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EVALUATION OF ENDOCAN AND ENDOGLIN AS PREDICTIVE MARKERS OF ENDOTHELIAL DYSFUNCTION IN WISTAR ALBINO RATS TREATED WITH A SINGLE DOSE OF STZ AND HFD

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Keywords:

Endocan, Endoglin, Endothelial Dysfunction, Streptozotocin, High fat diet, Diabetes mellitus

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ABSTRACT: A major susceptibility indicator for type 2 diabetes and cardiovascular diseases is obesity-related insulin resistance. Vascular endothelial cells strongly express the coreceptors for members of the transforming growth factor (TGF) superfamily, endocan and endoglin. Examining endocan and endoglin as potential indicators of cardiovascular complications in HFD rats with or without type 2 diabetes mellitus is the goal. The following four groups; normal diet-HFD, normal diet-STZ, and HFD-STZ were each comprised of eight wistar rats. Both types of type 2 DM groups had significantly higher levels of plasma glucose, insulin, glycosylated haemoglobin (HbA1c), and homeostatic model assessment (HOMA-IR) when compared to the control group ($P < 0.001$). Comparing the HFD and HFDSTZ groups to the STZ and control Normal Diet groups, respectively, the serum lipid patterns in the HFD and HFD-STZ groups were drastically different levels were seen in comparison to the control group in all groups, but the HFD STZ- group had higher percentage change values. Both the HFD-STZ and the normal diet STZ groups had significantly higher levels of soluble endoglin in their sera ($P < 0.001$), and these elevations were similar to those of VCAM. In the Normal Diet and HFDSTZ groups, soluble Endocan and endoglin significantly correlated with plasma glucose, insulin, and HOMA-IR as well as with total cholesterol in the groups HFD and HFD-STZ. Consequently, soluble endocan, endoglin may suggest they are useful.

INTRODUCTION: Both the morbidity and mortality caused by the consequences of type 2 diabetes mellitus (T2DM) are rising globally [1]. The modern lifestyle, which includes altered eating patterns, over nutrition, and physical inactivity is largely to blame.

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Reactive Oxygen Species (ROS) are produced in excess by hyperglycemia; likewise, this occurs whenever the antioxidant defence capacity is overwhelmed, which results in a chemical unbalance that may create a toxic and harmful environment.

The activation of pro-inflammatory signaling pathways, increased proinflammatory cytokine release, and subsequent persistent inflammatory responses, as well as the activation of apoptotic cell death and tissue damage, are only a few of the molecular mechanisms that ROS triggers [2]. Thus, research has suggested that the emergence of

insulin resistance (IR) type 2 diabetes mellitus (T2DM) influenced by oxidative stress (OS) and systemic inflammation brought on by hyperglycemia [3]. IR is associated with higher rates of cerebrovascular disease and coronary artery disease in addition to doubling the risk of developing cardiovascular disease (CVD) [4]. A common finding in T2D is dyslipidemia secondary to IR [5]. Increased secretion of proinflammatory cytokines, adipokines, and free fatty acids from visceral adipose tissue depots are the reasons [6], these cytokines not only promote structural and functional alterations in protein and lipoprotein molecules, but they also cause abnormalities in endothelial cells, which lead to atherosclerosis [7].

Endocan is an intriguing proteoglycan that is closely linked to inflammation and concurrent endothelial dysfunction [8]. Many cardio metabolic disorders, including type 2 diabetes, fatty liver diseases, hypertension, have greater levels of this inflammation marker, according to recent investigations [9]. Nonetheless, obesity is a recognized predictive factor for a number of cardio metabolic diseases [10]. A few of the postulated mechanisms relating obesity and cardiovascular disease include the increased inflammatory cytokines in adiposities, the imbalance between free radical generation and antioxidant protection, the increased transport of liberated fatty acids, and hepatocyte malfunction (CVD). Decreased nitric oxide production with concomitant vasoconstriction, altered insulin signaling pathways, and endothelial dysfunction are other mechanisms that contribute to this pathogenesis [11].

In light of this, endocan is becoming a possible biomarker of endothelial dysfunction and is shown that it's more prevalent in type-2 diabetes and cardiovascular disease. This proteoglycan has the ability to drive endothelial cells to release a variety of proinflammatory cytokines, speed up leukocyte migration, and enhance blood vessel permeability, making it a viable biomarker for detecting high atherosclerotic disease risk loads [12]. Although a number of earlier researchers found that T2D patients had increased amounts of endocan than controls, other investigations found the contrary, *i.e.,* that T2D patients had lower endocan levels. As a result, the pathophysiological function of this biomarker is varied. Understanding of the many stages of diabetes, including prediabetes and overt Type 2 diabetes, is lacking [13]. Endothelial dysfunction typically manifests in early, generally relatively simple type 2 diabetes and is evidenced by reduced endothelium-dependent vasodilatation. The condition frequently co-occurs with cardiovascular risk factors such as hypertension, obesity, and dyslipidemia. It has also been shown that endothelial dysfunction is a powerful predictor of future unfavourable cardiovascular events [14]. Circulatory biomarkers have been successful in identifying therapeutic targets in addition to forecasting the onset of diabetes and its implications [15].

