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The Influence of Bone Geometry and Trabecular Morphology on Tensile Strength in the Humerus of the Zucker Diabetic Sprague Dawley Rat

Influencia de la Geometría Ósea y la Morfología Trabecular en la Resistencia a la Tracción del Húmero de la Rata Zucker Diabetic Sprague Dawley

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SUMMARY: Bone strength is a multifaceted property, with bone geometry (size, length, width, cortical area, and trabecular distribution) providing a critical contribution alongside bone microarchitecture. Therefore, the present study aimed to evaluate the influence of bone geometry and trabecular morphology on tensile strength in a rat humerus. The study used 15 male rats composed of control Sprague Dawley (SD) (n=6) and Zucker Diabetic Sprague Dawley (ZDSD) (n=7). Fasting blood glucose and oral glucose tolerance tests were used to monitor diabetes. Upon termination at 20 weeks of age, humeri were harvested, and a sliding calliper was used for osteometric measurements. Microfocus computed tomography (Micro CT) was performed for assessments of trabecular number (TbN), thickness (TbTh), spaces (TbSp), bone volume (BV), and bone volume ratio (BV/TV) as well as the midshaft cortical and the medullary canal areas. Diabetes was confirmed by deranged fasting blood glucose values and poor oral glucose tolerance finding in the ZDSD group. Diabetic rat humeri had less mass and smaller osteometric dimensions. While the medullary canal and cortical areas as well as the thickness of the trabeculae (TbTh) showed group similarities, the diabetic group exhibited a lower number of trabeculae (TbN) and a greater distance between them (TSp). The geometry of the humerus and trabecular microarchitecture are altered, compromising bone strength and structural integrity in diabetic rats (ZDSD). This should be considered in the overall care for diabetic patients.

KEY WORDS: Humerus; Bone; Diabetes mellitus; Cortical bone; Bone fracture.

INTRODUCTION

Bone geometry, which encompasses size, length, width, cortical area, and trabecular distribution, is crucial for bone strength, complementing bone mineral density and tissue quality (Ammann & Rizzoli, 2003). Larger bones inherently possess greater strength, and increased cortical thickness enhances resistance to bending and torsion (Clarke, 2008). The trabecular network, with its arrangement and density, provides essential support against compressive forces and acts as a crucial shock absorber during movement (Oftadeh *et al*., 2015). Therefore, understanding the bone geometry and trabecular morphology is vital to accurate fracture risk assessment and management.

While bone density may remain unaffected, diabetes compromises bone quality, leading to increased fracture risk (Lekkala *et al*., 2023). This is due to alterations in bone microarchitecture (Murray & Coleman, 2019). Although diabetes affects both the humerus and the femur, the clinical manifestations vary. For example, hip fractures, particularly of the proximal femur, are a significant concern in older adults with diabetes, as the disease exacerbates the risk of osteoporosis (Dufour *et al*., 2021). The role of the femur in locomotion makes fractures in this area particularly debilitating. However, humerus fractures, while less impactful on mobility, significantly alter daily living activities. In fact, proximal humerus fractures are among the most common fracture types (Chu *et al*., 2004). Individuals with type 2 diabetes are known to have an increased risk of falls due to diabetic neuropathy (Freire *et al*., 2024) which is associated with lower limb fractures (Bell & Goncalves, 2020). Nevertheless, research specifically addressing the link between type 2 diabetes and humerus fractures is limited as studies predominantly focus on femur fractures. This research gap is critical, as proximal humeral fractures resulting from complications of diabetic bone contribute significantly to the overall disease burden.

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Aspects of bone structure research remain a challenge and require animal models, as it is not possible to test bone strength among humans due to ethical considerations. However, while rodent models are essential and frequently used to study type 2 diabetes and bone health, no model perfectly mimics the human condition. Among these, is the Zucker Diabetic Sprague Dawley (ZDSD) rat, which is increasingly valued for its translational relevance (Wang *et al*., 2022). Its design specifically replicates the progressive stages of human type 2 diabetes from prediabetes to overt diabetes, closely mirroring disease development.

