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Prospective hematological and biochemical evaluation of spontaneously overweight and obese dogs

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ABSTRACT

Across species overweight and obesity are associated with numerous disorders. To evaluate the occurrence of disturbances in terms of canine overweight and obesity, the authors undertook a prospective examination of hematological and biochemical parameters in 45 overweight and obese dogs, and compared the data with those obtained in 28 healthy normal-weight dogs. Neutrophil count, total cholesterol concentration and alkaline phosphatase activity were increased in the total group of overweight and obese dogs ($P<0.01$; $P<0.007$; $P<0.000007$), while concentrations of blood urea nitrogen decreased ($P<0.007$). Overweight was characterized by increased neutrophil count, cholesterol and triglycerides ($P<0.03$; $P<0.00005$; $P<0.02$), while obesity resulted in an increase in glucose, alkaline phosphatase and total cholesterol ($P<0.02$; $P<0.002$; $P<0.0004$), and a decrease in blood urea nitrogen and creatinine ($P<0.0004$; $P<0.004$). The obtained results support the idea that neutrophils could be involved in canine obesity-related pathology. Overweight and obesity were characterized by disturbances in the glucose metabolism and dyslipidemia. One of the interesting aspects of our examination was that obesity in dogs was related to a decrease in urea and creatinine concentrations in the circulation, which may be a consequence of increased glomerular filtration or hyperlipidemia. This study implies that canine obesity significantly affects alkaline phosphatase activity. A favorable circumstance related to the epidemic proportions of obesity in dogs is that most related potential health problems can be successfully prevented by maintaining a normal body weight.

Key words: canine, weight excess, neutrophils, glucose, dyslipidemia

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Introduction

Overweight and obesity have reached epidemic rates today and represent a major health problem in human and veterinary medicine. Recent studies have shown that between 40 % - 55 % of dogs are overweight, with a continuous upward trend (SWITONSKI and MANKOWSKA, 2013; DE GODOY and SWANSON, 2013). This condition affects dogs and other pets adversely in many ways. It is associated with increased incidence of numerous diseases, such as: impairment of glucose metabolism, osteoarthritis, orthopedic diseases, abnormalities in circulating lipid profiles, cardiorespiratory diseases, urinary and reproductive disorders, increased mortality risk, dermatological and respiratory diseases, anesthetic complications and increased occurrence of various neoplasms (GERMAN, 2006).

In recent years, the nature of fat deposits has become better understood. Long regarded as just physiologically inert energy-storage, adipose tissue is now generally accepted as an important endocrine organ, with numerous metabolic activities. White adipose tissue secretes biologically active substances called ‘’adipokines” (ATHYROS et al., 2010). The majority of adipokines act as proinflammatory cytokines, resulting in a persistent state of low-grade inflammation (SCHÄFFLER and SCHÖLMERICH, 2010; CHMELAR et al., 2013).

Hematology laboratory tests have long been used in canine medicine in the assessment of health. Despite the widespread problems of overweight and obesity in canine medicine, studies examining the effects of naturally-gained obesity on hematological and biochemical parameters are scarce. Chronic inflammation affects many hematological parameters, including erythrocytes, leukocytes and platelets (CHEN at al., 2013). Moreover, the most common cause of anemia in dogs is the inflammatory state. In spite of the fact that anemia caused by inflammation is commonly found in veterinary and human cases, the underlying mechanism has not yet been completely understood (CHIKAZAWA et al., 2013). In addition to being a common cause of anemia, pro-inflammatory cytokines are potent inducers of leukocyte production.

In addition to hematological disturbances, there is a great deal of evidence demonstrating that overweight and obesity are related to dysregulation of glucose and lipid metabolism (RAND et al., 2004). Abdominal obesity and impaired postprandial lipid metabolism have long been recognized as being associated with atherosclerosis and coronary heart disease in humans (FREEDMAN et al., 2001; FOLSOM et al., 1998), while in dogs atherosclerosis, coronary heart disease and stroke are rare and not known to be associated with obesity (VERKEST, 2014a). Moreover, although obesity is known to cause insulin resistance, there is no current data proving that obesity is actually a risk factor for diabetes mellitus in this species (RAND et al., 2004).