A type I transmembrane glycoprotein called endoglin, also known as CD105, may have a role in hematopoiesis as well as the development of the heart and blood vessels and angiogenesis. A 180 kDa homodimer with disulfide connections makes up glycoprotein [16]. Endoglin is produced by alternative splicing into two isoforms: the long isoform (L-endoglin) and the short isoform. of endoglin [17]. The metalloproteinase MMP-14's proteolytic cleaving activity in the extracellular domain close to the membrane can result in the production of an endoglin soluble form. It has been demonstrated that endoglin interacts with TGF-receptor 1 and TGF-receptor 2. On vascular endothelial cells, it is strongly expressed. Certain endothelial receptors of the transforming growth factor - ß (TGF-ß) superfamily, such as endoglin and activin like kinase-1 (ALK-1) proteins are necessary for vascular integrity.

TGF-ß can activate two different type I receptors (ALK1 and ALK5) in endothelial cells through binding to the TGF-ß type II receptor, and each one has opposing effects on endothelial cell proliferation and migration [18]. Endoglin is essential for maintaining the proper balance between ALK1 and ALK5 signalling, which controls how quickly endothelial cells proliferate in response to TGF-ß. Atherosclerotic arteries showed endoglin expression, primarily in endothelial cells and smooth muscle cells in different kinds of arteries seen in both mice and humans, suggesting that they may play a role in atherogenesis. Also expressed in cardiac fibroblasts, endoglin controls angiotensin II's profibrogenic effects [19].

Endoglin plasma levels and glycemia in diabetic patients have now been linked, according to research that supports the relationship between endoglin and metabolism [20]. Changes in glucose metabolism, or the metabolic syndrome, are clearly correlated with endothelial dysfunction, and the release of soluble endoglin (sol. Eng) during hypoxic stress is a sign of vascular disorders linked to hypertension and diabetes in both humans and animals [21]. The current study's objectives were to explore the relationship between sol. endoglin and hyperglycemia, and endothelial dysfunction in obese and/or Type 2 diabetic patients, and ascertain whether sol. Endocan and endoglin can be used as a potential biomarkers for predicting future adverse cardiovascular events in those patients.

MATERIAL AND METHODS:

Experimental Animals: Male Wistar albino rats were procured from the Biogen Laboratory Animal Facility in Bangalore India, weighing between 170-230 Gms. Four rats were housed in each polypropylene cage and for experiments. During the 12:12 hour day and dark cycle, the main animal housing is kept at a constant room temperature of 25° and has a relative humidity of 45–55%. Before the start of experiment, they were kept for a week to get used to the lab setting and were provided with regular lab feed and filtered water.

Experimental Design:

Following acclimatization, each of the 32 Animals was Randomly Divided into four Groups 8 in Each Group and Treated as follows:

Group I: HFD for 42 days.

Group II: HFD for 42 day and STZ 40mg/kg

Group III: Normal Diet for 42 days and STZ 40mg/kg.

Group IV: Normal Diet for 42 days.

During 42 days, rats in groups I and II received a 60% HFD **Table 1** (Protein 20%, Fat 60%, and Carbohydrate 20%), while groups III and IV received a standard diet **Table 2** (Fat% k cal - 16.Carbohydrate% k cal)-64% Protein% k cal 2%). (Purina rations) [22]. The appropriate diets were fed to rats for 42 days. The diet's composition is shown in the table below. The HFD was purchased from VRK Nutritional Solutions in Sangli, Maharashtra. The chemical and reagents used were of the analytical grade.