The direct assessment of bone structural integrity provided by three-point bending tests is critical for evaluating the effects of diseases such as osteoporosis and diabetes on bone strength (Monahan *et al*., 2023). In addition, these tests are used to evaluate the effectiveness of treatment, the fracture mechanisms and the healing process. With the help of trabecular morphology evaluation and strength tests, the effectiveness of diabetes bone therapy is assessed and understanding of the risk of fractures improved by preclinical tests that are usually carried out before human trials. These tests reveal fragility due to changes in microstructures and material properties (Ahmad *et al*., 2003). In type 2 diabetes, three-point bending tests are essential because bone mineral density scanners can miss the risk of fracture due to changes in bone quality (Ammann & Rizzoli, 2003).

Given all the above, the objective of the current study was to obtain insight on the influence of bone geometry and trabecular morphology on tensile strength in the ZDSD rat. To do so, the study examined the geometry of the humerus, analysed the trabecular structure from microfocus X-ray computed tomography (micro-CT) scans and assessed bone strength in diabetic humeri and the controls. Due to the bone regional fracture risk differences, the proximal epiphysis trabecular organisation and mid-diaphysis cortical and medullary areas were subject of analysis in the present study (Ahmad *et al*., 2003).

MATERIAL AND METHOD

Ethics Clearance. The University of Witwatersrand Animal Ethics Committee granted the study's ethical approval (AESC 2015/07/28/C) and the guidelines of this committee were adhered followed.

Study animals. The study used 15 male rats composed of control Sprague Dawley (SD) (n=6) and Zucker Diabetic Sprague Dawley (ZDSD) (n=7). The SD rats were obtained from Central Animal Services (CAS), University of Witwatersrand, while the ZDSD rats came from PreClinomics, Indianapolis, Indiana, USA. SD rats are the parental strains of ZDSD rats and are used as nondiabetic controls (Creecy *et al*., 2016). All rats in their individual cages were kept in pathogen-free conditions and in a temperature-controlled environment of 230C±20C with 12 hours of light and dark cycle. All rats were fed ad libitum food and water.

Blood tests

Fasting blood glucose. To assess diabetes, rats were subjected to weekly fasting blood glucose tests following a 12-hour overnight fast. Tail vein blood was analysed with a glucometer (Performa Accutrend, Roche Diagnostics, Germany). Rats with fasting blood glucose above >8.0 mmol/L were considered diabetic.

Oral glucose tolerance test (OGTT). Monthly oral glucose tolerance tests (OGTT) were conducted after a 12-hour fast. Baseline glucose (T0) was measured, followed by an oral glucose dose (2 g/kg). The blood glucose levels were then monitored at 15, 30, 60, and 120 minutes after glucose intake, with blood samples taken from the tail vein.

Termination and bone harvesting. At the age of 20 weeks, rats were terminated with a 1 ml of lethal dose sodium pentobarbital (Euthanase, 200 mg/ml; Kyron Laboratories Pty Ltd, South Africa). The bilateral humeri were removed, and muscles were dissected out. Individual bones were then kept in 10 % buffered formalin for later processing.

Microfocus X-ray Computed Tomography (Micro CT). Micro-CT imaging of bilateral humeri was performed using a Nikon XTH 225/320 LC microtomography scanner. The humeri were mounted in plastic tubes and stabilised with low-density Styrofoam, which allowed for minimal X-ray absorption. Then, this assembly was placed on a rotating manipulator within the scanning chamber for the acquisition of tomographic data. Scanning was performed with 70 kV and 400 μA X-ray settings, filtered with 1mm aluminum. A complete 360-degree rotation, with 1-degree increments, was used to capture the data. Each scan was 8 minutes in duration, achieving a resolution of 18 μm

Osteometric landmarks and trabecular parameters assessed. Osteometric measurements, including full bone length, bicondylar breadth, and humerus head diameters, were obtained using a digital caliper after weighing the bones (Fig. 1, Table II). After reconstruction, VG Studio Max ®3.2 was employed for data analysis (Bouxsein *et al*., 2010). The following trabecular morphometric parameters were assessed: trabecular number (TbN), thickness (TbTh), spacing (TbSp), and bone volume ratio (BV/TV) the proximal epiphysis of the bone in addition to the bone volume

Table I. Humerus osteometric parameters.

Parameter	Description
Full humerus length	The distance between the highest point of the head of the humerus and the furthest point on the humerus distal aspect
Epicondylar breadth	The maximum transverse distance between the medial and lateral epicondyles
Humerus head diameter	Distance between the most bulging part in an anteroposterior, mediolateral, supero-inferior direction when looking from the top
Mid diaphysis AP diameter	Anteroposterior diameter at the 50th percentile
Mid diaphysis ML diameter	Mediolateral diameter at the 50th percentile
Robusticity index	Sum of the diameter of the ML and AP midshaft diameter multiplied by the 100 and divided by the bone length

(BV), (Table III). Cortical and medullary canal areas were measured from the humerus midshaft on cross-sectional slices (Fig. 1 and Table I).

