Echographic analysis of the alterations musculoskeletal associated with endothelial dysfunction and obesity

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Abstract

Background: Modern imaging plays a central role in the care of obese patients, with an integral focus on its use and accessibility in individuals with this condition with alterations of various organs.

Objective. To perform an echographical analysis of musculoskeletal system disorders, endothelial dysfunction and the left ventricle in obese rats.

Methods. Sprague Dawley rats (250±5 g) were used and divided into two groups: control group (C) fed a standard diet and the obese group (Ob), fed with a hyper caloric diet of high fructose-fat for 4 mounts. Body weight, cholesterol, triglycerides, glucose, inflammatory cytokines and adhesion molecules (ICAM-1, VCAM-1) were measured. Additionally, two-dimensional echocardiography and abdominal ultrasound and musculoskeletal system studies in the lower extremities were performed.

Results . Body weight in the Ob group was increased compared to the control group, ($p < 0.001$); in addition, increased glucose, cholesterol and triglycerides of were found in the Ob group vs the C group, ($p < 0.05$), and as well as increased adhesion molecules ICAM-1 and, VCAM-1 ($p < 0.01$). On ultrasound, 75% of the Ob group presented showed 75% fatty liver and distal joint abnormalities.

Conclusion . Endothelial dysfunction and changes at the level of the musculoskeletal system with the presence of joint cysts in the posterior region of the distal joint of the lower extremities were observed in obese rodents.

Background

Overweight and obesity are defined as an abnormal or excessive accumulation of fat that is harmful to health and is an important risk factor for no communicable diseases, such as cardiovascular diseases (mainly heart disease and strokes), associated metabolic disorders (glucose intolerance, insulin resistance, hyperlipidemia, diabetes and hypertension), musculoskeletal disorders (especially osteoarthritis) and some cancers (endometrial, breast, ovarian, prostate, liver, gallbladder, kidney and colon) [1].

Some mechanisms that are triggered by obesity involve the inflammatory process, with the production of proinflammatory cytokines such as interleukine-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α). In addition, the endothelial dysfunction that is induced by the activation of adhesion molecules (ICAM-1, VCAM-1) is the cause of several vascular pathologies [2–5]. To understand the pathophysiological mechanisms, experimental models are used, as murine models (rats) are a valuable tool to understand these processes and their histological characteristics as well as the mechanisms linked to the comorbidities of these metabolic diseases [6]. In obesity, the accumulated storage of lipids in different organs, such as the liver, and heart, increases the macrophages of adipocyte origin, altering the essential lysosomal catabolism program for triglyceride hydrolysis and generating hepatic steatosis [7, 8].

Within the enormous complexity of the individual, family and social management of the obese patient, imaging does not escape the inherent difficulties that come with the care of this type of population. The possibility of using widely tested imaging techniques in humans, such as ultrasound or echocardiography, has resulted in studying the structure and function of organs in small rodents [9].

Ultrasound is an economical, accessible, fast, precise, simple, comfortable, and noninvasive procedure. It does not cause pain, radiation is not used, it has high sensitivity and accuracy to obtain images and it is essential in the study of a variety of organs such as the liver and the musculoskeletal system. Two-dimensional echocardiography is the study of the heart in two dimensions; it allows us to analyze the organ as a whole and the relationships that the cardiac structures maintain with each other. Two-dimensional echocardiography is very useful in the study of congenital anomalies, in the differentiation between thrombi and intracardiac masses and in the analysis of regions of difficult access with the one-dimensional echocardiogram [9].

Although there are ultrasound studies in rats where the various morphological and functional aspects are both analyzed at the cardiac level, mainly in the left ventricle, none of them has been considered important for a joint analysis of both the left ventricle and the hepatic, renal and musculoskeletal systems represented in humans. Therefore, we report here in this study the echographic analysis of the left ventricle, liver, musculoskeletal disorders and endothelial dysfunction in obesity.