TABLE 1: COMPOSITION OF HIGH FAT DIET

Sr. no.	Ingredients	Detected Value
1.	Moisture	5.50 5%
2.	Protein	18.20%
3.	Fat	35.30%
4.	Fiber	2.50%
5.	Calcium	1.27%
6.	Phosphorus	0.66%
7.	Total Ash	4.10%
8.	Carbohydrates	20%
9.	Energy	5200 kcal/kg 20%
10.	Energy through Protein	1050 kcal/kg 20%
11	Energy through Fat	3120 kcal/kg 60%
12.	Energy through Carbohydrate	1030 kcal/kg 20%

TABLE 2: COMPOSITIONS NORMAL DIETS

Sr. no.	Ingredients (g/kg)	
1	Sucrose	500
2	Casein	200
3	Lard	0.00
4	Corn starch	150
5	Cellulose	50
6	Mineral mixture	35
7	Soybean Oil	50
8	Vitamin mixture	10
9	Choline bitartrate	2
10	L-Cystein	3
11	Fat (% kcal)	16
12	Carbohydrate (% kcal)	64
13	Protein (% kcal)	20
14	Energy (kcal/g)	4.00

Establishment of a Type 2 Diabetes Model Induced by HFD/STZ: Rats were given a single intraperitoneal injection of streptozotocin (STZ) (Ref. no JPS 22-23 1386 Code S0130 Sigma Aldrich, USA) at a low dose (40 mg/kg body weight, dissolved in 0.05 M citrate buffer, pH 4.5) after 42 days of high fat diet induction. The HFD was administered to the rats for 42 days in order to produce type 2 diabetes. The effects of STZ (40 mg/kg body weight) and the HFD were both studied to find the optimum dose for producing T2DM. One week following the injection of STZ, the plasma glucose levels in the control groups (ND and HFD) were determined, and rats with a glucose concentration of more than 250 mg/dL received only the vehicle (0.9% saline solution). The rats' individual diets were permitted to be consumed until the study's conclusion. Because of their HFD, the diabetic group of rats developed insulin

resistance; as a result, even a little insult from a modest dose of STZ would impair -cell activity and cause hypoinsulinemia.

Until the completion of the project, fasting plasma glucose and body weight were assessed every week. At the end of the experiment, all the rats were starved overweight and an overdose of the anesthetic ketamine hydrochloride (Ketalar, Pf) was used for euthanasia. Micro capillary tubes were used to collect the blood from retro-orbitally plexus.For the examination of serum Fasting plasma glucose, lipid profile and endothelial markers in serum was separated by centrifugation (4000 rpm, 10 min), after the blood collection.

Assay of Biochemical Parameters:

Evaluation of Glucose, Lipid Profile and Endothelial Dysfunction Markers: After a 12-hour fast, 3 ml of blood was drawn while being gently sedated with ether via a retro-orbital puncture. The blood was then placed in a sterile test tube with EDTA. Many biochemical markers were measured using commercially available kits, including fasting plasma glucose (GOD/POD technique), plasma cholesterol (CHOD/PAP method), triglyceride (GPO / PAP method), and HDL (Peg precipitation method) [23, 24, 25]. LDL cholesterol was determined using the formula published by Friedwald *et al.*

LDL-C = Total cholesterol - [HDL+ VLDL]

VLDL = Triglyceride /5 in this case

Using a store-bought kit the manufacturer's recommendations were followed while measuring insulin using the Sensitive Rat Insulin Enzyme Immunoassay Kit (EZRMI-13K, Millipore, Billerica, MA, USA).Using ELISA, the serum endocan and endoglin protein levels were determined. In accordance with the manufacturer's recommendations, an ELISA kit was used to measure the levels of endocan and endoglin (Cat no: ab193722; Abcam). The values were shown as pg/ml for serum.

Statistical Evaluation: In the current study, descriptive and inferential statistical analysis was completed. Results for categorical data are reported in Number (%) whereas results for continuous measurements are presented as Mean ± SD (Min-Max). The 5% level of significance is used to determine significance. To ascertain whether there are any statistically significant differences between the means of three or more independent (unrelated) groups, the one-way analysis of variance (ANOVA) is used. After an ANOVA, use a Post-Hoc Tukey test.

Statistical Software: For the data analysis, SPSS 22.0 and R environment ver. 3.2.2 were utilised, and Microsoft Word and Excel were used to produce graphs, tables, and other output

RESULTS:

Effect of Experimental Diet and STZ (40mg /kg BW) on Biochemical Parameters: The results shown in **Table 3 Fig. 1** reveal a the considerable variation between averages of the four groups, with the HFD + STZ group and Normal Diet + STZ group's mean values of (320.1±48.8) with a p-value of <0.001 being significantly higher than the HFD and ND group's (129.1±11.5).

These findings show that a high fat diet and the presence of streptozotocin result in significantly higher glucose levels, suggesting that a person's risk of developing diabetes may be increased by both an unhealthy diet and environmental factors.

Overall, the results suggest that there is a statistically considerable variation between the four values according to fasting plasma glucose a 48th day later of the experiment these findings demonstrate that fasting plasma glucose levels vary depending on the group and are highly statistically significant when comparing the four groups cardiovascular issues.