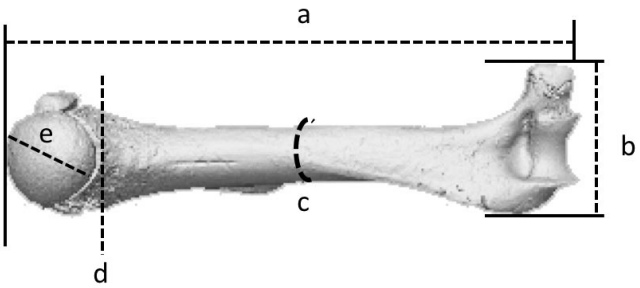

Fig. 1. A 3-dimensional reconstruction of the humerus illustrating the specific areas analysed. (a), full humerus length; (b), epicondylar breadth; (c), 50th percentile (midshaft) mark; (d), proximal ROI for trabecula morphological assessment; (e), head diameter (Image, courtesy of R. Ndou and G.F Dlamini).

Three-point bending. Humeri underwent three-point bending assessments using a Shimadzu tensile tester, (EZ-X S 200V E, Shimadzu South Africa, Pty Ltd). A 13 mm support span and 5 mm/min loading rate were used, with midshaft loading in the mediolateral plane. Load-displacement curves were recorded until fracture.

Data analysis. Microsoft Excel Office 365 (Microsoft Corporation) was used for data management and SPSS® version 28 (IBM®) for statistical analysis. Group mean differences for the blood glucose, OGTT, osteometric, trabecular morphometric parameters as well as cortical and medullary midshaft areas were compared using the t test. Data were reported as mean and standard deviation. The significance level was set at $p<0.05$

RESULTS

Fasting blood glucose. Significant differences in fasting blood glucose occurred during the study duration between the groups with ZDSD (9.5 mmol/L) showing higher values than the SD controls (5.7mmol/L) starting at week 16 ($p=0.001$) up to week 20, where the ZDSD (22.07 mmol/L) continued to exhibit higher numbers compared to SD2 (4.07 mmol/L) ($p<0.001$) (Fig. 2A).

Oral glucose tolerance test. The ZDSD group (19.28 ± 6.31 mmol/L) had significantly higher glucose levels at time zero when compared to SD (5 ± 0.57 mmol/L controls) ($p<0.001$) (Fig. 2B). The trend remained the same as seen120 minutes post glucose load administration, with ZDSD showing

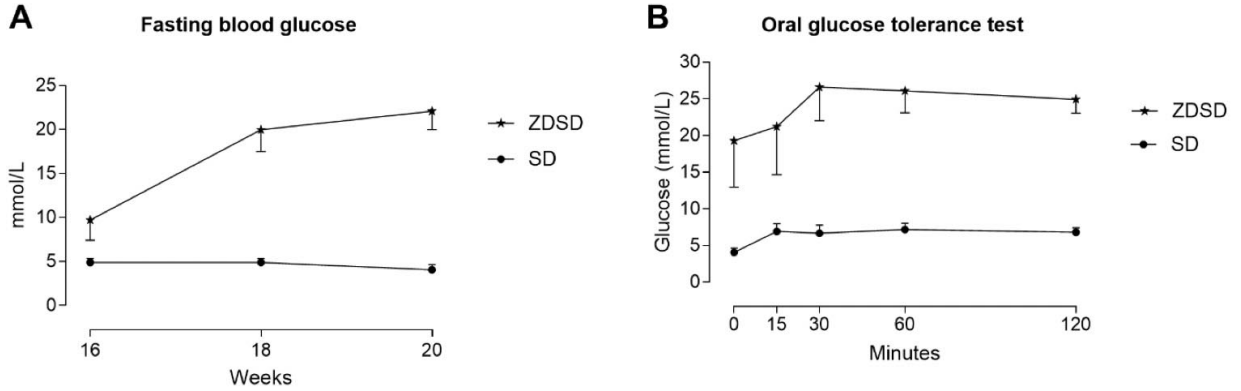

Fig. 2. Blood glucose. A, Fasting blood glucose at 16 to 20 weeks showing significantly higher blood glucose levels in ZDSD rats from week 16 to 20 ($p<0.001$). B, Oral glucose tolerance test showing that ZDSD had abnormal glucose disposal, while SD showed optimal glucose handling ($p<0.001$). SD; Sprague Dawley rats. ZDSD; Zucker Diabetic Sprague Dawley rats. The error bars represent the standard deviation.

hyperglycaemia (24.08 ± 1.88mmol/L) than SD controls (4.6 ± 0.61 mmol/L) (p<0.001) (Fig. 2B).

