UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE ODONTOLOGIA

TASSIANE PANTA WAGNER

OBESIDADE PODE AUMENTAR A OCORRÊNCIA DE DESTRUIÇÃO PERIODONTAL ESPONTÂNEA EM RATOS WISTAR

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Trabalho de Conclusão de Curso apresentado ao Curso de Graduação em Odontologia pela Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Cirurgião-Dentista.

Orientador: Prof. Dr. Cassiano Kuchenbecker Rösing

Co-orientador: Juliano Cavagni

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RESUMO

WAGNER, Tassiane Panta. **Obesidade pode aumentar a ocorrência de destruição periodontal espontânea em ratos Wistar.** 2012. 23 f. Trabalho de Conclusão de Curso (Graduação em Odontologia) – Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2012.

Objetivo: avaliar o efeito da obesidade na ocorrência de perda óssea alveolar espontânea em ratos Wistar.
Materiais e métodos: vinte e oito ratos foram randomizados em dois grupos. O grupo controle recebeu ração padronizada e água. O grupo teste recebeu uma dieta hipercalórica e altamente gordurosa durante 110 dias. As respectivas dietas estiveram disponíveis para ambos os grupos *ad libitum*. O peso corporal e o Índice de Lee foram avaliados. Ao final do período experimental os ratos foram sacrificados por decapitação, as maxilas retiradas e os tecidos moles química e mecanicamente removidos com hipoclorito de sódio 9%. Análises morfométricas foram realizadas com um programa de fotografias digital. Foi considerada positiva a presença de destruição periodontal espontânea quando a média de perda óssea alveolar foi ≥.51mm. Análises estatísticas foram realizadas utilizando-se o teste do qui-quadrado, o teste de Mann-Whitney e teste-t para amostras independentes (nível de significância $P \leq 0.05$).
Resultados: Depois de 110 dias de exposição à dieta de cafeteria padronizada, uma diferença estatisticamente significativa no peso corporal (g±DP) (478±43 vs. 580±60) e Índice de Lee (3.07±0.05 vs. 3.24±0.07) foi observada entre os grupos, sugerindo obesidade no grupo teste. A mediana de perda óssea alveolar (mm±DP) nos grupos teste e controle foi .45±.17 e .41±.08, respectivamente. A presença de destruição periodontal espontânea foi detectada em 20 sítios nos animais submetidos à dieta de cafeteria enquanto no grupo controle foi observada em apenas 8 sítios, de acordo com ponto de corte estabelecido. Uma diferença estatisticamente significativa foi detectada entre os grupos (P=.009).
Conclusão: Pode-se concluir que obesidade aumenta a ocorrência de destruição periodontal espontânea em ratos Wistar.

Palavras-chave: Obesidade; destruição periodontal espontânea; dieta de cafeteria.

ABSTRACT

WAGNER, Tassiane Panta. **Obesity may increase spontaneous periodontal breakdown in Wistar rats.** 2012. 23 f. Final Paper (Graduation in Denstistry) – Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2012.

Aim: to evaluate the effect of body weight on the occurrence of spontaneous alveolar bone loss in Wistar rats.
Material and methods: Twenty-eight rats were randomly divided in two groups. Control group received standardized rat chow diet and water. Test group received high fat/hypercaloric diet during 17 weeks. The diet was available for both groups *ad libitum*. Body weight and Lee Index were evaluated. At the end of the experimental period, rats were killed by decapitation and maxillae were defleshed with 9% sodium hypochlorite. Morphometric analysis was performed in digital standard photographs. Presence of spontaneous periodontal breakdown was considered when median alveolar bone loss was ≥.51mm. Statistical analysis was performed with chi-square test, Mann-Whitney test and independent samples t-test (significance level $P \leq 0.05$).
Results: After 17 weeks of exposure to standard cafeteria (CAF) diet, a statistically significant mean difference in body weight (g±SD) (478±43 vs. 580±60) and Lee Index (3.07±0.05 vs. 3.24±0.07) was observed between groups suggesting obesity in test group. Median of alveolar bone loss (mm±SD) for test and control groups was .45±.17 and .41±.08, respectively. In animals submitted to cafeteria diet, 20 sites were classified as spontaneous periodontal breakdown, whereas in control animals, only 8 sites exhibited periodontal breakdown according to the cut-off point. A statistically significant difference among groups was detected (P=.009).
Conclusion: It may be concluded that obesity increases spontaneous periodontal breakdown in Wistar rats.

