

Research Article

Evaluation of insulin resistance in overweight and obese dogs

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Abstract

Prevalence of obesity in dogs has been increasing in the last decade, being the most common form of malnutrition and consequently has increased the appearance of metabolic diseases in this species. The objective of this study is to compare biochemical and endocrine profiles related to insulin resistance between lean and obese canine patients and to find similarities with the human metabolic syndrome. A total of 20 dogs were divided into two groups (lean and obese) of 10 dogs each, evaluating body mass index, HOMA-IR, HOMA-B, insulin, glucose, cholesterol, triglycerides, HDLc, LDLc, cortisol, T4total and freeT4. The results showed significant increase in BMI, HOMA-IR, insulin, glucose, cholesterol, HDLc, triglycerides and cortisol in obese patients, similar to metabolic syndrome described in humans.

Introduction

Obesity is the most common form of malnutrition in dogs and is defined as an increase of more than 15% of optimal body weight by the accumulation of adipose tissue [1]. There are predisposing factors such as: castration, sedentary lifestyle, high fat diets, and endocrine diseases such as hypothyroidism [2]. The prevalence of this disease has been increasing in recent years in companion animals with 30 to 40% of overweight pets and 5 to 20% are obese, and consequently increasing the occurrence of metabolic diseases such as dyslipidemia and insulin resistance or glucose intolerance [3,4]. Obese individuals present alterations in concentrations of fasting glucose, insulin, cortisol, lipids and lipoproteins, such as elevated cholesterol and triglycerides, as well as increased cholesterol-carrying lipoproteins: VLDL (very low density lipoprotein), low-density lipoprotein (LDL) with decreased levels of HDL (high-density lipoprotein) [5,6]. As in humans, obesity in dogs and cats is associated with a variety of metabolic dysfunctions [7].

Insulin resistance implies resistance to the effects of insulin on glucose uptake, metabolism or storage, and in obesity it is manifested by a decreased transport of glucose stimulated by insulin [8]. To compensate for this resistance, more insulin

must be secreted, not being clear how it is increased. Possible mediators of this phenomenon are glucose and some hormones like cortisol, which in obese humans tend to increase its plasma and urinary concentration [9]. HOMA_{IR} (Homeostatic Evaluation Model for Insulin Resistance), which is the ratio of fasting glucose and insulin concentrations to determine the degree of insulin resistance of the patient, [6,10,11] in the same way as the human, obese dogs show elevation in HOMA-IR indicating a decrease in insulin sensitivity in these patients [6,12,13].

Materials and methods

Population of study

A total of 20 dogs were divided into two groups of 10 dogs each. Owners authorized blood sample collection and participation in this study. The groups consisted of an age range between 1 year and 11 years, all of them being of different sizes. Visual body score (VBS) was used to assign them to each group. For this method, the fat that covers the ribs, under the back, around the base of the tail and ventrally along the abdomen was considered and assigned numbers from 1 to 5, with 3 being the ideal weight of the patient, 4 in overweight and 5 for obese patients [4,14,15]. The VBS evaluation was made by three

observers. Patients who scored with numbers 4 and 5 for this method that corresponded to overweight and obese patients were assigned to the “obese group”, while patients who scored 3 were assigned to the “lean group”. In both groups, 5 males and 5 females were distributed equally between castrated and non-castrated females to avoid effects of castration on lipids metabolism [16,17].

Calculation of body mass index

Body mass index (BMI) was measured using formula described by [1]: Body mass index (BMI) = Body weight (BW) in kg/(height at shoulder in cm × length from occipital protuberance to base of tail in cm).

Biochemical studies in blood

In the two groups blood samples (12-hour fast) were obtained by venipuncture of the cephalic vein using 3 ml syringes with 23Gx1 NIPRO® needles and in Vacuette® MiniCollect tubes to analyze glucose, total cholesterol, HDL-cholesterol (HDLc), LDL-cholesterol (LDLc), and triglycerides. To avoid glucose consumption by the erythrocytes, the blood was collected in a separate tube with fluorinated anticoagulant, then centrifuged and separated to measure blood glucose. In another tube without anticoagulant blood was collected to measure total cholesterol, HDL cholesterol fraction and triglycerides after allowing the clot to form, centrifuging and separating the serum. These variables were measured using the VITROS 250® analyzer. The LDL cholesterol fraction was calculated using the Friedewald formula: LDL-cholesterol= Total cholesterol – (HDL-cholesterol + Tg/5) [18].