The mean values for Fasting Plasma Glucose (FPG) shown in **Table 3**. **Fig. 3** the considerable variation between averages of the four groups, the group –II (HFD + STZ) and group-III (ND + STZ) group's mean values of (376.83±47.38, 320.16±48.87) with a p-value of <0.001 being significantly higher than the group-I (HFD) and group-II (ND) group's (165.03±5.27, 129.1±11.5.

The mean HOMA IR Values in group- I (HFD), and group-IV (ND) were found to be considerably lower (p<0.001) than those in group-II (HFD + STZ), group-III (ND + STZ). The values of HOMA IR for the four group were group I (HFD), group-II (HFD + STZ), group-III (ND + STZ), group-IV

(ND) (9.6±1.48, 12. 19±1.92, 11.61±0.55, 7.12±0.92) and they are shown in **Table 3** & **Fig. 4**. With regard to HbA1c the average values in group-I (HFD), and group-IV (ND) were noticeably lower ($p<0.001$) than those in group-II (HFD + STZ), group-III (ND + STZ) The values of HbA1c of the four group were group I (HFD), group-II (HFD + STZ), group-III (ND + STZ), group-IV (ND) (5.83±0.35, 11.21±0.44, 9.41±0.45, 5.19±0.14) and are indicated in **Table 3** & **Fig. 5.**

Focusing upon the overall mean of the fasting plasma insulin concentration in group- I (HFD), and group-IV (ND) showed a significant elevation ($p<0.001$) in comparison to group-II (HFD + STZ) , group-III (ND + STZ).

The values for Fasting Insulin (µU/mL) in the four group were group I (HFD), group-II (HFD+STZ), group-III (ND + STZ), group-IV (ND) (28.7±0.9, 13.29±0.6, 12.8±1.69, and 21.83±0.91) and they are displayed in **Table 3** & **Fig. 6. Table 3** and **Fig. 7, 8, 9** and **10** demonstrate that serum concentrations of TC, TGs, and LDL-C were markedly increased while HDL-C was reduced by roughly 50% in rats.

The mean serum Endocan level was significantly higher in HFD + STZ (305.79±41.45 pg/mL) compared to Normal Diet + STZ (232.54±28.25 pg/mL), ND (166.83±9.69 pg/mL), and HFD (180.06±12.3 pg/mL) *(*$p<0.001$) the values described in **Table 3 Fig. 12.**

The values shown in **Table 3 Fig. 13** show that the mean serum Endoglin level was considerably higher in HFD + STZ (7.940.54pg/mL) than in Normal Diet + STZ (60.44pg/mL), ND (4.62 pg/mL), and HFD (5.44pg/mL) ($p< 0.001$). This finding implies that serum Endoglin levels may be significantly affected by the interaction of a high-fat diet and STZ-induced diabetes.

TABLE 3: FPG / HOMA-IR /HBA1C/ FASTING INSULIN LIPID PROFILE AND ENDOCAN ENDOGLIN-COMPARISON IN FOUR DIFFERENT GROUPS OF RATS STUDIED

Biochemical parameters	High Fat Diet	High Fat Diet and STZ	Normal Diet and STZ	Normal Diet	P Value
Fasting Plasma Glucose mg/dl	165.03±5.27	376.83±47.38	320.16±48.87	129.11±15.99	<0.001**
HOMA IR Value	11.61±0.55	12.19±1.92	9.6±1.48	7.12±0.92	<0.001**
HbA1C %	5.83±0.35	11.21±0.44	9.41±0.45	5.19±0.14	<0.001**
Fasting Insulin (µU/mL)	28.7±0.9	13.29±0.6	12.8±1.69	21.83±0.91	<0.001**
Total Cholesterol mg /dl	138.83±1.66	206.03±18.44	167.94±4.68	94.15±9.8	<0.001**
Triglyceride mg /dl	165.9±3.07	172.76±3.53	171±7.32	84.34±6.46	<0.001**
HDL-Cholesterol mg/dl	34.86±3.09	19.72±0.59	21±0.82	50.29±1.9	<0.001**
LDL –Cholesterol mg/dl	64.08±6.84	147.93±2.53	47.26±2.31	18.48±1.36	<0.001**
VLDL Cholesterol	33.18±0.73	34.43±0.6	34.28±1.48	16.8±1.32	<0.001**
ENDOCAN pg/ml	180.06±12.3	305.79±41.45	232.54±28.25	166.83±9.69	<0.001**
ENDOGLIN pg/ml	5.44±0.49	7.94±0.54	6±0.44	4.62±0.52	<0.001**

The data is displayed as mean SEM (n = 8). Significant variations between columns are denoted by different letters ($p < 0.001$). The data were analysed using one-way ANOVA and the Tukey post-hoc test.