Humerus osteometry. The ZDSD bones demonstrated a statistically significant decrease in mass compared to the SD controls (p<0.001) (Table II). Similarly, SD rats had significantly longer bones with a wider epicondylar breadth compared to ZDSD rats (p=0.009; p<0.0001, respectively). Humerus head width was wider in SD controls than in ZDSDs (p<0.001) (Table II). Moreover, a significant increase in midshaft anteroposterior diameter was observed in SD controls compared to ZDSDs (p<0.001) whereas the midshaft mediolateral diameters were similar for the ZDSDs and their SD controls (p=0.195) (Table II). A comparison of the 2 groups showed that significantly more robusticity among the SD controls than the ZDSDs (p<0.001) (Table II).

Tensile strength parameters. Both the maximum and the break force showed higher values in SDs when compared with ZDSDs (p=0.001; p=0.032, respectively) (Table III). Similarly, SD controls had significantly higher yield force values than ZDSDs (p=0.003). In contrast, maximum time to fracture was similar between SD controls and ZDSDs (p=0.135). While both SD and ZDSDs had similar stiffness values (Table III), there were group differences in the elastic modulus as SD rats recorded significantly higher values for this parameter than SD controls (p=0.263 and p=0.026, respectively) (Table III).

Table II. Osteometric measurements of the humerus.

Parameter	SD (n=12)	ZDSD (n=14)	p value
Mass (g)	0.65±0.04	0.57±0.02	<0.001
Full length (mm)	31.66±1.55	30.81±0.35	0.009
Epicondylar breadth (mm)	7.68±0.19	7.24±0.26	<0.001
Humerus head width (mm)	5.56±0.24	5.11±0.25	<0.001
Mid shaft AP diameter (mm)	6.26±0.25	4.75±0.49	<0.001
Mid shaft ML diameter (mm)	2.62±0.28	2.71±0.13	0.195
Robusticity Index (%)	28.04±1.28	24.36±1.43	<0.001

Table III. Tensile strength properties.

	SD (n=12)	ZDSD (n=14)	p value
Maximum force (N)	97.36±8.13	75.08±7.20	0.001
Break force (N)	87.56±15.59	73.37±8.15	0.032
Yield force (N)	74.14±13.70	52.78±15.56	0.003
Maximum time (sec)	14.09±3.49	12.35±3.04	0.135
Maximum displacement (N)	0.71±0.17	0.62±0.15	0.139
Stiffness (N/mm)	140.10±28.69	123.02±26.95	0.263
Elastic modulus (N/mm^2)	2104.76±493.35	1630±760.09	0.026

Table IV. Trabecular morphometry.

Parameter	SD (n=12)	ZDSD (n=14)	p value
Bone volume (BV mm^3)	24.99±1.97	21.19±2.22	0.121
Bone volume ratio, (BV/TV, (%)	27.60±9.97	11.74±4.50	<0.001
Trabecular thickness (TbTh, mm)	0.25±0.08	0.21±0.02	0.171
Trabecular number (bN)	1.31±0.86	0.78±0.30	<0.001
Trabecular spacing (TbSp, mm)	0.19±0.22	1.29±0.71	<0.001

Table V. Cortical and medullary canal areas.

Parameter	SD (n=12)	ZDSD (n=14)	p value
Cortical area 50th percentile (mm^2)	16.00 ±2.59	15.11 ±1.47	0.335
Medullary area 50th percentile (mm^2)	5.52 ±1.17	5.46 ±1.29	0.930

Proximal humerus trabecular morphometry. There were similarities in humerus bone tissue volume (BV) between SD controls and ZDSDs (p=0.121) (Table IV and Fig. 2A and B). The ZDSDs displayed lower bone volume ratio (BV/TV) relative to the SD controls (p<0.001). Trabeculae thickness (TbTh) among the ZDSDs was similar to that of the SD controls (p=0.171). However, ZDSDs displayed lower trabecular number (TbN) than the SD controls (p<0.001), and the spacing was wider in ZDSD's in comparison to SD controls (p<0.001) (Table IV and Fig. 3A and B).