TSH must be between the reference range (<0.35ng/mL) in all dogs in order to be part of this study. Insulin, cortisol and thyroid hormones (total T₄ and free T₄) were evaluated (from the same blood sample obtained to measure the above-mentioned variables). Hormone samples were frozen at -30°C until processed. All were analyzed by chemiluminescence method (IMMULITE, 1000®, Siemens corp). For cortisol the inter- and intra-assay coefficients of variation for cortisol were 8% and 5%, respectively; insulin, inter- and intra-assay coefficients of variation (canine performance) were 4.5% and 4.3%, respectively and sensitivity of 0.005 ng/ml; TSH, intraassay and inter-assay CV were 3% and 4.3%, respectively and the sensitivity was 0.03 ng/ml; total T₄, intra-assay coefficient of variation was 3.1%, inter-assay coefficient of variation was 4.8%, Sensitivity 0,20 ug/dl; free-T₄, intraassay and inter-assay coefficient of variation were 4 and 3.4% respectively. Sensitivity 0,03 ng/ml. HOMA_{IR} index for the assessment of insulin resistance and HOMA_B were calculated using Oxford's HOMA Calculator version 2.2.3.

Statistical methodology

Distribution of the variables (parametric or non-parametric) was determined through D'Agostino-Pearson's normality test. The obtained data were compared among the populations by means of the non-parametric test of Mann Whitney. Data are expressed as medians and minimum and maximum range. A

correlation study was made by the Spearman correlation test. A value of P<0.05 was considered significant for all tests.

Results

Population of study

A total of 20 dogs divided into two groups: a group of dogs assigned as lean dogs (n = 10) and another group of dogs assigned as overweight and obese (n = 10). Each group had a homogenous distribution in terms of sex and reproductive status. Patients were in a range between 1 year and 11 years, which can be classified into three groups: young adults (patients between 1 and 3 years); adults (patients between 4 and 6 years old); and matures (patients older than 7 years). Breeds of the patients evaluated were in majority mongrel dogs, followed by Labrador Retrievers and Beagle.

Body mass index

It was observed that BMI is significantly higher in the obese than in the normal weight (P <0.05). (Figure 1).

Blood glucose, insulin and HOMA-IR and HOMA-B index

Both glycemia, insulin and HOMA-IR index were significantly higher in the obese group compared to lean dogs (P <0.05). HOMA-B (beta cell function) did not show differences between the groups (Figures 2-5).

Serum lipids

Total cholesterol (P<0.05), triglycerides (P<0.01) and HDL (P<0.05) were significantly higher in the obese compared to lean dogs, with no significant difference in LDL. (P>0.05). (Figures 6,7).

Cortisol and thyroid hormones

Cortisol concentrations were significantly higher (P<0.05) in the obese group. Thyroid hormones did not show significant differences between both groups (Figures 8,9).

Correlation analysis

VBS was correlated with the rest of the variables showing a

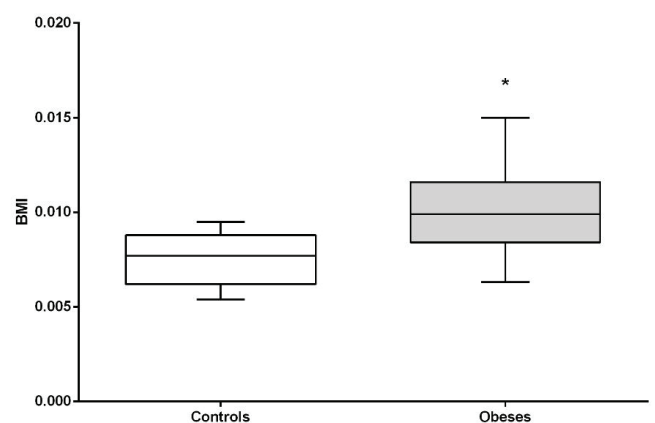


Figure 1: BMI comparison for both groups. It is observed that BMI is higher in obese. *P <0.05.

significant correlation with all variables except cholesterol, its fractions and thyroid hormones (Table1).

