001). (Table I) (Fig 1).

After a 28-day treatment period, the groups treated with different doses of CLN (CLN1+D.M, CLN5+D.M, and CLN10+D.M) showed reduced triglyceride levels compared to the diabetic group (*p*= 0.0020,0.0091,0.0039) respectively.

CLN10+D.M group exhibited the most substantial reduction in triglyceride levels (*p*= 0.000,0.00). (Table II) (Fig 2).

Table II : Impact of different doses of Cilnidipine (CLN) on serum triglyceride level (mg\dl) after a 28-day treatment period.

Groups Parameter	Control (n=10)	Control+ M.C (n=10)	D.M (n=10)	D.M+ M.C (n=10)	CLN1+D.M (n=10)	CLN5+D.M (n=10)	CLN10+D.M (n=10)
Triglyceride Level (mg\dl) Mean	75.75 a	74.75 a	183.8 e	184.8 e	137.8 d	98.25 c	83.50 b
SEM	1.702	1.548	1.941	0.7071	0.7500	0.4787	2.901
P- Value				0.000***			
Control vs. Control M.C		0.998					
Control vs. D.M			0.000***				
Control vs.D.M+M.C				0.000***			
Control vs. CLN1+D.M					0.0020*		
Control vs. CLN5+D.M						0.0091*	
Control vs. CLN10+D.M							0.0039*
D.M vs. D.M+M.C				0.998			
D.M vs. CLN1+D.M					0.00312*		
D.M vs. CLN5+D.M						0.000***	
D.M vs. CLN10+D.M							0.000**
CLN1+D.M vs. CLN5+D.M						0.0054*	
CLN1+D.M vs. CLN10+D.M							0.007*
CLN5+D.M vs. CLN10+D.M							0.005*

In the present study, normality tests (Kolmogorov-Smirnov, Shapiro-Wilk) were conducted on all groups to assess data distribution.

Subsequently, the data underwent one-way ANOVA, followed by the Post Hoc Tukey test, to examine differences between the groups. In the results, small superscript letters (a, b) indicate that the groups with the same letter exhibited no significant differences, while different letters signify distinctions between groups. Furthermore, significance levels were denoted as follows: * for a significant difference at $p < 0.05$ and ** for highly significant differences at $p < 0.01$.

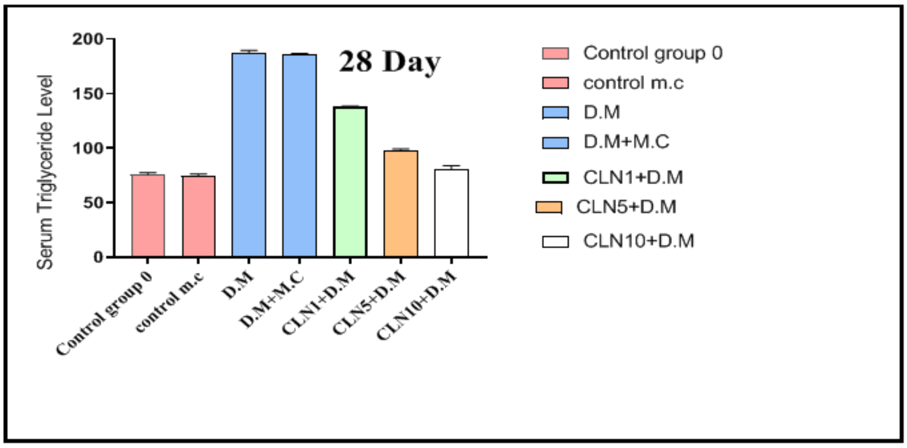

Fig 2 : Impact of cilnidipine (CLN) on serum triglyceride level (mg\dl) at day 28 from treatment period .

(Table III) and (Fig 3) showed a significant differences in serum HDL-c level between NC groups and CLN1+D.C, CLN5+D.C, CLN10+D.C (*P*= 0.000). In comparing to the diabetic control groups, CLN5+D.C and CLN10+D.C, showed a significant elevation in serum HDL- c level especially with CLN10+D.C (*P*= 0.000) .