Methods

Animals and Model of obesity

This was an experimental, cross-sectional and analytical study. The population was a murine model of rats of the Sprague Dawley strain obtained and used from an inbred colony of bioterium of the Specialty Hospital of the National Medical Center, Mexican Social Security Institute (Mexico City, Mexico), a total of 20 males were used and weighing 200-250 g. Animals were randomly allocated and were divided into the control group C (n=12) fed the standard diet (Formulab 5008 Diet; PMI Nutrition International, Brentwood, MO, USA), the Ob group (n=8) was fed a hypercaloric diet (high in fructose 30%), until 6 months of age, the rats stayed with this diet. All cages contained wood shavings, bedding and a cardboard tube for environmental enrichment. All rats had *ad libitum* access to a standard pellet diet and water; they were housed in groups of 4 rats, in conventional cages at room temperature (22-25°C), under a light cycle of 12 hours' light/12 hours' dark since at the start of the trial and hygienically controlled room. We have worked with this experimental model in other projects [5]. The hypercaloric diet was used to induce obesity and insulin resistance in (Ob group) experimental rats.

Ethical statement

All experiments were performed in accordance with relevant guidelines and regulations of bioterium of the Specialty Hospital of National Center Medical, of the Mexican Social Security Institute (CMN SXXI-IMSS), in accordance with the Official Mexican Standard (NOM-062-ZOO-1999, revised 2001) for the care

and use of laboratory animals. Also, we obtained written informed consent to use the animals in our study. This study was approved by the Ethical Committee and the Local Research and Health Committee of the Mexican Social Security Institute, with number registered 3601-2015-95. The animals were treated according to the Official Mexican Standard for the care, use and sacrificing laboratory animals. All rats were fed until 12 months of age were anesthetized and sacrificed by cardiac puncture (NOM-062-ZOO-1999, revised 2001).

Metabolic parameters and Body weight

Body weight. From the beginning to group C (n=12) and Ob (n=8) their weight was recorded until the end of the study. Food and water intake were recorded for week.

Blood samples were collected at 8 am (during a fasting 7 hours at 6 month of age) from the tail vein in order to measure the blood biochemical parameters and inflammatory cytokines. The blood samples were transferred into tubes containing anticoagulant for measurement of blood biochemical parameters and inflammatory cytokines, respectively. The samples were centrifuged at 5200 g for 15 minutes. Plasma was separated and stored at -70 °C until use for bioassay analyses.

Blood parameters were determined by One drop of blood was placed on the blood glucose test strips of the FreeStyle Optium Xceed glucometer (Abbot Diabetes Care Ltd, OYL, UK).

Determinations of levels of total cholesterol, triglycerides (TG), high density lipoproteins (HDL) and low-density lipoproteins (LDL) were made on a Cardiocheck apparatus after placing one drop of blood (see previous section on blood samples) on a reactive strip, according to the manufacturer's instructions.

Quantification of insulin and index HOMA-IR, insulin was measured for chemioluminiscence using Insulin IMMULITE kit (LKIN1 insulin IMMULITE);

Insulin resistance was calculated the index HOMA-IR through the formula of homeostasis model assessment-insulin resistance (HOMA-IR) index: insulin (μU/mL) × glucose (mg/dL)/405.

TNF-α, IL-6, adhesion molecules ICAM-1 and VCAM-1 were analyzed using enzyme immunoassay kits by ELISA R&D kit (R&D Systems, Inc., Minneapolis, MN, USA).

After, all rats were fed until 12 months of age. For collection of blood samples by cardiac puncture, also analysis of cytokines in tissue, rats were sacrificed with deeply anesthetized and administered pentobarbital (25 mg/kg, i.p.) [10].

Ultrasound analysis.