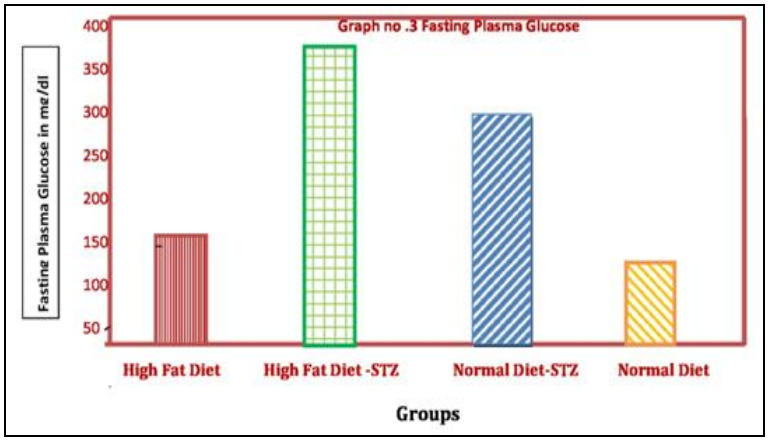

FIG. 3: THE OUTCOME OF DIET AND STZ ON FASTING PLASMA GLUCOSE IN THE EXPERIMENTAL GROUP

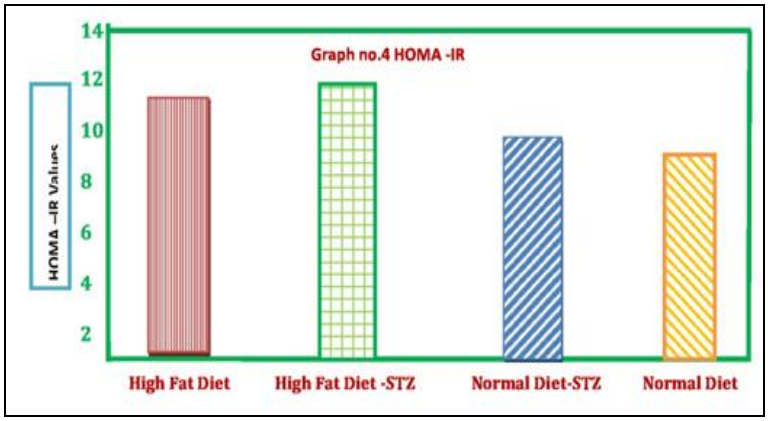

FIG. 4: THE OUTCOME OF DIET AND STZ ON HOMA IR IN THE EXPERIMENTAL GROUPS

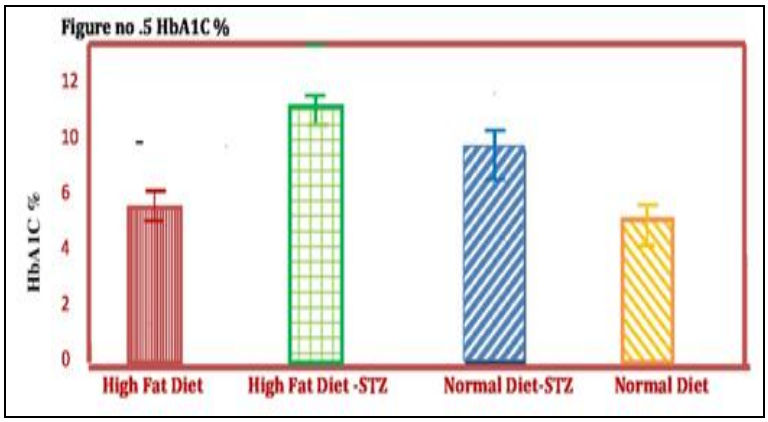

FIG. 5: THE OUTCOME OF DIET AND STZ ON HBA1C THE EXPERIMENTAL GROUPS

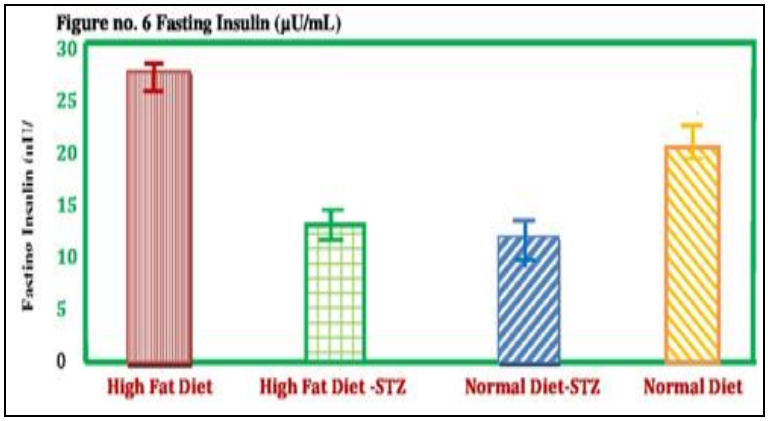

FIG. 6: THE OUTCOME OF DIET AND STZ ON IN FASTING INSULIN IN THE EXPERIMENTAL GROUPS