Across different species, obesity is associated with numerous disorders, but in canine medicine little information is available on the impact of chronic overweight and obesity on blood cell number, hematological indices and biochemical parameters evaluating

kidney and liver function. Thus, the objective of this study was to examine the relationship of overweight and obesity with hematological and biochemical parameters in generally healthy overweight and obese dogs.

Materials and methods

Animals. A total of 45 overweight and obese, but otherwise healthy dogs and 28 healthy, normal-weight dogs were included in this prospective study. The dogs were randomly selected from overweight and obese dogs among the patients of the "Branimir" veterinary clinic, Zagreb. Various breeds were represented, but Labradors and Golden Retrievers were the most frequent breeds in both groups. There were 30 females and 15 males in the overweight and obese group (O), and 14 females and 14 males in the normal-weight control group (C). A detailed history of all animals was obtained. All the dogs had been overweight or obese for at least for 6 months. Exclusion criteria were any ongoing medical therapies and concomitant chronic or acute illnesses. The weight status of the dogs was determined by the body condition score (BCS), always assessed by the same veterinarian, using a 5-point scale (LAFLAMME, 1997). The weight of the dogs was compared with the standard weight for the breed, and rib palpation, waist visibility and abdomen tucking were used to determine BCS. The normal-weight dogs with BCS 3 represented the control group (C), BCS 4 represented overweight (O_1) dogs and BCS 5 represented obese (O_2) dogs. There were 26 animals with BCS 4 and 19 animals with BCS 5. Control dogs with BCS 3 were deemed healthy, on the basis of normal history, complete physical examination and laboratory data: complete blood count, serum biochemistry and urinalysis. The study protocol was approved by the Ethics Committee for Animal Experimentation, Faculty of Veterinary Medicine, and University of Zagreb, Croatia. All the dogs' owners gave written informed consent before entering the study.

Laboratory analysis. Blood was collected after an overnight fast via cephalic venipuncture into Vacutainer EDTA tubes (Becton Dickinson, Rutherford, NJ). Red blood cell count (RBC), white blood cell count (WBC), hemoglobin concentration (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) were evaluated using a "Horiba ABX automatic blood cell counter (Diagnostics, Montpellier, France) and the original manufacturer's reagents. Blood cell morphology and WBC differential count were evaluated in Wright stained blood films. Creatinine (CRE), blood urea nitrogen (BUN), glucose (GLUC), total cholesterol (tCHOL), and triglyceride (TRIG) concentrations, and the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) were measured in sera samples, using an Olympus AU600 biochemical autoanalyser (Olympus Corporation, Tokyo, Japan) with the manufacturer's reagents and standard methods.

Data analysis. Normal distribution of all variables was tested using the Kolmogorov-Smirnov test. Differences between obese and lean dogs were tested by either the Student t test or the Mann-Whitney U test. Statistical analyses were performed with computer software (Statistica for Windows, StatSoft Inc.), with the level of significance set at $P<0.05$.

Results

All obtained hematological and biochemical results are shown as mean and standard deviation (SD). There were no statistically significant differences between overweight, obese and normal-weight dogs regarding erythrocyte number and indices, or hematocrit and hemoglobin concentration (Table 1).