(Table IV) and (Fig 4), presented the impact of different doses of Cilnidipine (CLN) on serum low-density lipoprotein (LDL-c) levels after a 28-day treatment period in

Table III : Impact of different doses of Cilnidipine (CLN) on serum high density lipoprotein cholesterol (HDL-c) (mg\dl) after 28-day treatment period

Groups **Parameter**	**Control (n=10)**	**Control+ M.C (n=10)**	**D.M (n=10)**	**D.M+ M.C (n=10)**	**CLN1+D.M (n=10)**	**CLN5+D.M (n=10)**	**CLN10+D.M (n=10)**
High Density Lipoprotein Cholesterol(mg\dl) Mean	23 d	23.94 d	14.80 c	15.00 c	16.00 c	16.60 c	17.40 c
SEM	1.79	1.19	1.48	2.115	0.4082	0.500	1.291
***P*- Value**				0.000***			
Control vs. Control M.C		0.987					
Control vs. D.M			0.000***				
Control vs.D.M+M.C				0.000***			
Control vs. CLN1+D.M					0.000***		
Control vs. CLN5+D.M						0.000***	
Control vs. CLN10+D.M							0.000***
D.M vs. D.M+M.C				0.839			
D.M vs. CLN1+D.M					0.000 ***		
D.M vs. CLN5+D.M						0.000 ***	
D.M vs. CLN10+D.M							0.000 ***
CLN1+D.M vs. CLN5+D.M						0.0618	
CLN1+D.M vs. CLN10+D.M							0.102
CLN5+D.M vs. CLN10+D.M							0.281

In the present study, normality tests (Kolmogorov-Smirnov, Shapiro-Wilk) were conducted on all groups to assess data distribution.

Subsequently, the data underwent one-way ANOVA, followed by the Post Hoc Tukey test, to examine differences between the groups. In the results, small superscript letters (a, b) indicate that the groups with the same letter exhibited no significant differences, while different letters signify distinctions between groups. Furthermore, significance levels were denoted as follows: * for a significant difference at $p < 0.05$ and ** for highly significant differences at $p < 0.01$.

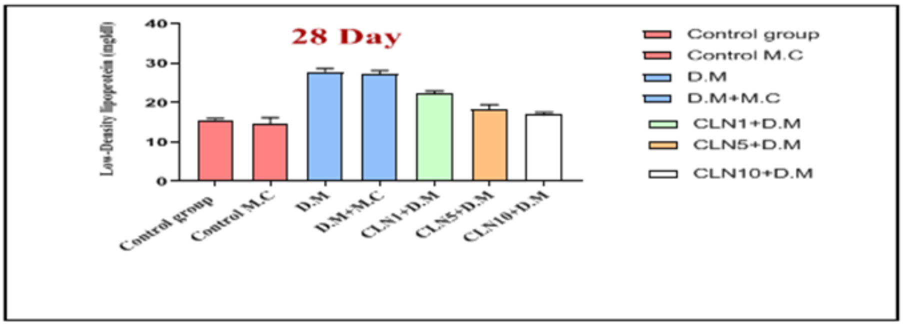

Fig 3 : Impact of cilnidipine (CLN) on high density lipoprotein cholesterol (HDL-c) (mg\dl) after 28 day treatment period

various groups. The control group showed the lowest mean serum LDL level, denoted by the letter “a”, while the group with diabetes (D.M) exhibited the highest mean LDL level, denoted by the letter “c”. The groups treated with CLN at different doses (CLN1+D.M, CLN5+D.M, CLN10+D.M) showed intermediate mean LDL levels, denoted by the letter “b”.

The control group and control+ M.C group had comparable VLDL-c levels, whereas the D.M group (representing diabetic rats) showed significantly elevated VLDL-c levels. The D.M+M.C group had VLDL-c levels similar to the D.M group. In contrast, the CLN1+D.M, CLN5+D.M, and CLN10+D.M groups exhibited reduced VLDL-c levels compared to the diabetic group. Statistical analysis revealed significant differences among the groups, with the CLN10+D.M group displaying the most considerable reduction in VLDL-c levels. These results suggested that cilnidipine

Table IV : Impact of different doses of cilnidipine (CLN) on serum low-density lipoprotein (LDL-c) (mg/dl) after 28-day treatment period.

Groups **Parameter**	**Control** **(n=10)**	**Control+ M.C** **(n=10)**	**D.M** **(n=10)**	**D.M+ M.C** **(n=10)**	**CLN1+D.M** **(n=10)**	**CLN5+D.M** **(n=10)**	**CLN10+D.M** **(n=10)**
Serum LDL(mg\dl)	15.60	16.60	27.85	27.20	22.84	18.23	16.35
Mean	a	a	c	c	b	b	a
SEM	0.5228	1.711	0.873	1.013	1.314	0.5603	0.4856
***P*- Value**				0.000***			
Control vs. Control M.C		0.998					
Control vs. D.M			0.000***				
Control vs.D.M+M.C				0.000***			
Control vs. CLN1+D.M					0.0031**		
Control vs. CLN5+D.M						0.0012**	
Control vs. CLN10+D.M							0.0765
D.M vs. D.M+M.C				0.999			
D.M vs. CLN1+D.M					0.0489*		
D.M vs. CLN5+D.M						0.0001**	
D.M vs. CLN10+D.M							0.001**
CLN1+D.M vs. CLN5+D.M						0.06	
CLN1+D.M vs. CLN10+D.M							0.00107**
CLN5+D.M vs. CLN10+D.M							0.008**

In the present study, normality tests (Kolmogorov-Smirnov, Shapiro-Wilk) were conducted on all groups to assess data distribution.