To carry out the study, the rat was placed in the left lateral decubitus position, with a slight inclination of the head and placing the transducer in the different acoustic windows. The equipment used was a Philips Affiniti 70 with a linear transducer of 9 mHz, where the results were obtained in millimeters. During the echocardiographic examination, two cuts were used for the evaluation of the heart: the left longitudinal

parasternal section and the right longitudinal parasternal section. In the left longitudinal sternal section, it is possible to visualize the right ventricle, aorta with aortic valve, left atrium, mitral valve and left ventricle [11].

The right longitudinal sternal section that appears on the left and the base (atria) on the right, with the rotation of the transducer in the right direction, shows the left ventricular outlet, aortic valve, aortic root and proximal ascending aorta [12].

The measurement of the left ventricle in diastole was performed from the left septal endocardium to the posterior wall endocardium, measured below the level of the mitral valve. The interventricular septum is between the mitral ring in its posterior part and the endocardial surface of the high septum in its anterior part. In the free wall of the VI, the diastolic thickness is measured; its value is approximately equal to the diameter of the IVT, and its birth is parallel to it.

Statistical Analysis

The data are presented as means ± standard deviation (SD) of each group. The study groups were statistically analyzed the difference in means between group C *vs* Ob with a Student t test, the level of statistical significance was considered with a value of $p < 0.05$. For each study variable: glucose, insulin, lipid profile, HOMA-IR index, proinflammatory cytokines, TNF-α, IL-6, adhesion molecules ICAM-1 and VCAM-1 statistical analysis was carried out using Graph Pad Prism. (GraphPad Prism 8 for Windows, San Diego, CA); $p < 0.05$ was considered significant.

Results

Figure 1 shows the differences in food consumption in the study groups, in Obese group with hypercaloric diet had a rise compared with control ($p < 0.001$). Also, an increase in body weight was observed in the Ob group *vs* the C group (22.5% ± 25 *vs* 100% 20, $p<0.001$). In addition, the Ob group showed an increase in fasting glucose, lipid profile and HOMA-IR index (400% ± 45 *vs* 100% ± 2, $p < 0.001$); therefore, also of lipids analyzed these rats were considered obese rats with metabolic alterations (Table 1). This experimental model demonstrated endothelial dysfunction, manifested by inflammatory cytokines TNF-α, also adhesion molecules that are indicators of endothelial damage, such as ICAM-1 (187.6% ± 9 *vs* 100% ± 5, $p < 0.0001$) and VCAM-1 (129.4% ± 10 *vs* 100% ± 2, $p < 0.05$) (Table 2).

In the Ob group, an increase in these adhesion molecules and in proinflammatory cytokines such as TNF-α was demonstrated, with a significant difference compared with the C group (320% ± 3 *vs* 100% ± 0.05, $p<0.001$), and of IL-6. According to the measurements of the metabolic parameters and cytokines, the Ob group, with the consumption of the hypercaloric diet, presented endothelial damage. In addition, modern imaging allowed us to evaluate an integral approach of the control group, where the aorta and left ventricle (VI) were observed. For VI, an increase in the septum and wall was found in the Ob group (Table 3, Figure 2).

However, in Figure 3A, the analysis of the two-dimensional ultrasound being more complete, fat filtration was observed in the obese group, with the presence of fatty liver (Table 3); on the other hand, a homogeneous hepatic parenchyma was found to be isoechoic in the control group (Figure 3B).

Another analysis of the ultrasound dimensions that was obtained in the Ob group showed alterations in pelvic dilatation in the kidney compared to the control group where the kidney was echogenic, with no evidence of dilation (Figure 3C, D).

In the ultrasound images at the musculoskeletal level, we can observe alterations in the Ob group, where changes were found due to fat deposits, demonstrating the presence of cysts at the articular level, in the posterior region of the distal joint, where it is possible to view the damage due to accumulated fat (Table 3, Figure 3E).