Discussion

Currently obesity in the urban dog is considered an epidemic as in the human [19,20] caused by a positive energy balance and accumulation of adipose tissue with abdominal

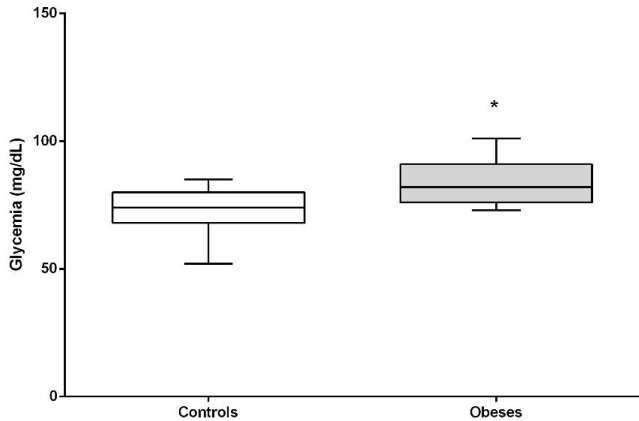


Figure 2: Comparison of blood glucose concentration for both groups. Significant increase is shown in obese patients compared to lean dogs (controls). * P <0.05.

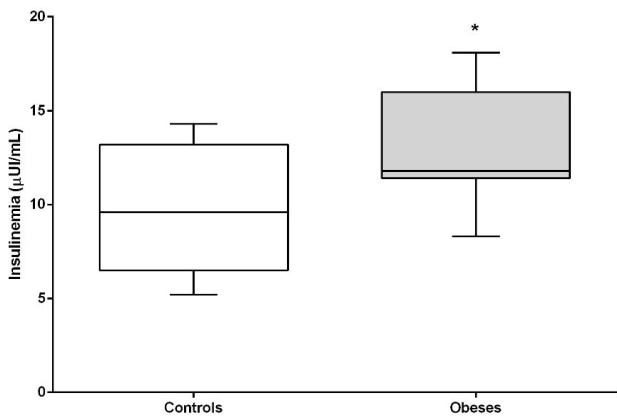


Figure 3: Blood Insulin compared to both groups. A significant elevation is shown in obese patients. * P <0.05.

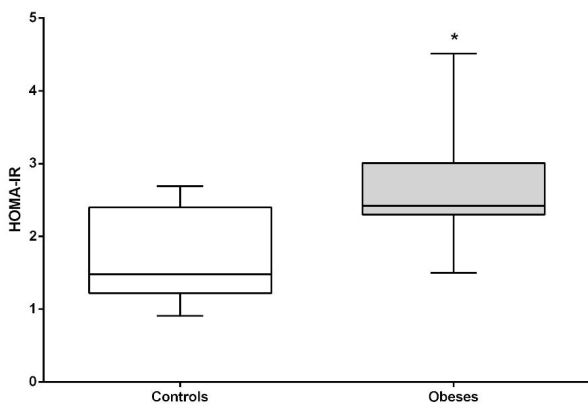


Figure 4: HOMA-IR Index comparison for both groups. Significant elevation is shown in obese patients. * P <0.05.