Subsequently, the data underwent one-way ANOVA, followedshadowedby the Post Hoc Tukey test, to examine differences between the groups. In the results, small superscript letters (a, b) indicate that the groups with the same letter exhibited no significant differences, while different letters signify distinctions between groups. Furthermore, significance levels were denoted as follows: * for a significant difference at $p < 0.05$ and ** for highly significant differences at $p < 0.01$.

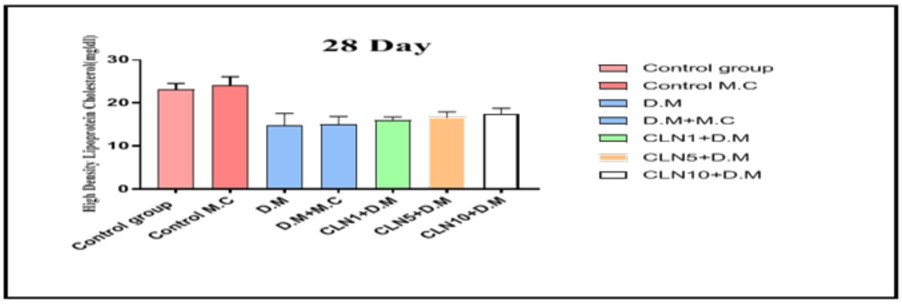

Fig 4 : Impact of cilnidipine (CLN) on low-density Lipoprotein (LDL-c) (mg/dl)) at day 28 from the treatment period

treatment may effectively lower VLDL-c levels in diabetic individuals, especially at a dose of CLN10+D.M, during a 28-day treatment period (Table V) (Fig 5).

Statistical Analysis

Statistical analysis utilized SPSS 23. Data preparation occurred in Excel 2010. Normality checked with Kolmogorov-Smirnov and Shapiro-Wilk tests ($p > 0.05$ indicates normality). Parametric tests followed normal distribution. Descriptive stats presented as mean ± SEM. One-way ANOVA with Tukey's post hoc for comparisons ($p < 0.05$ significant, $p < 0.01$ highly significant). Paired t-test used for related groups at days 14 and 28. GraphPad Prism 8 for graphical representation.

Discussion

The deterioration of the plasma lipoprotein

Table V : Impact of different doses of cilnidipine (CLN) on serum very low density lipoprotein cholesterol (VLDL-c) (mg\dl) after 28-day treatment period

Groups **Parameter**	**Control** **(n=10)**	**Control+ M.C** **(n=10)**	**D.M** **(n=10)**	**D.M+ M.C** **(n=10)**	**CLN1+D.M** **(n=10)**	**CLN5+D.M** **(n=10)**	**CLN10+D.M** **(n=10)**
Very Low-Density Lipoprotein (mg\dl)	12.8	13.95	27.44	27.05	24.83	20.95	19.36
Mean	a	a	c	c	bc	b 0.4500b	b
SEM	0.9201	1.075	3.545	2.589	1.296	0. 4500	0.6765
***P*- Value**				0.000***			
Control vs. Control M.C		0.987					
Control vs. D.M			0.000***				
Control vs.D.M+M.C				0.000***			
Control vs. CLN1+D.M					0.000***		
Control vs. CLN5+D.M						0.000***	
Control vs. CLN10+D.M							0.000***
D.M vs. D.M+M.C				0.999			
D.M vs. CLN1+D.M					0.0310*		
D.M vs. CLN5+D.M						0.0111*	
D.M vs. CLN10+D.M							0.001***
CLN1+D.M vs. CLN5+D.M						0.090	
CLN1+D.M vs. CLN10+D.M							0.0700
CLN5+D.M vs. CLN10+D.M							0.6030

In the present study, normality tests (Kolmogorov-Smirnov, Shapiro-Wilk) were conducted on all groups to assess data distribution.

Subsequently, the data underwent one-way ANOVA, followed by the Post Hoc Tukey test, to examine differences between the groups. In the results, small superscript letters (a, b) indicate that the groups with the same letter exhibited no significant differences, while different letters signify distinctions between groups. Furthermore, significance levels were denoted as follows: * for a significant difference at $p < 0.05$ and ** for highly significant differences at $p < 0.01$.