Discussion

In the present work, the results of this experimental model of obesity revealed alterations in metabolic parameters, such as lipids and HOMA-IR index, as mentioned by other studies where the use of hypercaloric diets similar to that used in this study, is associated with the early onset of lipid-like metabolic alterations [13], besides the endothelial damage that is had with the intake of hypercaloric diets, showing increase in TNF-α and adhesion molecules (ICAM-1 y VCAM-1). Together, with the ultrasound evaluation, the alterations of joint cysts and liver damage are highlighted. In individuals with metabolic alterations, it is difficult to diagnose and reverse this damage and also have the complications of cardiovascular diseases.

In the evaluation of the ventricular anatomy, although the cut-off point for normal relative parietal thickness in humans is 0.42 mm, this criterion was highly specific in our animals because the rats presented a relative parietal thickness below that limit. In addition, ultrasound changes in the liver were found as fatty liver in 75% of the rats (6 exemplary). It is known that one of the main organs affected by long-term obesity is the liver, where the increase in lipogenesis and the decrease in mitochondrial β-oxidation of nonesterified fatty acids, as well as hepatic triglyceride secretion, can contribute to the accumulation of fat in the liver, leading to the appearance of liver steatosis [12, 14]. In addition, in a prospective longitudinal study, 86% of patients with non-alcoholic fatty liver (HGNA) and progressive fibrosis were obese, and only 27% of those with fibrosis remained stable [15].

At the renal level, changes such as pelvic dilation were found in 50% of the specimens. On the other hand, changes were observed at the level of the musculoskeletal system with the presence of joint cysts in the posterior region of the distal joint of the lower extremities of the rodents, which predominated in the females; therefore, certain joint alterations can be characterized according to gender.

An excessive body weight creates a greater load stress, which in the musculoskeletal system affects muscle-skeletal and articular levels, causing joint misalignment (deformities) in the lower extremities and inflammatory and degenerative processes, which could decrease physical functioning due to

associations with mobility and pain [16]. An increase in proinflammatory cytokines, such as TNF-α, was observed in this study. It is known that in both humans and mice, an imbalance between TNF-α and adiponectin (a hormone of adipose tissue) seems to play an important role in the progression of steatosis to steatohepatitis. [16, 17].

Adipose tissue is now recognized as a multifunctional organ. It plays an important role as an energy storage organ but also releases inflammatory mediators, proinflammatory molecules TNF-α and IL-6, and some other mediators such leptin, adiponectin, and resistin. In addition, endothelial damage increases molecules such as monocyte attractant chemoprotein 1 (MCP-1) and plasminogen activator inhibitor (PAI-1). IL-6, TNF-α and leptin act on immune cells and cause local and systemic inflammation [18, 19, 20]. Adhesion molecules were increased in the Ob group, which confirms endothelial damage, which has an impact on the joints. In addition, ICAM-1 and VCAM-1 are known to be activating molecules of endothelial dysfunction because they play a crucial role in the adhesion of cells to the endothelial surfaces and in the integrity of the vascular wall, generating an accumulation of cells and sparking oxidative stress, and can be modulated by body composition and eating pattern [21].

In several studies, it is known that the mechanical stress caused by overload or repetitive use can trigger tendon pathology. There are also extrinsic factors (posture and activity) and intrinsic factors (genetics and metabolic characteristics) that can interfere with their development [15]. Changes in both static and dynamic alignment of the lower extremities could alter balance and gait and trigger pain throughout the lower limbs [22].

In this work was found the presence of Baker's cyst (QB), or popliteal cyst, which was first described in 1840 by Adams [23, 24] and later by Baker [25]. In 1877, Baker published his experience on this entity, which gave rise to his name going to designate this type of cyst. Baker’s cyst is defined as an abnormal cluster of synovial fluid in the gastrocnemius-semimembranosus bursa or, failing that, a herniation of the posterior joint capsule with synovial fluid tension [25, 26,27].