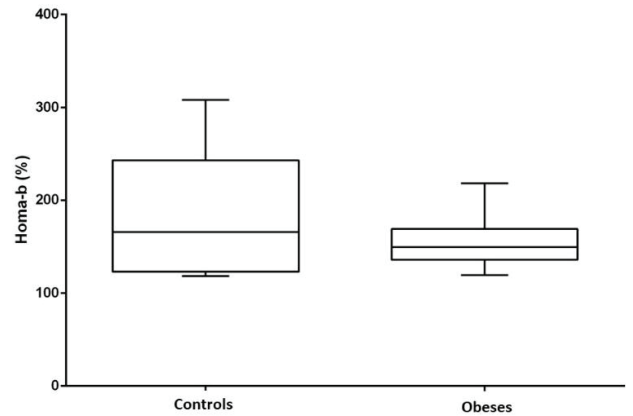


Figure 5: HOMA-B Index comparison for both groups. No significant difference is shown.

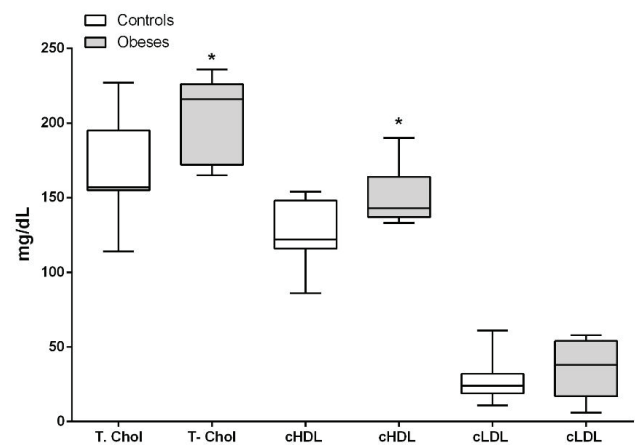


Figure 6: Comparison of total cholesterol and its HDL and LDL fractions for normal weight and obese groups. Significant increase was found for Total Cholesterol and HDL. * P <0.05.

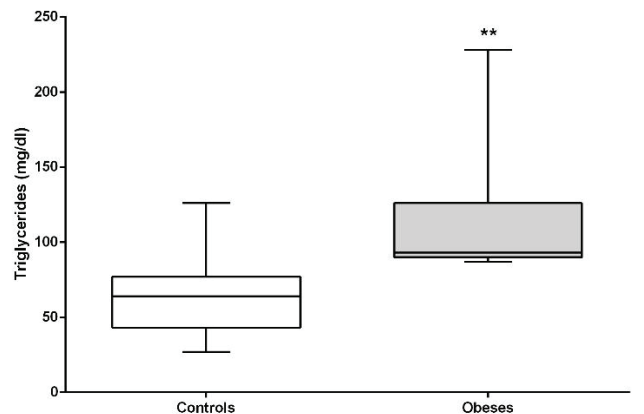


Figure 7: Triglyceride comparison for lean and obese groups. A significant increase in triglycerides was found in obese patients. * P <0.01.

predominance (visceral fat). This type of adipocyte is described as smaller and unstable and is associated with metabolic disorders because leptin and adiponectin are affected, and for being susceptible to inflammation [21,22], this is the initial step for the development of Metabolic Syndrome that finally

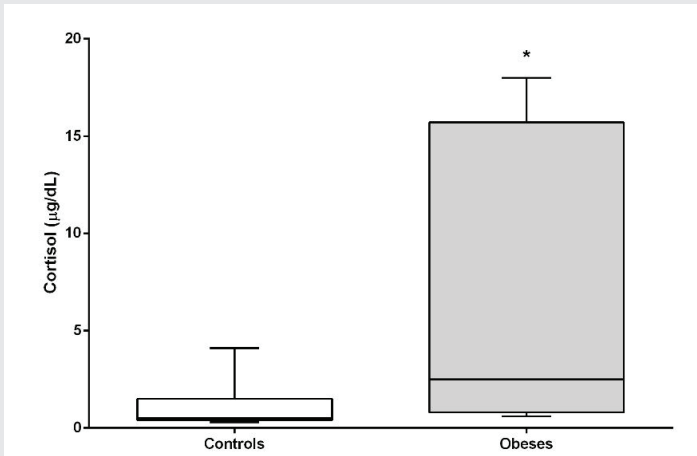


Figure 8: Comparison of blood cortisol for both groups. Significant elevation is shown in obese patients compared to controls. * P <0.05.