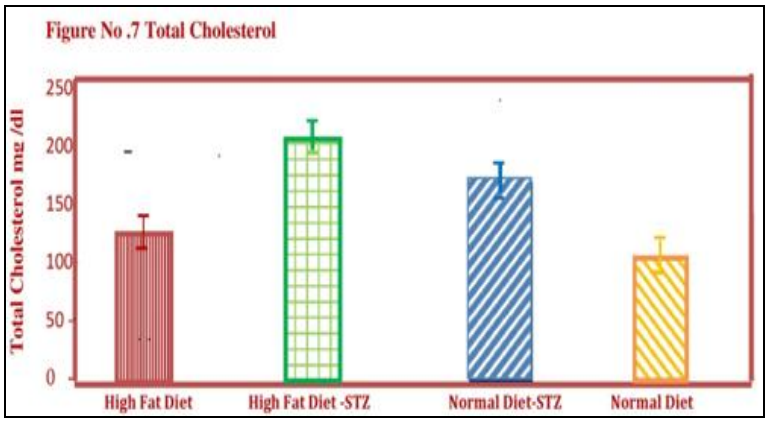

FIG. 7: THE OUTCOME OF DIET AND STZ ON TOTAL CHOLESTEROL IN THE EXPERIMENTAL GROUP

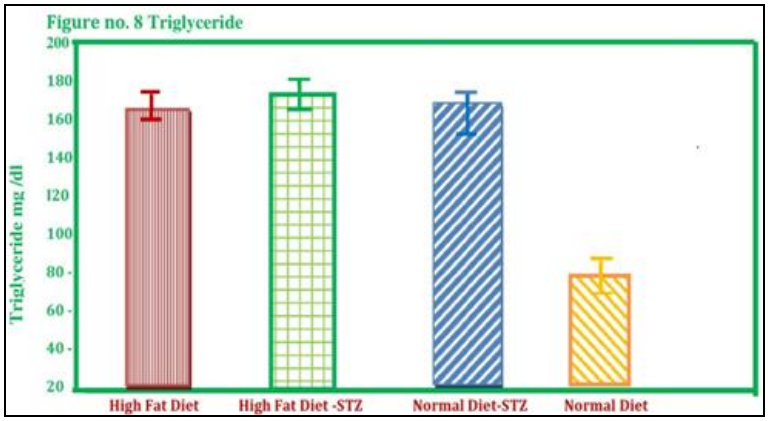

FIG. 8: THE OUTCOME OF DIET AND STZ ON TRIGLYCERIDE IN MG/DL IN THE EXPERIMENTAL GROUP

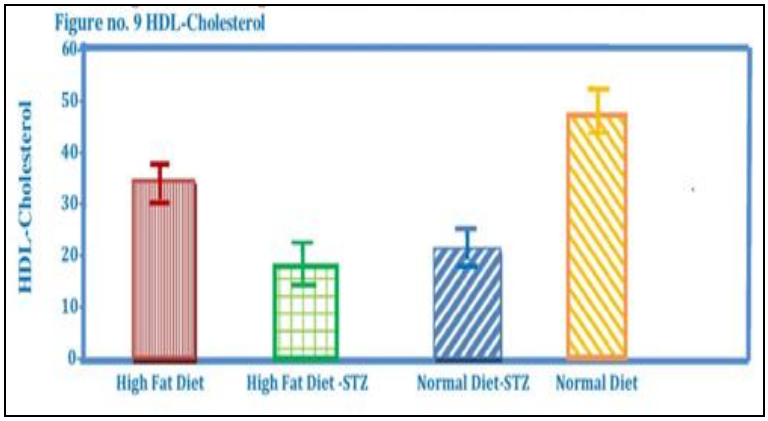

FIG. 9: THE OUTCOME OF DIET AND STZ ON HDL-CHOLESTEROL IN MG/DL IN THE EXPERIMENTAL GROUP

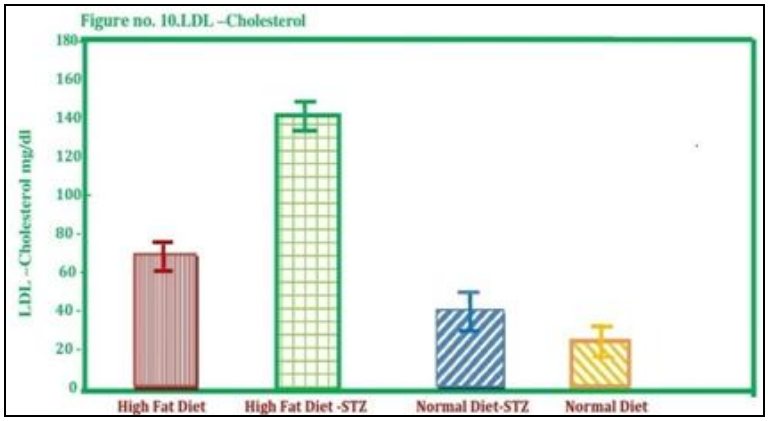

FIG. 10: THE OUTCOME OF DIET AND STZ ON LDL-CHOLESTEROL IN MG/DL IN THE EXPERIMENTAL GROUP