Cross-sectional cortical and medullary canal areas. ZDSDs exhibited a similar cortical area to that of their SD controls (p=0.335) (Table V). Again, the medullary canal area was similar in ZDSDs and SD controls (p=0.930).

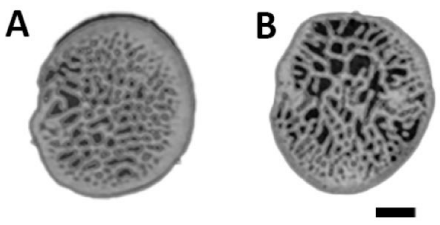

Fig. 3. Representation of trabecular microarchitecture. A, Sprague Dawley with compacted trabeculae. B, Zucker Diabetic Sprague Dawley with relatively fewer trabeculae that appear with wider spacing. Scale barr represents 0.5 mm.

DISCUSSION

The current study analysed the geometry of the humerus and trabeculae microarchitecture by micro-CT to determine their impact on bone strength using three-point bending in ZDSD rats. The proximal epiphysis and mid-diaphysis were investigated because fracture risk in diabetes is variable based on specific subregions of a bone (Ahmad *et al*., 2003). Male ZDSD rats were chosen for this study because they achieve full bone development before developing type 2 diabetes, allowing examination of the effects of diabetes on mature bone (Fajardo *et al*., 2014) to determine the impact of the dieses on bone fragility.

The ZDSD rats showed decreased bone mass as they had significantly lighter bones than SD controls. This observation is consistent with diabetes-induced bone loss as reported in previous research (Prisby *et al*., 2008). ZDSD rats also exhibited shorter humerus length, epicondylar breadth, head diameter, and less robusticity, suggesting impaired growth due to diabetes. The reduced length and less robusticity in diabetic rats imply a diminished ability to proportionally adjust bone dimensions. Bone dimensions are crucial for strength as lager bones are stronger (Clarke, 2008). In particular, this is an initial study reporting on humeral robusticity in ZDSD rats.

Analysis revealed no discernible differences in midshaft cortical and medullary canal areas between controls and ZDSDs. This finding was unexpected, given that other results from this study, such as 3-point bending and robusticity, suggested weakened diabetic bones in the diabetic group. This is in contrast with the literature that shows that reduced cortical area weakens bone (Osterhoff *et al*., 2016). Although cortical and medullary canal areas were similar, diabetes may have compromised the bone material quality within the cortical region. This possibility is supported by the observed low bone mass in the diabetic group.

After testing the strength of the humerus bones, the present study found that diabetic ZDSD rats required significantly less force to break them compared to healthy SD rats. Two key aspects of bone strength: maximum force and break force were measured. The maximum force is indicative of how much stress the bone can withstand before irreversible deformation. This reflects the bone's ability to absorb energy. The break force is the amount of force needed to fracture the bone once it has reached its limit. In the diabetic rats, both values were lower. This means that their bones were weaker and broke more easily. Therefore, these findings illustrate that the diabetic rats' humerus bones could not absorb as much energy before fracturing, and once they reached their limit, they fractured with less force. This result is consistent with previous research showing that diabetes increases the risk of bone fractures (Ahmad *et al*., 2003; Reinwald *et al*., 2009; Creecy *et al*., 2016).

The yield force, which represents the point where the bone starts to deflect, was also assessed and was significantly lower in the diabetic ZDSD rats than in the control SD rats. This means that the diabetic bones began to deform with less force applied and aligns with what other researchers have found (Reddy *et al*., 2001). This weakening effect could explain why people with diabetes are more likely to experience fractures, as seen in human studies (Janghorbani *et al*., 2007; Vestergaard *et al*., 2009; Valderrábano & Linares, 2018). Furthermore, we measured the elastic modulus, which reflects the amount of load (force) that a unit of bone could absorb prior to irreversible deformation (capability for elastic deformation). Past studies found that diabetic rats had a significantly lower elastic modulus compared to control rats. This means that diabetic bones could not absorb as much force before permanently deforming. Again, this supports previous findings that diabetes weakens bone structure and makes it more prone to damage (Reddy *et al*., 2001; Jepsen *et al*., 2015).