Conclusion

The results obtained from this study suggested that ultrasound is an excellent diagnostic tool that is accessible and easy to use in the chronic diseases that are increasing in our population, and it allows the integration of alterations in different organs, joints and tissues and better monitoring and treatment in support of reducing complications and improving the quality of life of patients.

In this study, also we showed a relationship between endothelial dysfunction and changes at the level of the musculoskeletal system with the presence of joint cysts in the posterior region of the distal joint of the lower extremities were observed in obese rodents.

Abbreviations

C: control group; ELISA: Enzyme immunoassay; HDL: High Density Lipoprotein; HGNA: Non-Alcoholic Fatty Liver; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; ICAM-1: Intercellular Adhesion Molecule-1; IL-6: Interleukine-6; IMSS: Mexican Social Security Institute; LDL: Low Density Lipoprotein; MCP-1: Monocyte Attractant Chemoprotein 1; Ob: hypercaloric diet group; PAI-1: Plasminogen Activator Inhibitor; QB: Baker's cyst; SD: standard deviation; TG: Triglycerides; TNF-a: Tumor Necrosis Factor-a; VCAM-1: Vascular Adhesion Molecule-1; VI: left ventricle; VLDL: Very Low Density Lipoprotein.

Declarations

Acknowledgements

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Authors' contributions

All the authors engaged in the surveys. AMC and LMA designed this article. MIPO, NAEC and DMC acquired and collected the data. AMC, DMC and LMA organized and analyzed all the information. AMC, NAEC and LMA drafted the manuscript. All the authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethical Committee and the Local Research and Health Committee of the Mexican Social Security Institute, with number registered 3601-2015-95. The animals were treated according to the Official Mexican Standard for the care, use and sacrificing laboratory animals. All rats were fed until 12 months of age were anesthetized and sacrificed by cardiac puncture (NOM-062-ZOO-1999, revised 2001).

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Tables

Table 1
Metabolic parameters of control (C) and hypercaloric diet (Ob) rats

	C n = 12	**Ob n = 8**	**% difference of Ob vs C**
Body weight (g)	385 ± 20	472 ± 25**	122.5
Fasting Glucose (mg/dL)	69 ± 2	165 ± 45*	239.1
HOMA-IR	4 ± 1	16 ± 3***	400
Triglycerides (mg/dL)	109 ± 7	225 ± 19***	206.4
Cholesterol (mg/dL)	70 ± 5	98 ± 3***	140
HDL (mg/dL)	50 ± 5	32 ± 3***	-64
LDL (mg/dL)	25 ± 5	58 ± 4***	232
VLDL (mg/dL)	33 ± 2	48 ± 4***	68.7

Determination of body weight (g), fasting glucose, cholesterol and triglycerides levels in control (C) and obese (Ob) rats. Values represent the mean ± SD of 8–12 animals per group. Values *p < 0.05, **p < 0.001, ***p < 0.0001 significantly different from control group.

Table 2

Effects on cytokines and CAMs in groups of study.

	Control n = 12	Obese n = 8	% difference of Ob vs C
TNF-α (pg/mL)	5 ± 0.5	16 ± 2**	320
IL-6 (pg/mL)	9 ± 1	23 ± 5	255.5
IL-10 (pg/mL)	3 ± 1	4 ± 2	133.3
ICAM-1 (ng/mL)	65 ± 5	122 ± 9***	187.6
VCAM-1 (ng/mL)	85 ± 2	110 ± 10*	129.4
Results are presented as values of the mean ± SD, n = 8–12 animals per group. Values * p < 0.05, ** p < 0.001, *** p < 0.0001 significantly different from control and obese group.			