Keywords: Obesity. Spontaneous periodontal breakdown. Cafeteria diet.

SUMÁRIO

1 INTRODUÇÃO

A periodontite é uma doença de natureza infecto-inflamatória que acomete os tecidos de sustentação dos dentes (ligamento periodontal, osso alveolar e cemento) causada pelo biofilme subgengival. É influenciada por alguns fatores ambientais, comportamentais, biológicos e medicamentosos.

Nos últimos 10 anos vem aumentando o interesse por parte da literatura em periodontia a respeito da relação entre obesidade e doença periodontal, tanto em estudos clínicos quanto epidemiológicos. Estudos em modelos animais são escassos. A utilização de modelos animais para o estudo dos processos etiopatogênicos que envolvem obesidade e doenças periodontais deve ser considerada. Isso porque as similaridades anatômicas, histopatológicas, microbiológicas e bioquímicas destes modelos com os seres humanos é notável e as diferenças não têm sido consideradas um fator suficientemente importante para que os mesmos sejam descartados.

O presente estudo trata-se de um experimento no qual foi avaliada a influência da obesidade na ocorrência de destruição periodontal espontânea. Foi realizado em modelo animal, com ratos Wistar, protocolado e aprovado pelo Comitê de Ética de Pesquisa Animal do Hospital de Clínicas de Porto Alegre.

2 ARTIGO

Obesity may increase spontaneous periodontal breakdown in Wistar rats

Tassiane Panta Wagner[(a)]

Juliano Cavagni[(b)]

Eduardo José Gaio[(b)]

Rodrigo Otávio Citó César Rêgo[(c)]

Iraci Lucena da Silva Torres[(d)]

Cassiano Kuchenbecker Rösing[(e)]

(a) Undergraduate student, Faculty of Dentistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

(b) PhD student, Faculty of Dentistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

(c) Associate Professor, Division of Periodontics, School of Pharmacy, Dentistry and Nursing, Universidade Federal do Ceará, Fortaleza, Brazil;

(d) Associate Professor of Pharmacolgy, Departament of Pharmacolgy, Institute of Basic Health Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

(e) Professor of Periodontology, Faculty of Dentistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

***Corresponding Author:**

Juliano Cavagni

Av. Neusa Goulart Brizola, 555/ap. 403

Porto Alegre/RS, Brazil

ZIP Code: 90460-230

Phone: +55 51 3273 2499

Email: jcavagni@hotmail.com

INTRODUCTION

Obesity, the major nutritional disorder in developed and developing countries, is characterized by extreme body fat accumulation related to lean body mass[1]. It is known to increase risk for several chronic inflammatory diseases and conditions such as cardiovascular disease, type 2 diabetes mellitus, and arthritis[2]. Systematically, clinical studies demonstrated higher blood levels of proinflammatory cytokines in obese patients when compared to non-obese subjects[3-5].

In the last decades, the evidence linking obesity to the occurrence of periodontal disease has grown both in epidemiological and clinical studies. Presence of worse periodontal disease parameters such as bleeding on probing, severe periodontal pockets and alveolar bone loss were noticed in individuals with higher indicators of obesity[6-11]. It is still unclear whether obesity truly precedes periodontitis. However, the underlying biological mechanisms for the association of obesity and periodontitis most likely involve adipose tissue-derived cytokines and hormones[12]. Additionally, recent studies suggest an association between obesity and putative periodontopathogens (red complex) in obese subjects[13].