Table 1. Red blood cell number and indices, hematocrit and hemoglobin concentration in normal weight, overweight and obese dogs (mean ± SD)

Group	RBC ($\times10^{12}$/L)	RDW	MCV (fL)	MCH (pg)	MCHC (g/L)	HB (g/L)	HTC (%)
C	6.9 ± 0.75	14 ± 1.1	71 ± 3.0	23 ± 1.6	330 ± 14	161 ± 17	49 ± 5.4
O	7.0 ± 0.72	14 ± 1.1	71 ± 3.2	24 ± 1.7	324 ± 57	167 ± 20	50 ± 5.2
O_1	6.9 ± 0.62	14 ± 1.1	71 ± 2.9	24 ± 1.9	319 ± 73	164 ± 22	49 ± 4.8
O_2	7.3 ± 0.79	14 ± 1.2	71 ± 3.8	23 ± 1.3	331 ± 16	171 ± 17	52 ± 5.5

RBC - red blood cells, RDW - red distribution width, MCV - mean cell volume, MCH - mean cellular hemoglobin, MCHC - mean cellular hemoglobin concentration, HB - hemoglobin concentration, HTC - hematocrit, C - control normal weight dogs (N = 28), O - total overweight and obese dogs (N = 45), O_1 - overweight dogs (N = 26), O_2 - obese dogs (N = 19), *$P<0.05$ comparing O, O_1 and O_2 with C

No statistically significant differences in the total leukocyte number and differential blood count were observed, except for neutrophils (NEU), being significantly increased in the O ($P<0.01$) and O_1 groups ($P<0.03$) while compared with C group (Table 2).

Table 2. Number of leukocytes and differential blood picture from normal weight, overweight and obese dogs (mean ± SD)

Group	WBC ($\times10^9$/L)	NEU (%)	MO (%)	LY (%)	EO (%)	NS (%)
C	10 ± 2.8	58 ± 9.3	1.7 ± 2.2	35 ± 8.8	5.1 ± 4.3	0.04 ± 0.19
O	9.4 ± 2.7	65 ± 16*	1.6 ± 2.0	29 ± 15	4.2 ± 4.4	0.20 ± 0.41
O_1	9.0 ± 2.6	65 ± 15*	1.3 ± 1.3	29 ± 14	4.4 ± 5.0	0.19 ± 0.40
O_2	10 ± 2.7	64 ± 17	2.1 ± 2.7	29 ± 16	3.9 ± 3.6	0.22 ± 0.43

WBC - total leukocyte count, NEU - segmented neutrophils, MO - monocytes, LY - lymphocytes, EO - eosinophils, NS - nonsegmented neutrophils, C - control normal weight dogs (N = 28), O - total overweight and obese dogs (N = 45), O_1 - overweight dogs (N = 26), O_2 - obese dogs (N = 19), *$P<0.05$ comparing O, O_1 and O_2 with C

We found that tCHOL was significantly elevated in the whole overweight and obese groups compared to the control normal-weight dogs (P<0.000007). Blood urea nitrogen significantly decreased in the O (P<0.007) and O_2 groups (P<0.0004), while CRE was lower only in the O_2 group (P<0.004). Concentrations of GLUC showed a significant increase in the O_2 group (P<0.01), while TRIG was elevated in the O_1 group, compared with the control lean dogs (P<0.02). The results are shown in Table 3.

Table 3. Biochemical parameters in normal weight, overweight and obese dogs (mean ± SD)

Group	BUN (mmol/L)	CRE (μmol/L)	BIL (μmol/L)	GLUK (mmol/L)	TRIG (mmol/L)	tCHOL (mmol/L)
C	6.6 ± 1.7	100 ± 11	3.7 ± 1.7	4.7 ± 0.8	1.1 ± 1.0	5.7 ± 1.1
O	5.3 ± 2.0*	92 ± 20	3.6 ± 1.7	5.7 ± 3.9	1.6 ± 1.5	8.1 ± 3.1*
O_1	5.7 ± 2.3	95 ± 24	3.6 ± 1.7	6.0 ± 5.2	2.0 ± 1.8*	8.5 ± 3.7
O_2	4.8 ± 1.5*	88 ± 15*	3.7 ± 1.8	5.2 ± 0.5*	1.2 ± 0.8	7.6 ± 2.2