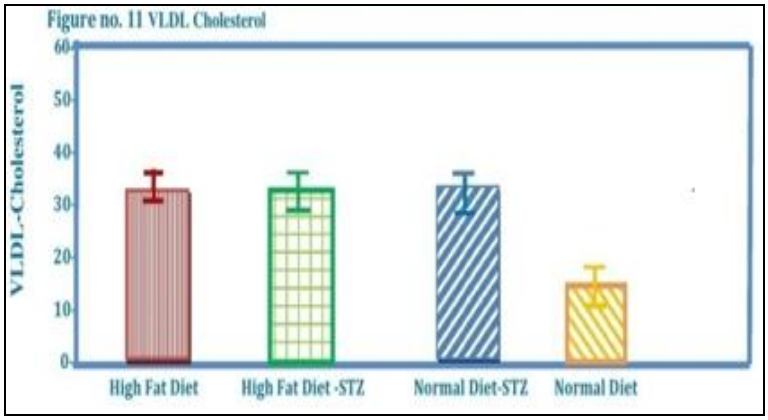

FIG. 11: THE OUTCOME OF DIET AND STZ ON VLDL-CHOLESTEROL IN MG/DL IN THE EXPERIMENTAL GROUP

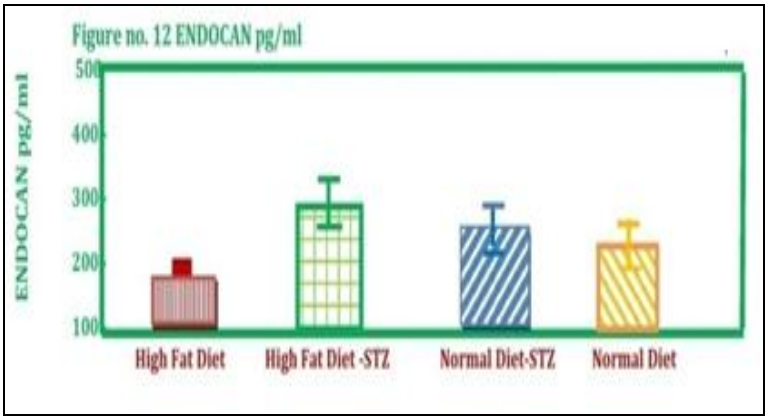

FIG. 12: INPACT OF DIET AND STZ ON ENDOCAN PG/ML IN THE EXPERIMENTAL GROUP

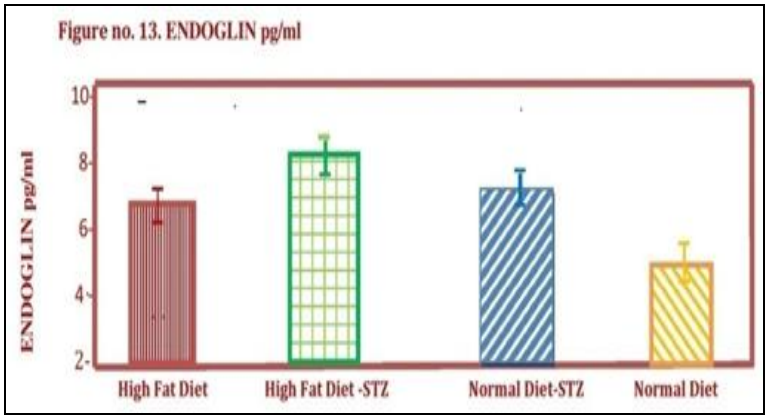

FIG. 13: INPACT OF DIET AND STZ ON ENDOCAN PG/ML IN THE EXPERIMENTAL GROUP. The highs and lows with and without STZ in Wistar rats and a p-value lower than 0.001 was considered significant.