In the etiopathogenic process of periodontal diseases, the inflammatory pattern is one of the determinants of alveolar bone loss[14]. The production of inflammatory cytokines by the adipose tissue has also been considered important in the homeostasis of periodontal breakdown[12]. In this sense, studies in animals have shown evidence that obese animals tend to respond to the challenge of inducing disease differently. The study by Verzeletti et al (2012) demonstrated increased ligature-induced bone loss in obese rats. However, Simch et al (2008) did not observe higher degrees of periodontal breakdown in overweight rats.

Studies evaluating the occurrence of spontaneous alveolar bone loss related to fat accumulation are nonexistent. Therefore, the hypothesis to be tested is that obesity increases spontaneous periodontal breakdown in rats. The aim of this study was to evaluate the effect of obesity on the occurrence of spontaneous alveolar bone loss in Wistar rats.

METHODS

STUDY DESIGN

This is a prospective, randomized, controlled, and blinded animal model study. The protocol followed all recommendations of the *ARRIVE* (Animal Research: Reporting In Vivo Experiments) guidelines for report of studies in animals[15]. The study protocol was submitted and approved by the Animal Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, Brazil (protocol number 110051). The protocol complies with the regulations set down by the Universal Declaration of Animal Rights (UNESCO – January 27, 1978) and the International Ethical Guidelines for Biomedical Research Involving Animals (Council for International Organizations of Medical Sciences – CIOMS). Figure 1 demonstrates de flowchart of the study.

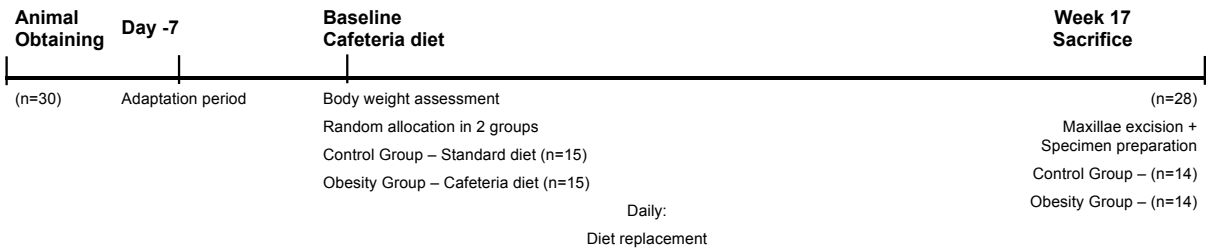

Figure 1 – Study flowchart.

ANIMALS

Twenty-eight (out of thirty), 60 days-old, male Wistar rats (weighting approximately 350g) completed the present study. Animals were housed in groups of 4-5 under a light/dark cycle of 12 hours and room temperature (22°C ± 2°C) with free access to water and the allocated diet. All necessary procedures to minimize pain and discomfort were carried out by experienced researchers.

The sample size calculation was based in a study by our group, in which a significant difference was observed on spontaneous alveolar bone loss[16]. Taking into

consideration the variability of measurements of alveolar bone loss, and accepting as significant differences among experimental groups of .06mm, with alpha and beta errors of .05 and .2, respectively. The estimated number of animals in each group was 13. Based on attrition rates observed in our previous studies, 15 rats in each group were included.

RANDOMIZATION AND GROUP ALLOCATION

Animals were randomly divided into 2 experimental groups according to body weight. A stratified randomization strategy was used in order to minimize possible group impairment at baseline. Strata comprised tertiles of body weight and randomization was performed by draw within these categories in the following groups:

Control group: Standardized rat chow (Nuvilab CR-1, NUVITAL®, Curitiba, PR, Brazil).

Obesity group (Cafeteria diet-induced obesity): High fat and hypercaloric diet.

CAFETERIA DIET-INDUCED OBESITY

A palatable hyperlipidic and hypercaloric diet consisted of 55% carbohydrates, 20% lipids, 20% proteins and 5% of other constituents (sodium, calcium, vitamins, preservatives, minerals, etc.), adapted from a hyperlipidic diet known as cafeteria diet (CAF diet) or western diet[17]. The percentage of nutrients was calculated from the information provided by the manufacturer. CAF diet comprised sausage, filled cookies, wafer, condensed milk, chips and soft drink. Animals also had access to standard chow and water.