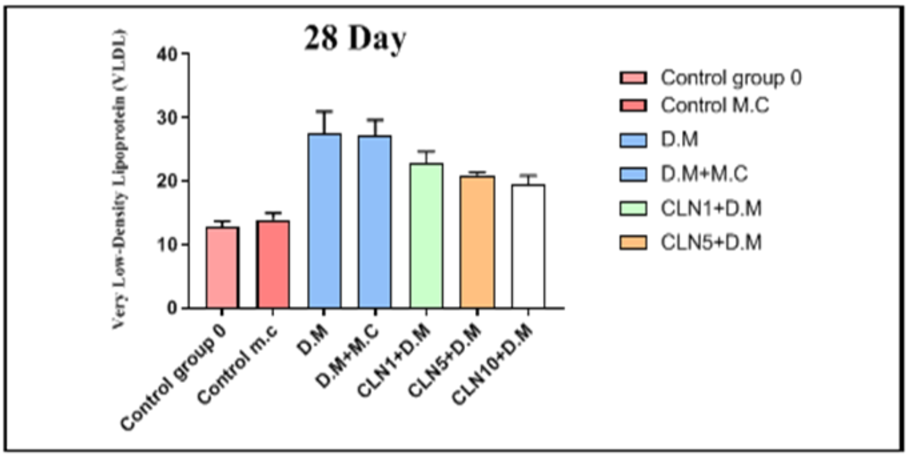

Fig 5 : Impactof cilnidipine (CLN) on very low-density Lipoprotein (VLDL-c) (mg/dl) at day 28 from treatment period

profile is almost always associated with diabetes mellitus, and as a result, it can lead to an increase in atherogenesis in diabetic patients [Daisuke *et al.*,2012].

A study conducted by Khatun Kali [Khatun *et al.*,2022] demonstrated that CLN had improved the lipid profile by blocking α-adrenoceptors, potentially enhancing tissue uptake of lipids and triglyceride hydrolysis by lipoprotein lipase. It was hypothesized that CLN might also reduce total cholesterol synthesis, decrease hepatic triglyceride output, and enhance LDL metabolism by increasing its binding to hepatic receptors.Several studies have reported favorable changes in lipid profiles with the use of cilnidipine, including reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-c), and triglyceride levels [Kaneshiro,2007]. Another study observed improvements in lipid metabolism among hypertensive patients with type 2 diabetes, noting reductions in triglyceride levels and increases in high-density lipoprotein cholesterol (HDL-c) levels with cilnidipine treatment [Dangi *et al.*,2016].The precise mechanism by which cilnidipine influences lipid metabolism remains not fully elucidated. Nevertheless, it is suggested that cilnidipine may exert a favorable impact on lipid profiles by reducing sympathetic nerve activity, which can contribute to dyslipidemia [Kumar *et al.*, 2016]. Cilnidipine has been shown to decrease sympathetic nerve activity by blocking calcium channels in sympathetic nerve endings, resulting in reduced release of neurotransmitters like norepinephrine. This decrease in sympathetic nerve activity may lead to decreased lipolysis (fat breakdown) and increased lipid uptake and storage in adipose tissue, contributing to improvements in lipid profiles [Kaneshiro,2007]. Additionally, cilnidipine may directly affect lipid metabolism by activating peroxisome proliferator-activated receptors (PPARs), nuclear receptors that play a pivotal role in regulating lipid and glucose metabolism. Activation of PPARs has been associated with increased lipid uptake and decreased lipid synthesis, ultimately contributing to improved lipid profiles [Kumar *et al.*, 2016].

The N-type calcium channelblocking, cilnidipine circuitously leads to α-receptor blockade, which enhances lipid profiles through peripheral vasodilation, facilitating lipid uptake &glucose by muscle cells. This blockade may also increment the accessibility of lipoprotein lipase heading fortriglyceride hydrolysis. Moreover, hepatic α-1-adrenoceptor blockade may adjust glycogenolysis and gluconeogenesis, diminution-triglyceride production from the liver, decrease cholesterol synthesis, and promote the mandatory binding of LDLs to their receptors in liver [Kumar *et* al., 2016[.

In a study conducted by Shravanthi Manthri *et al.* [Shravanthi *et al.*, 2015] observed a significant decrease in serum triglyceride levels in hypertensive rats fed a high-fat diet and treated with cilnidipine for 12 week. The authors suggested that cilnidipine, by blocking the N-type calcium channel, indirectly caused α-receptor blockade, thereby improving lipid profiles through peripheral vasodilation, potentially enhancing glucose and lipid uptake by muscle cells. This blockade might have further more increased the obtainability of lipoprotein lipase for triglyceride hydrolysis. Additionally, hepatic α-1-adrenoceptor blockade might have influenced glycogenolysis, gluconeogenesis, triglyceride output, cholesterol production and accelerate the binding of low-density lipoproteins (LDLs) to their hepatic receptors.

Conclusion

As a conclusion, treatment with cilnidipine for 28 day in alloxan- induced diabetic rats cause a significant reduction in serum cholesterol level, serum triglyceride level, LDL-c, VLDL-c and highly significant increment in HDL-c especially with CLN 10mg.

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