The present study found no statistically significant differences in bone volume (BV) between controls and ZDSD rats. However, as expected, the bone volume ratio (BV/TV) was lower in ZDSDs than SDs in agreement with existing scientific literature (Uppuganti *et al*., 2016). Regarding ZDSDs, this suggests that bone tissue volume ratios decreased due to hyperglycaemia, which is consistent with the findings of previous research (Prisby *et al*., 2008). Patients with type 2 diabetes lacking the BV/TV increase face a significantly elevated risk of bone fragility (Lekkala *et al*., 2019). Therefore, the low BV/TV in ZDSD rats in the present study may have attributed to the fragility of bones detected in three point bending tests.

Further examination of the trabecular morphology revealed some key differences between the diabetic group (ZDSDs) and the control group. Although the thickness of the trabeculae (TbTh) was similar between the two groups, the diabetic group had a lower number of trabeculae (TbN) and a greater distance between them (TSp). This means that the diabetic bones had fewer trabeculae, and were spread further apart, creating larger gaps. This pattern suggests that in diabetes there might be a disruption in the normal process of bone remodelling. Normally, bone is constantly broken down (resorption) and rebuilt (deposition) (Clarke, 2008). Our findings indicate that in diabetes, there may be less new bone being formed (deposition) or more old bone broken down (resorption). This imbalance would result in fewer

trabeculae and larger gaps between them, even if the individual trabeculae themselves maintained their thickness. This observation aligns with previous research demonstrating that diabetes weakens bones by interfering with the delicate balance between bone resorption and new bone formation (Ahmad *et al*., 2003). These results support the idea that diabetes can exacerbate trabecular architectural loss, making the bone weaker and more prone to fracture.

CONCLUSION

The geometry of the humerus and trabeculae microarchitecture are altered, compromising bone strength and structural integrity in diabetic rats (ZDSD). This should be considered in the overall care for diabetic patients. Caution must be exercised when extrapolating these humerus findings to humans, as the humerus is weight-bearing in rodents but not in human.

DLAMINI, G. F.; PERRY, V.; JAPHTA, N. L. & NDOU, R. Influencia de la geometría ósea y la morfología trabecular en la resistencia la tracción del húmero de la rata Zucker Diabetic Sprague Dawley**.** *Int. J. Morphol., 43(4)*:1442-1448, 2025.

RESUMEN: La resistencia ósea es una propiedad multifacética, en la que la geometría del hueso (tamaño, longitud, ancho, área cortical y distribución trabecular) aporta una contribución crítica junto con la microarquitectura ósea. Por lo tanto, el presente estudio tuvo como objetivo evaluar la influencia de la geometría ósea y la morfología trabecular sobre la resistencia a la tracción en el húmero de rata. El estudio utilizó 15 ratas macho, compuestas por un grupo control Sprague Dawley (SD) (n=6) y un grupo Zucker Diabetic Sprague Dawley (ZDSD) (n=7). La glucosa en sangre en ayunas y las pruebas de tolerancia oral a la glucosa se emplearon para monitorear la diabetes. Al finalizar, a las 20 semanas de edad, se extrajeron los húmeros y se realizaron mediciones osteométricas con un calibrador deslizante. Se efectuó microtomografía computarizada de foco fino (Micro CT) para la evaluación del número de trabéculas (TbN), grosor (TbTh), espacios (TbSp), volumen óseo (BV) y la relación volumen óseo/volumen total (BV/TV), así como de las áreas corticales de la diáfisis media y del canal medular. La diabetes se confirmó mediante valores alterados de glucosa en ayunas y una pobre tolerancia oral a la glucosa en el grupo ZDSD. Los húmeros de las ratas diabéticas presentaron menor masa y dimensiones osteométricas más pequeñas. Si bien el canal medular, las áreas corticales y el grosor trabecular (TbTh) mostraron similitudes entre los grupos, el grupo diabético exhibió un menor número de trabéculas (TbN) y una mayor distancia entre ellas (TbSp). La geometría del húmero y la microarquitectura trabecular se encuentran alteradas, comprometiendo la resistencia y la integridad estructural ósea en ratas diabéticas (ZDSD). Esto debe considerarse en la atención integral de los pacientes diabéticos.

PALABRAS CLAVE: Húmero; Hueso; Diabetes mellitus; Hueso cortical; Fractura ósea.

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