Diet was replaced daily to allow consumption of fresh and varied food, as well as water, soft drink and condensed milk. All foods were available *ad libitum* both for obesity and control groups.

BODY WEIGHT AND LEE INDEX ASSESSMENTS

Animals were weighted at baseline and at week 17. Additionally, at the end of experimental period, the naso-anal length was measured in order to calculate the Lee Index[18], by means of the following formula:

$$\sqrt[3]{BW(g)} / NAL(cm).10$$

This index corresponds to the ratio between the cube root of body weight (g) and naso-anal length (cm) of the animals multiplied by 10.

SACRIFICE

Animals were sacrificed 110 days after baseline by decapitation 24 hours after the last body weight assessment.

SPECIMEN PREPARATION

Maxillae were removed, sectioned, and defleshed in 9% sodium hypochlorite for 2 hours and the remained soft tissue was removed mechanically. After this period, specimens were washed and dried. For a better visualization of the cemento-enamel junction (CEJ), maxillae were stained with 1% methylene blue, according to Fernandes et al. (2007)[19].

MORPHOMETRIC ANALYSIS

The morphometric analysis was performed by standard digital photographs. Pictures were taken using a 6.1 megapixel digital camera (Nikon™ Coolpix, Ayutthaya, Thailand) coupled to a tripod and equipped with 100mm macro-lenses with minimal focal distance. Specimens were fixed to an endodontic ruler, parallel to the ground. Photographs of the buccal and palatal aspects of right and left hemimaxillae were taken.

A calibrated examiner performed the measurements of the linear distances from the cemento-enamel junction to the bone crest, using Adobe Photoshop™ CS4

software (Adobe Systems Inc., San Jose, CA, USA). Group distribution was kept by an external researcher, in order to warrant blindness of the examiner. Five measurements were performed on each surface of second molar both buccally and palatally (two on the distal root, two on the mesial root and one on the furcation). The measurements in pixels were then converted into millimeters using the markings of the endodontic ruler to which the hemimaxillae were attached as reference (Figure 2).

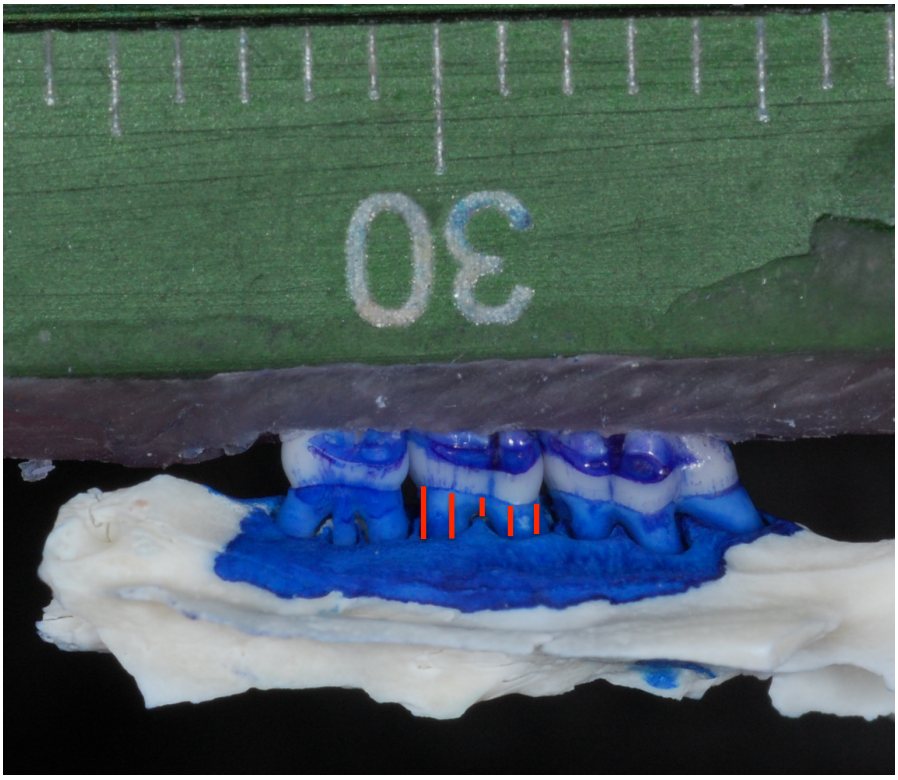

FIGURE 2 - Specimen and measurements on the buccal surface.