BUN - blood urea nitrogen, CRE - creatinine, GLUC - glucose, BIL - total bilirubin, TRIG - triglyceride, tCHOL - total cholesterol, C - control normal weight dogs (N = 28), O - total overweight and obese dogs (N = 45), O_1 - overweight dogs (N = 26), O_2 - obese dogs (N = 19), *P<0.05 comparing O, O_1 and O_2 with C

Activity of AST, ALT, YGT and ALP is shown in Table 4. The overweight and obese dogs displayed significantly increased activity of ALP (P<0.007), while activities of AST, ALT and YGT remained similar compared with normal-weight dogs. The activity of ALP was significantly increased in overweight (P<0.007) as well as obese dogs (P<0.002).

Table 4. Enzyme activities in normal weight, overweight and obese dogs (mean ± SD)

Group	AST (IU/L, 37 ºC)	ALT (IU/L, 37 ºC)	YGT (IU/L, 37 ºC)	ALP (IU/L, 37 ºC)
C	34 ± 8.3	53 ± 27	3.3 ± 2.1	42 ± 25
O	36 ± 12	98 ± 190	5.3 ± 9.6	231 ± 427*
O_1	38 ± 14	119 ± 244	6.7 ± 13	243 ± 506*
O_2	35 ± 9.9	68 ± 66	3.3 ± 1.8	216 ± 305*

AST - aspartate aminotransferase, ALT - alanine aminotransferase, YGT - gamma glutamyl transferase, ALP - alkaline phosphatase, C - control normal weight dogs (N = 28), O - total overweight and obese dogs (N = 45), O_1 - overweight dogs (N = 26), O_2 - obese dogs (N = 19), *P<0.05 comparing O, O_1 and O_2 with C

Discussion

Although determination of blood cell count and hematological indices are today widely available and inexpensive, there is a paucity of research focusing on blood cells in spontaneously overweight and obese dogs. In addition, the results of research conducted

on humans and animals published so far regarding the association between obesity and hematological disturbances, have been inconsistent.

It is now well-established that obesity results in a state of chronic low-grade inflammation (SOLINAS and KARIN, 2010). We hypothesized that dogs with a higher body condition score would have decreased RBCs, HB and HTC due to the chronic inflammatory state, but overweight and obese dogs showed normal hematology regarding RBC count, RBC related indices HB and HTC. Similar to our findings, some researchers found no relationship between anemia and obesity in rodents (HARISHANKAR et al., 2011) while in obese humans there was higher risk of development of anemia (TUNGTRONGCHITR et al., 2000). In contrast to our results, studying the impact of obesity on HTC and HB levels some authors concluded that obese individuals have even higher values compared to normal-weight individuals (RAO and MORGHOM, 1986; ZHANG et al., 2010; ORNELAS et al., 2011). Despite some indicators of proinflammatory status (increased NEU), weight excess in the investigated dogs was not associated with impairment of red blood cell count.

No significant differences were found between the groups with respect to total WBC count and differential blood count. The exception was NEU, being significantly increased in the overweight population in comparison with lean control dogs. This is in agreement with the study by RYDER et al. (2014), who found that neutrophils correlated positively with increased visceral fat in humans. The results of MAHASSNI and SEBAA (2012) also showed significant increases in NEU, LY and total WBCs counts in obese states in humans. Researching obesity in cats, JASO-FRIEDMANN et al. (2008), found no differences in WBC, NEU or LY counts between obese and lean cats. As the first immune cells to respond to inflammation, NEU have been recently implicated in obesity (CHMELAR et al., 2013), but the exact role of proinflammation in canine overweight and obesity is currently unknown. Adipose tissue dysfunction is found to be associated with systemic low-grade inflammation (SCHÄFFLER and SCHÖLMERICH, 2010). Having a short life span, NEU indicates the continuous activation of the immune system and chronic low-grade inflammation associated with canine overweight and obesity. In addition to an inflammatory state, one of the possible causes of increased NEU is the hypercholesterolemia that was present in both the investigated groups, the overweight and obese dogs. Namely, it was shown that an increase in tCHOL induces elevation of blood NEU (YVAN-CHARVET et al., 2008; DRECHSLER et al., 2010).