Table 3

Descriptions of two-dimensional echocardiography of kidney and skeletal muscle (lower extremities) and left ventricles (LV), partition IV y wall of LV express in mm

C			Ob		
Left ventricle	10 mm	9 mm	6 mm	8 mm	13 mm
Partition IV	2 mm	2 mm	1 mm	1 mm	1 mm
Wall LV	2 mm	2 mm	2 mm	2 mm	1 mm
Liver	normal	normal	non-alcoholic fatty liver	non-alcoholic fatty liver	non-alcoholic fatty liver
Skeletal muscle system	normal	normal	without changes	change in fat	cystic lesions
Other		normal			Pielica dilation at the bilateral renal level

Figures

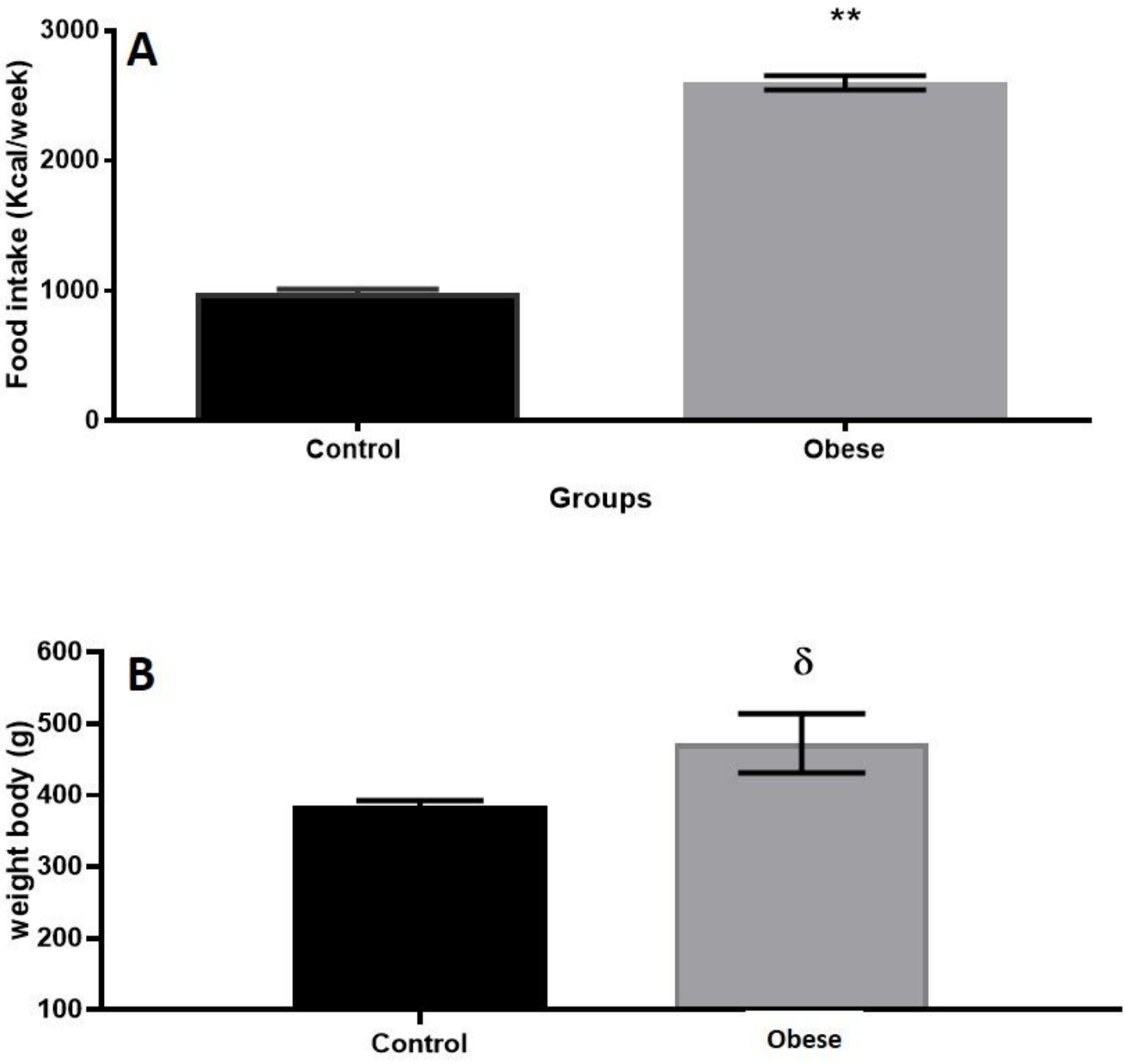

Figure 1

A) Effect on Food intake of groups of study. B) Represent weight body in different groups. Results are presented as values of the mean ± SD, n=8-12 animals per group. Values *p<0.05, **p<0.001, t Student test, significantly different from control group