All procedures for specimen preparation, photographs as well as morphometric analysis were performed at the Laboratory of Periodontology of the Federal University of Rio Grande do Sul and followed the methods proposed by Fernandes et al. 2007[19].

DEFINITION OF SPONTANEOUS PERIODONTAL BREAKDOWN

The primary outcome of the present study was the occurrence of periodontal breakdown. For that, a cut-off point was established, in order to define periodontal breakdown occurrence. An analysis of all measurements was performed and the 75 percentile was considered the cut-off point. Thus, measurements ≥.51mm were considered as spontaneous periodontal breakdown.

REPRODUCIBILITY

Twenty pictures for the morphometric analysis were randomly selected to be double-measured with a one-week interval. The intra-class correlation (ICC) coefficient between measurements was .98

Body weight measurements were repeated in 20% of the sample at baseline and 30% at week 17. The calculated ICC was .87 and .99 at baseline and week 17, respectively.

Repeated measurements of naso-anal length was performed in 9 animals at the end of experimental period and the reproducibility of the Lee Index demonstrated an ICC of .94.

STATISTICAL ANALYSIS

For all evaluated parameters the normality was tested by Shapiro-Wilk test. Mean body weight and Lee Index were calculated for obesity and control groups and compared by means of independent sample t-Test.

Median and interquartile range of the distance from the CEJ to the alveolar bone crest for buccal and palatal sites were calculated and compared by means of Mann-Whitney test. Sites classified as positive for periodontal breakdown occurrence were compared among obesity and control groups by means of chi-square test. All analyses were performed in Stata 10.1 for Macintosh (Stata™, College Station, TX). The level of significance was set as .05.

RESULTS

Two animals (one from the obesity and one from the control group) died during the experiment. The necropsies revealed no relationship to the protocol. Body weight of animals at baseline was of approximately 350g, with no statistically significant difference among groups. After 17 weeks of exposure to CAF or standard diet, a statistically significant difference in body weight was observed among groups and is demonstrated in Table 1. Animals exposed to the hyperlipidic and hypercaloric diet presented increased body weight as compared to controls.

Table 1 – Mean weight in grams (± SD) for groups and time periods.

Group	**Baseline**	**Week 17**
Control	345 ± 37	478 ± 43
Obesity	347 ± 28	580 ± 60
P Value*	=.8	<.01

Note: *Independent sample t-test

Figure 3 demonstrates the Lee Index at week 17. The observed means for obesity and control groups were 3.24±0.07 and 3.07±0.05, respectively. A statistically significant difference was demonstrated among groups, suggesting obesity. (*P*<.05).