The effect of overweight and obesity on metabolic parameters has not been reported extensively in dogs, and most research evaluating the impact of obesity on biochemical indicators in dogs has been conducted on experimental models. Moreover, the pathophysiological associations between obesity and renal dysfunction are less well understood. Serum concentrations of BUN were lower in all the overweight and obese

dogs, as well as in obese dogs. Lower CRE concentrations in comparison to the lean dogs, were only observed in the obese group. There are two possible explanations. It is widely accepted that CRE concentrations may serve as an indicator of muscle mass (HJELMESATH et al., 2010). Thus, decreased CRE in obese dogs could be the consequence of lower muscle mass volume in relation to proliferated adipose tissue. Researching obesity in humans, numerous authors have agreed that obesity may be considered to be a state of relative hyperfiltration (RITZ, 2008; LAVILLE, 2011; WICKMAN and KRAMER, 2013). The factors involved could be: energy intake (high protein and salt), hyperinsulinemia, and enhanced tubuloglomerular feedback because of increased sodium reabsorption (RUTKOWSKI et al., 2006). In addition, some authors speculate that the decrease of BUN and CRE concentrations, as a consequence of increased glomerular hyperfiltration, may be associated with increased metabolic risk and diabetes development in humans (TOMASEWSKI et al., 2007; LORENZO et al., 2009). Therefore, the importance of lower BUN and CRE concentrations in canine obesity should not be underemphasized.

Weight excess, disturbances in glucose metabolism and dyslipidemias are some of the components of the metabolic syndrome. To date only a few epidemiological studies have been performed to define this condition in canine obesity. Serum glucose concentration was only elevated in obese dogs, while overweight dogs retained normal glucose concentrations, compared with those obtained in normal-weight dogs. Researching metabolic changes in canine obesity, PENA et al. (2014) also concluded that weight excess is characterized by an increase in serum glucose. Overweight and obesity in dogs have been well-accepted as causes of insulin resistance (LARSON et al., 2003; GAYET et al., 2004; VERKEST et al., 2011). However, insulin resistance in dogs could be present without overt signs of diabetes (ZORAN, 2010). Moreover, it appears that very few dogs develop overt diabetes as a consequence of obesity-induced insulin resistance (RAND, 2004). In addition, there are no current data proving that obesity is actually a risk factor for DM in canines (GERMAN, 2006). Taken together, further epidemiological data examining the relationship between canine diabetes and obesity are needed, to clarify the possible mechanisms involved in impairment of glucose homeostasis in the condition of adipose tissue proliferation.

Hyperlipidemia is one of the common metabolic disorders observed in obesity in humans and animals (DE GODOY and SWANSON, 2013). Our results showed elevated tCHOL concentrations in the overweight and obese groups together and the obese group. Concentrations of TRIG were only increased in the overweight group. Secondary hyperlipidemia represents the most common form of canine dyslipidemia that may be a result of obesity (PANAGIOTIS and STEINER, 2010). Published data studying canine overweight and obesity have also confirm that lipid alterations may occur, with increases in cholesterol and triglyceride concentrations (PENA et al., 2014; VEIGA et al., 2008). In spite

of the fact that obese dogs develop increased circulating concentrations of triglycerides and cholesterol, they do not develop atherogenic changes. Namely, atherosclerosis, coronary heart disease and stroke are rare and are not known to be associated with obesity in dogs (VERKEST, 2014), so it would be interesting to analyze what proteins in circulation or endothelium are included in such protection.