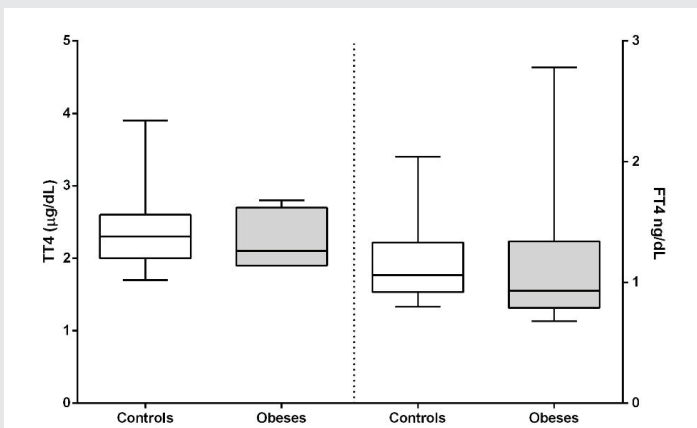


Figure 9: Comparison of total T4 and free T4 thyroid hormones for both groups. No significant differences were found. * P <0.05.

Table 1: Correlation between VBS vs. variables.

	VBS	
	r	P
BMI	0.68	<0.001
Glucose (mg/dL)	0.63	<0.01
Insulin (µIU/mL)	0.45	<0.05
HOMA _{IR}	0.61	<0.01
Cortisol (µg/dL)	0.51	<0.05
Cholesterol (mg/dL)	0.42	0.08
HDL-cholesterol (mg/dL)	0.43	0.07
LDL-cholesterol (mg/dL)	0.07	0.7
Triglycerides (mg/dL)	0.59	<0.01
Total T4 (µg/dL)	-0.14	0.6
Free T4 (ng/dL)	-0.37	0.1

will end in diabetes mellitus without the adequate therapeutics (exercise, change of habits, adequate food).

In the present study we studied overweight and obese dogs. Using the method of morphometry to determine BMI [1], we compared it with VBS finding congruence in both methods since the group of obese patients had higher BMI than the control

group. VBS is useful in clinical practice and would allow to have an approximate idea of what happens metabolically in the obese dog. This arises from the correlations observed in our study, where VBS correlated positively with glucose, triglycerides, insulin, HOMA_{IR} and cortisol. Therefore, patients with VBS of 4 and 5 would be expected at the time of consultation to have impaired fasting glucose, higher concentrations of fasting triglycerides and hyperinsulinism with insulin resistance because of clinical obesity.

This study found significant alteration in fasting blood glucose concentrations in obese patients compared to lean dogs. These results are in accordance with similar previous studies [23] and in contrast to another research [12] who did not find differences between obese and lean dogs. Although the fasting glucose values of this study were within the reference range considered normal, the glycemia of the obese population was higher than lean dogs, which would indicate that the glycemic control is not adequate, as it has been described in human medicine in obese patients [24]. Some authors propose that blood glucose remains within its normal concentrations due to the hyperinsulinism that occurs in these patients, being a way to compensate and maintain the homeostasis of glucose at the expense of a greater synthesis and release of insulin [25].

Patients in the obese group presented hyperinsulinism coinciding with other studies, both in dogs and humans [12, 24, 25]. This is due to the compensatory response of the pancreatic beta cell to the increase in fasting glucose and greater difficulty of admission in peripheral tissues due to the lower insulin sensitivity [26], even at the expense of exhaustion and trigger the process of cellular apoptosis [27]. If beta cell overwork is not controlled and reversed, the risk of progressing to the state of diabetes mellitus is high [28].

The HOMA-IR index has been previously described in humans and dogs as an estimator of the insulin resistance state or peripheral sensitivity [6,10,29]. In our study, HOMA-IR was high in the obese group, indicating peripheral insulin resistance in this population. It is known that obesity causes insulin resistance by various mechanisms [8] and that this resistance can be reversed when the body weight decreases and the visceral adipose tissue decreases [12,30]. In this way, the peripheral sensitivity to insulin is restored by decreasing the adiponectin and the inflammatory cytokines responsible in part for the processes of insulin resistance. HOMA-B did not show any significant difference between the groups, this may suggest that beta-cells function remains stable despite peripheral insulin resistance.