DISCUSSION: Obesity is at the centre of the insulin resistance syndrome, which also includes hyperinsulinemia, hypertension, hyperlipidemia, and Type 2 diabetes, a greater chance of cardiovascular atherosclerosis [26]. This study investigated the relationships between sol. endoglin and insulin resistance, hyperlipidemia, oxidative stress, and endothelial dysfunction in both obese patients with and without type 2 diabetes. The study also looked into whether sol. endoglin might be used to predict future harmful cardiovascular events in people with type 2 diabetes and/or obesity [27].

Data show that obesity increased insulin resistance to a degree that was reflected in the higher HOMA-IR scores (54.09%). Moreover, both type 2 DM groups obese or not exhibited poor glycemic control and insulin resistance; nevertheless, obesity-related changes led to significant changes. These outcomes were in line with Obesity has been closely connected to insulin resistance in people who have Type 2 diabetes and those who are normoglycemic, according to Rexrode *et al.* [28], which increases the risk of cardiovascular disease in adults. Indelka *et al.* [29] came to the conclusion that obesity may have much more of an impact, rather than diabetes mellitus itself, is the action of insulin. The significant positive correlations between sol. The correlation between endoglin and plasma glucose, insulin, and HOMA-IR was confirmed in the diabetes groups. It showed a strong correlation between sol endoglin and blood sugar levels. According to Blazques-Medela *et al.* [30], patients with type 2 DM may be at increased risk for cardiovascular problems due to hypertension.

Impaired lipid metabolism in diabetic patients brought on by uncontrolled hyperglycemia is associated with cardiovascular issues [31]. In comparison to control participants and obese type 2 DM patients compared to non-obese patients, it was found that obese type 2 DM patients had unfavourable lipid profiles. These conclusions were drawn after comparing the results of the different blood lipid profile tests and discovering substantial variations in the groups' TC, LDL-C, TG HDL-C, and TC/HDL-C ratios. According to a report, obesity-related dyslipidemia frequently manifests

as high plasma triglyceride levels, low HDLC, normal LDL-C, and a preponderance of small, dense LDL-particles, and there is a linear relationship between the degree of obesity and the plasma levels of LDL cholesterol and triglycerides [32]. The obese groups with or without type 2 DM showed significant positive relationships between sol. endoglin and TC, indicating that hypercholesterolemia was associated with increased levels of sol. endoglin in the obese groups. Recent studies by Beiroa *et al*.[33] it has been proven for the first time that a high fat diet reduces the hepatic triglyceride levels in mice with heterozygous endoglin deficiency. The present study evaluated the degree of endothelial dysfunction metabolic syndrome. The results showed a significant association between the severity of MS and endothelial dysfunction, suggesting that metabolic syndrome may speed up the onset of heart disease. Further research is needed to investigate potential interventions to improve endothelial function in individuals with MS determined by serum endocan concentration [34].

Endothelial dysfunction and associated vascular problems are greatly impacted by proinflammatory conditions brought on by circulating diabetes-related variables. Endocan, also known as endothelial cell-specific molecule-1, is a dermatan sulphate proteoglycan that is mostly secreted by vascular endothelium. Endocan has been demonstrated to be a possible biomarker in coronary heart disease, however it is still unknown what role it plays in the pathogenesis of atherosclerosis (AS) in diabetes. In this investigation, we investigated the association between subclinical AS and serum endocan levels in type 2 diabetics (T2DM) [35].

Endothelial cells are stimulated by the endothelium's secreted endocan to release inflammatory cytokines, which raises vascular permeability. Additionally, it is independently correlated with the concentrations of soluble vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which increases leukocyte adhesion to endothelial cells and promotes leukocyte migration [36]. This increased inflammatory response plays a vital role in atherosclerotic plaque development and cardiovascular disorders.

CONCLUSION: It is clear that sol. endoglin endocan is linked to poor lipid metabolism, and poor glycemic control. Moreover, A key feature of people with obesity and/or diabetes is decreased endothelial function, which endoglin appears to be linked to. The findings were sufficient to determine the relative potency of cardiovascular risk prediction based on the patient's endoglin level.

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CONFLICTS OF INTEREST: Nil

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