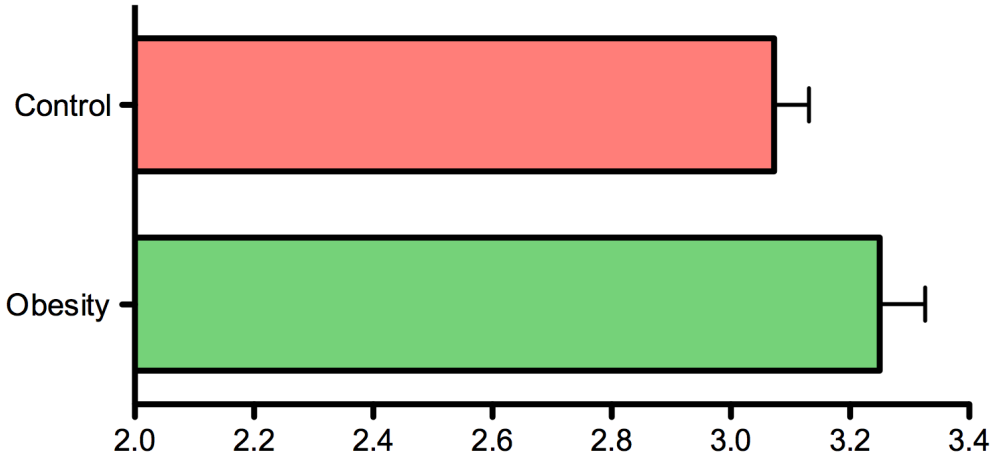

Figure 3 – Mean Lee Index (g/cm) at week 17 for obesity and control group.

Figure 4 shows data distribution of alveolar bone loss for both obesity and control groups at the end of experimental period. It could be observed that median (percentile 25 and 75) of alveolar bone loss was .438 (.236 – .555) and .411 (.344 – .499) for obesity and control groups, respectively. No significant differences were observed between groups (*P*=.11).

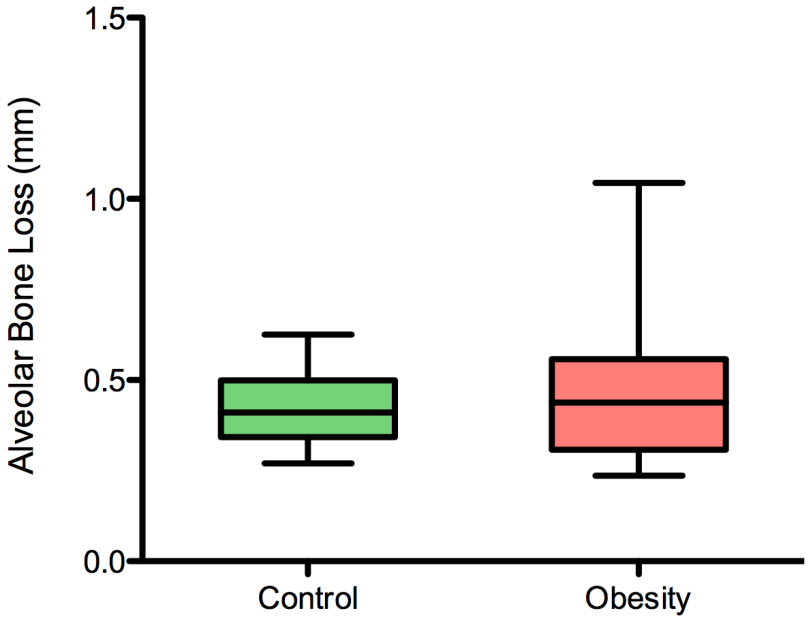

Figure 4 – Median and interquartile range (mm) of alveolar bone loss for Obesity and Control groups. Mann-Whitney test (*P*>.05).

No adverse events were observed during the experiment. The main outcome of the present study is demonstrated in Table 2. In animals submitted to CAF diet, 20 sites were classified as experiencing spontaneous periodontal breakdown, whereas in control animals, only 8 sites exhibited periodontal breakdown according to the present cut-off point. A statistically significant difference among groups was detected (*P*=.009).

Table 2 – Occurrence of periodontal breakdown on sites according to group.

Group	Sites With periodontitis	Sites Without periodontitis
Control	8	48
Obesity	20	36
Chi-square test	*P*=0.009	

DISCUSSION

The present animal study evaluated the effect of obesity related parameters on spontaneous alveolar bone loss in Wistar rats. The results showed that the CAF diet-induced obesity was associated with an increase in occurrence of periodontal breakdown.

The study of pathogenesis of periodontal breakdown has experienced profound modifications in its understanding. This is related to the fact that most studies that evaluated etiopathogenic processes of periodontal diseases in rats used different disease induction models[20, 21]. One question has always been made in these models, related to a possible excessive amount of challenge present in the models (bacteria, ligatures, incisions etc.). However, recently inquiries have been made to these models since studies demonstrated that in areas where disease was not induced, it was possible to observe periodontal breakdown[22, 16].