The decrease in visceral adipose tissue is also important for the correct metabolism of lipids. Studies in humans and rats show a direct relationship between adipose tissue mass, triglyceride and total cholesterol levels [31]. We found in our work elevation in the concentrations of total cholesterol, HDL cholesterol and triglycerides. Similar studies [19], found alterations in total cholesterol only in obese canine patients. These same alterations in total cholesterol and triglycerides were described in obese felines who also had decreased concentrations of adiponectin associating it intimately with



triglycerides with insulin resistance [32], the same thing that has long been described in human medicine [33,34]. Some researchers also found alterations in cholesterol and triglycerides in obese dogs together with hyperinsulinism and higher plasma glucose concentrations, postulating that these anomalies are similar to what was described in humans as Metabolic Syndrome, so it postulates that 20% of dogs suffer from this syndrome which the author calls obesity-related metabolic dysfunction in dogs [35].

Other studies conducted in obese humans have also determined significant alterations in plasma lipid concentrations mainly in triglycerides and HDL [36,37] and significant alterations in total cholesterol, triglycerides, HDL and LDL [38]. The HDL cholesterol is high since it corresponds to 70% of total cholesterol, however, in terms of LDL there was no significant increase in our work.

The concentrations of thyroid hormones were normal, which indicates that these dogs did not suffer from hypothyroidism, so obesity is not attributable to this cause but to the fact of sedentary lifestyle and overfeeding. On the other hand it is clearly seen that obesity does not affect, at least as regards thyroxine concentrations, the function of the thyroid gland as it does with the endocrine pancreas. It would be interesting to further analyze the thyroid gland since it has been described that insulin resistance affects its functionality [39].

In humans, cortisol has been implicated as a physiopathological marker in idiopathic obesity, however, the concentrations of this circulating hormone are not always high [40]. In this work, obese dogs show an increase in serum cortisol levels. Given this, several explanations have been previously postulated in studies conducted in humans for the increase in cortisol secretion in obese patients: the first indicates that the increase in circulating cortisol levels is proportional to the increase in body mass [41]; a second explanation indicates a primary neuroendocrine abnormality causing an increase in central stimulation of the secretion of corticotropin-Releasing Hormone (CRH), corticotropin (ACTH) and cortisol [42] and a third postulates that there is an increase in the peripheral metabolism of cortisol with compensatory changes of the hypothalamic-pituitary-adrenal axis [41]. Local control of glucocorticoid production is carried out by the enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), which converts inactive cortisone into cortisol. This enzyme is widely expressed in several tissues, including visceral adipose tissue. Studies in humans have shown that obese patients express more 11 β -HSD1 in fat tissue compared to non-obese subjects [20,43]. Recently it was possible to verify in dogs with Cushing's syndrome (they have a large amount of visceral fat) that this enzyme is also more expressed [44]. This higher expression would explain the significant elevation of basal cortisol in obese dogs in this study. This excess of cortisol promotes hepatic gluconeogenesis, countering the action of insulin in the hepatocyte [45] and being one of the causes of the increase in fasting blood glucose. On the other hand, it should be considered that cortisol will affect the action of insulin in peripheral tissues and promotes lipolysis

with an increase in free fatty acids and triglycerides [46]. In this way, there are similarities between the metabolic syndrome that incorporates central obesity, dyslipidemia and insulin resistance with hypercortisolism.

In conclusion, obese dog has metabolic syndrome, and this is evidenced by the combination of insulin resistance, hyperglycemia, hyperinsulinemia and hypertriglyceridemia, being sustained by hypercortisolism that creates a vicious circle. Fasting hypertriglyceridemia is an indicator of insulin resistance, therefore if we consider these animals with high triglycerides and higher blood glucose levels, and based on the HOMAIR index, obese dogs in our study show insulin resistance.

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