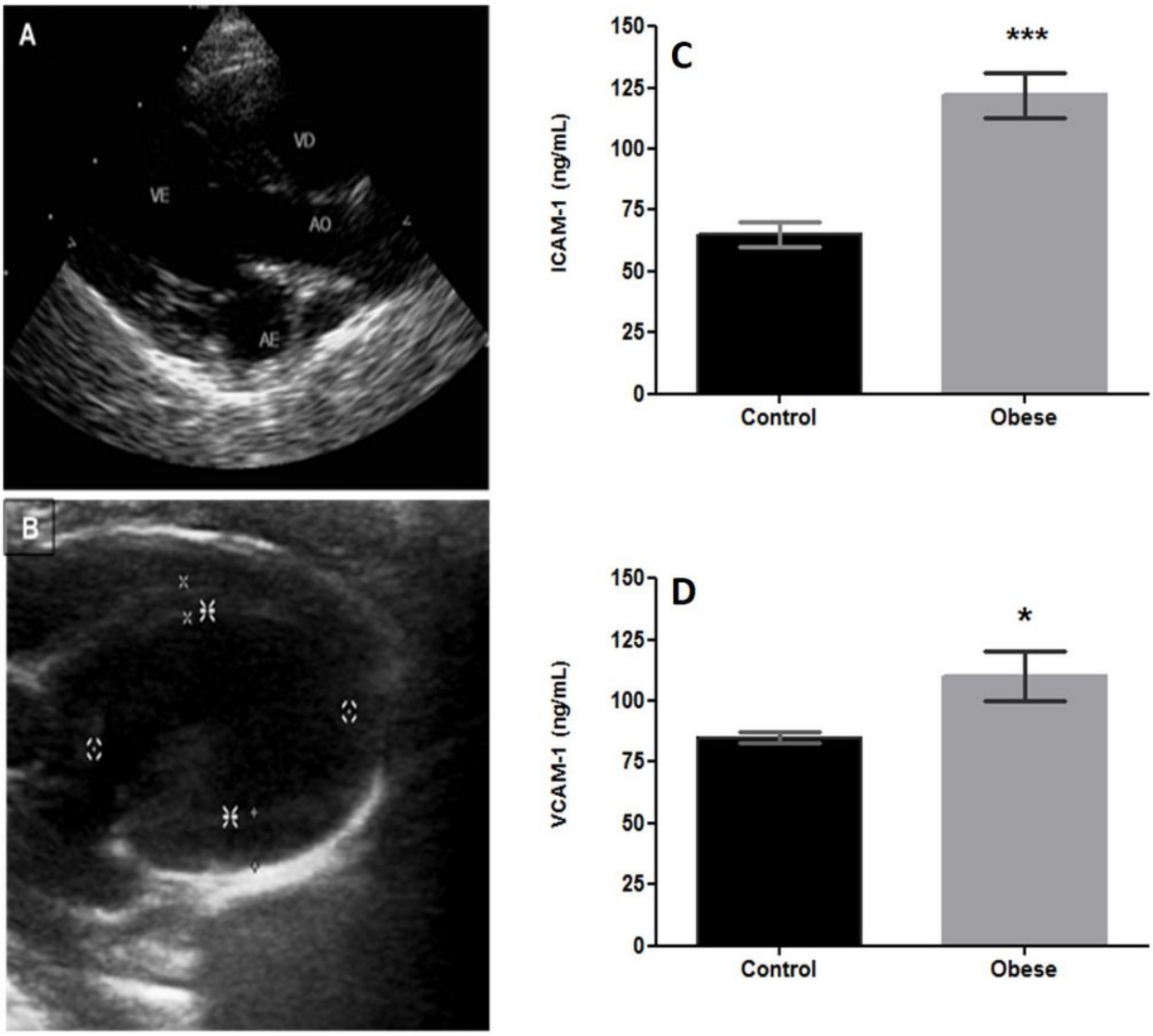

Figure 2

Two-dimensional echocardiography. A: The left longitudinal parasternal section, where it is possible to evaluate the aorta (AO), the left atrium (AE), and the right (RV) and left (Vi) ventricles in the control group. B: The approach for the left ventricle. The markers of endothelial dysfunction as CAMs in C; ICAM-1 and D, VCAM-1 are presented results as values of the mean ± SD.

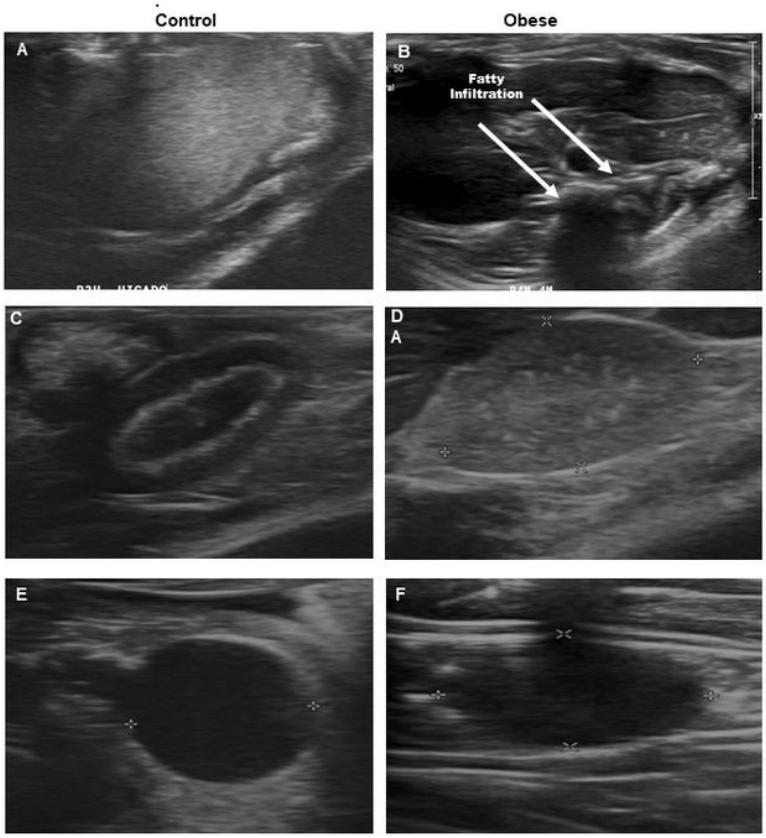

Figure 3

Two-dimensional echocardiography. A: The right hepatic lobe with fatty infiltration and an increase in echogenicity in a homogenous manner in the male Ob group. B: The hepatic parenchyma is homogeneous and isoechoic in the control group. C. The right kidney in a longitudinal section where we can visualize the pelvic dilation presented by the Ob group. D: The right kidney of another specimen can be seen where the renal sinus is echogenic, with no evidence of dilation in the Control group. E. in both images, there is a level approach to the distal joints of the hind legs of the rodents where cystic lesions were found. Two-dimensional echocardiography of: In both images, the approach is at the level of the distal joints of the hind legs of the rodents where cystic lesions were found that predominated in the Ob female group. F, Damage from these lesions can be observed.

Supplementary Files

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