The definition of cut-off points for presence or absence of periodontal breakdown is a core question. However, to the best of our knowledge, there was no definition about this issue in the literature. Our study used a definition of presence of periodontal breakdown based on 75 percentile of all measurements of the sample. Data distribution has been used in epidemiological research for definitions of disease, based on the assumption that the continuous distribution of the outcome is an expression either of severity or of the highly affected[23, 24]. In this sense, a cut-off point in the third quartile was determined in the present study in order to distinguish sites with the highest levels of periodontal breakdown from those experiencing limited alveolar bone loss.

Obesity has been considered an important risk indicator for periodontal disease[6-11]. However, the biological mechanisms for the association remain obscure. Indirect evidence suggest that adipose tissue cytokines and hormones could play a key role as modifiers of host response contributing to periodontal breakdown. Some studies have evaluated the effect of diet-induced overweight and obesity on ligature induced alveolar bone loss in rats[25, 26]. The results demonstrate that obesity can increase ligature induced alveolar bone loss. The present study evaluated spontaneous alveolar bone loss without any method of disease induction since the presence of a ligature, for example, could increase total amount of bacteria or represent an excessive challenge for host.

One important fact that has to be highlighted in the present study is that obesity was induced by CAF diet. Diet consistency and bedding could influence spontaneous alveolar bone loss due to attrition of chow and wooden chip on periodontal tissues[22]. However, in the present study, animals in obesity group received both CAF diet and rat chow, and both groups, obesity and control, were maintained in similar cages. Therefore, the comparability of the exposures in this sense limits the possibility of bias.

The exposure variable of the present study is obesity. A difference of approximately 18% in body weight was observed among groups. This has been assumed in the literature as inferring obesity[27]. Additionally to body weight measurements, the Lee Index was calculated and a statistically significant difference was observed in mean values. Therefore, one can assume that rats in the obesity group are obese.

CAF diet induced obesity can increase body weight, generate hyperinsulinemia, hyperglycemia, glucose intolerance and increased adiposity and hepatic steatosis[28, 29]. Therefore, one important limitation that has to be taken into consideration is the possible effects of these problems in periodontal breakdown, especially if rats became diabetics. However, epidemiological studies have also used reported diabetes as a sole indicator of glucose intolerance[8, 9]. The possibility of this interaction should not be ruled out. However, it is well known that obesity is strongly associated with diabetes and therefore both problems should be addressed of part of the same set of conditions.

The possible explanation for the increased periodontal breakdown in obese animals relates to the inflammatory status associated with obesity. Higher productions of pro-inflammatory cytokines such as IL-6, TNFα, etc. have been reported in obese individuals [3-5].

The study performed by Verzeletti et al (2012) encountered higher degrees of ligature-induced alveolar bone loss in obese rats, while the study by Simch et al (2008) could not demonstrate this difference in overweight rats. The classical study by Perlstein and Bissada[30] also demonstrated higher degrees of periodontal disease in obese rats. These findings are in accordance with epidemiological studies that have associated periodontal disease with obesity, but not with overweight[6, 9, 31]. This study relied on a rigid quality control using all possible mechanisms to avoid bias i.e. sample size calculation, randomization, blinding and reproducibility analysis. Therefore, increased internal validity is warranted. Also, with these methodological characteristics, a reduction in the number of animals in studies is possible. It should be emphasized that animal studies are still an important part of determining causality and Wistar rats are the most used model in periodontal research, especially because of the biological and anatomical similarities with human periodontium[32, 21]. It can be concluded that obesity increases the occurrence of spontaneous periodontal breakdown in Wistar rats.

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3 CONSIDERAÇÕES FINAIS

Os resultados deste trabalho demonstram que a utilização de uma dieta de cafeteria hiperlipídica e hipercalórica mostrou-se um modelo capaz de reproduzir em ratos Wistar, o aumento de peso que ocorre em seres humanos expostos frequentemente a esta dieta. Adicionalmente, a obesidade induzida por dieta de cafeteria está associada com aumento da ocorrência de destruição periodontal espontânea em ratos Wistar.