The four enzymes that are most commonly used in evaluating canine liver function are ALT, AST, YGT and ALP. Elevated serum hepatic enzyme activities may be associated with a high prevalence of fatty liver, which is frequently observed in obese humans (CHOI, 2003). No significant differences in AST, ALT and YGT activity were observed between overweight, obese and the normal lean, control dogs, while activity of ALP was significantly increased in overweight and obese dogs. A similar increase in ALP activity in obese rats was observed by MOZEŠ et al. (2004). The authors concluded that changes in ALP activity might be a consequence of overnutrition. Moreover, comparing the impact of a weight-loss program on canine ALP activity, some authors concluded that the activity of this enzyme significantly decreases after a successful weight-loss program (PENA et al., 2014). In contrast to our observations, some researchers have reported that abnormal serum levels of hepatic enzymes, such as ALT and YGT, are frequently found in obese dogs (TRIBUDDHARATANA et al., 2011). The results obtained indicated that there was no evidence of liver damage in canine overweight and obesity. Alkaline phosphatase, as an enzyme functionally involved in fat absorption and the transport of long-chain fatty acids in the intestinal mucosa (BERNARD et al., 1992), could be elevated in overweight and obese dogs due to overfeeding.

The incidence of obesity in dogs has assumed epidemiological proportions and potentially represents a major health problem in veterinary medicine. A comforting fact in addressing potential health problems related to obesity is that this problem can be simply resolved with successful weight-loss and appropriate prevention. Our results support the idea that NEU are involved in obesity-related pathology, and they extend previous findings in human and animals that accumulation of fat is associated with a state of chronic low-grade inflammation. One of the potentially interesting aspects of our examination is that obesity in dogs is related to the decrease of BUN and creatinine concentration in the circulation. This condition may be a consequence of glomerular hyperfiltration that could lead to further metabolic disorders associated with obesity. Overweight and obesity in the investigated dogs were characterized by disturbances in glucose metabolism and dyslipidemia, as previously reported. Further insight into the mechanisms involved in protection from atherosclerosis, stroke and diabetes in canine species could contribute to a better understanding of the causes of development of these disorders in other species, including humans.

Conflict of Interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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SAŽETAK

Prevelika tjelesna težina i pretilost povezane su s mnogobrojnim poremećajima u mnogih vrsta životinja. Da bi istražili promjene do kojih dolazi kod povećane tjelesne težine i pretilosti pasa, autori su prospektivno istražili hematološke i biokemijske pokazatelje u 45 pasa s povećanom tjelesnom težinom i pretilošću i usporedili rezultate dobivene u 28 zdravih pasa s normalnom tjelesnom masom. Broj neutrofila, koncentracija ukupnog kolesterola i aktivnost alkalne fosfataze bili su povećani u skupini pasa s prevelikom tjelesnom masom i skupini pretilih pasa ($P<0,01$; $P<0,007$; $P<0,000007$), dok je koncentracija ureje bila snižena ($P<0,007$). Povećana tjelesna težina pasa bila je popraćena povećanim brojem neutrofila, povećanom koncentracijom kolesterola i trigliceridima ($P<0,03$; $P<0,00005$; $P<0,02$), a pretilost je rezultirala povećanjem glukoze, alkalne fosfataze i kolesterola ($P<0,02$; $P<0,002$; $P<0,0004$) i snižavanjem ureje i kreatinina ($P<0,0004$; $P<0,004$). Dobiveni rezultati idu u prilog mišljenju da neutrofili mogu imati ulogu u patološkim procesima uzrokovanim pretilošću. Povećana tjelesna težina i pretilost očitovali su se poremećajima u metabolizmu glukoze i dislipidemijom. Jedan od zanimljivih rezultata ovog istraživanja je povezanost pretilosti i smanjenja koncentracije ureje i kreatinina u krvotoku, što može biti posljedica povećane glomerularne filtracije ili hiperlipidemije. Istraživanje ukazuje da pretilost pasa značajno utječe na aktivnost alkalne fosfataze. Većina zdravstvenih problema u pasa može se uspješno spriječiti održavanjem normalne tjelesne težine.

Ključne riječi: pas, pretilost, neutrofili, glukoza, dislipidemija