ARAŞTIRMA MAKALESİ

DISEASE PHENOTYPES AND CO-MORBIDITIES AMONG DOGS WITH SMALL INTESTINAL BACTERIAL OVERGROWTH

İNCE BAĞIRSAKTA AŞIRI BAKTERİYEL ÇOĞALMASI OLAN KÖPEKLERDE HASTALIK FENOTİPLERİ VE EŞLİK EDEN HASTALIKLAR

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Abstract

There has been growing interest at 'gut-brain-skin axis', which was an hyptohesis several years ago, however a reality now in. In the present study the aim was to unearth the disease phenotypes and related/linked co-morbidities in dogs with small intestinal bacterial overgrowth to those of exhibiting presumed leaky gut and intestinal barrier dysfunction. Out of 267 dogs in totally enrolled, 149 were diagnosed to have small intestinal bacterial overgrowth, in which were then participated/enrolled in two subclassfication were deemed available. In the present study in Group I involved 95 dogs with gastroentero-dermatological diseases, in which disease phenotypes were pyoderma+cutaneous adverse food reactions (n=25), inflammatory bowel disease+atopic dermatitis (n=17), inflammatory bowel disease+cutaneous adverse food reactions (n=13) and large bowel diarrhea+sarcoptic mange (n=11), as the vast majority. Comperatively group II enrolled 54 dogs with gastroenteritis in which inflammatory bowel disease (n=28), infectious diseases (n=16) and poisoning (n=10) were evident. Lactulose breath H_2 test dynamics at intestinal levels indicated that at Group I with gastroentero-dermatological diseases, H_2 baseline values (23.13±3.09 ppm) were statistically significant for inital and tentative diagnosis for small intestinal bacterial overgrowth, which inturn elevated at 90 th minutes values (28.36 ± 2.13 ppm), possessing an increase. Moreover at group II with solely gastroenterological diseases initial baseline values (34.25 ± 5.16 ppm) were diagnostic. At 90th minutes of lactulose breat testing H_2 values (ppm) (28.44 ±

Özet

Birkaç yıl önce bir hipotez olan, ancak artık bir gerçeklik haline gelen 'bağırsak-beyin-deri ekseni'ne olan ilgi giderek artmaktadır. Mevcut çalışmada amaç, ince bağırsakta aşırı bakteriyel çoğalma olan köpeklerde, sızdıran bağırsak ve bağırsak bariyeri disfonksiyonu olduğu varsayılan hastalıklara kıyasla hastalık fenotiplerini ve ilişkili/bağlantılı komorbiditeleri ortaya çıkarmaktı. Toplamda çalışmada irdelenen 267 köpekten 149'unda ince bağırsakta aşırı bakteriyel çoğalma tespit edilmiş olup, bu köpekler sonrasında halihazırda 2 grupta dahil edilmiş, değerlendirilmiştir. Mevcut çalışmada Grup I'e gastroentero-dermatolojik hastalıkları olan 95 köpek dahil edilirken, hastalık fenotipleri büyük çoğunlukta olduğu gibi piyoderma + kutanöz advers gıda reaksiyonları (n=25), inflamatuar bağırsak hastalığı + atopik dermatit (n=17), inflamatuar bağırsak hastalığı + kutanöz advers gıda reaksiyonları (n=13) ve kalın bağırsak ishali+sarkoptik uyuz (n=11) idi. Karşılaştırmalı olarak Grup II'de 54 köpekte; inflamatuar bağırsak hastalığı (n=28), bulaşıcı hastalıklar (n=16) ve zehirlenmenin (n=10) belirgin olduğu gastroenteritli köpekler kaydedildi. Bağırsak düzeylerinde laktüloz nefes H_2 testi dinamikleri, gastroentero-dermatolojik hastalıkları olan Grup I'de H_2 başlangıç değerlerinin (23.13±3.09 ppm) ince bağırsakta aşırı bakteriyel çoğalma için başlangıç ve geçici tanı için istatistiksel olarak anlamlı olduğunu ve bunların 90. dakika değerlerinde (28.36±2.13) artarak yükseldiğini gösterdi. Dahası, sadece gastroenterolojik hastalıkları olan Grup II'de başlangıç değerleri (34.25±5.16 ppm) tanısal değere sahipti.

2.42 ppm) were still indicative of SIBO. During lactulose breat testing there were also statistical difference regarding inter- group comparison during timeline; at 0.to 60. minutes (p=0.003, 0.009 and 0.005, respectively). It should not be unwise to draw preliminary conclusion that lactulose breat testing was capable of small intestinal bacterial overgrowth detection, in which disease phenotypes along with co-morbidities denominated at this study could have helped change diagnostic and probably treatment protocoles.

Keywords: Comorbidities, disease, dogs, intestinal bacterial overgrowth.

Laktüloz nefes testinin 90. dakikalarında H_2 değerleri (28.44±2.42 ppm) hala ince bağırsakta aşırı bakteriyel çoğalmayı göstermekteydi. Laktuloz nefes testi esnasında zaman çizelgesi boyunca gruplar arası karşılaştırmaya ilişkin olarak da istatistiksel fark vardı; 0. ila 60. dakikalarda (sırasıyla p=0.003, 0.009 ve 0.005). Bu çalışmada tanımlanan hastalık fenotipleri ve eşlik eden hastalıklar tanı ve muhtemelen tedavi protokollerinin değiştirilmesine yardımcı olmuş olabileceğinden, Laktüloz nefes testinin ince bağırsakta aşırı bakteriyel çoğalma tespitinde başarılı olduğu sonucuna varmak yanlış olmayacaktır.

Anahtar Kelimeler: Bağırsak, aşırı bakteriyel çoğalma, hastalık, komorbidite, köpekler.

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1. INTRODUCTION

It has been denoted that small intestinal bacterial overgrowth (SIBO) is a health treating issue exhibited by the overolad invasion and altered bacterial inhabitants within the small intestine (Sorathia, Chippa & Rivas., 2023). This altered relative abundance for healthy bacteria against pathogenic ones, recognized as dysbiosis, disarray the balance among beneficial/commensal and/or harmful pathogenic bacteria through gut habitat (Sekirov, Russell, Antunes et al., 2009). The latter issue might prone gastrointestinal and systemic diosrders exhibiting (Alemany, Soler-Artigas, Cabana-Domínguez et al., 2023; Staudacher, Mikocka-Walus & Ford, 2021; Zafar, Jimenez & Schneider, 2023). It might also influence gastrointestinal tract diseases and probably change existance of chronic diseases (Sroka, Rydzewska-Rosołowska, Kakareko et al., 2022). It has to be postulated that SIBO has been the subject of previous report among dogs (Rutgers, Batt, Elwood et al., 1995), without sufficient data. The aim of this study was to comprehensively evaluate and report the comorbidities and disease phenotypes in dogs diagnosed with SIBO.

2. MATERIAL AND METHODS

2.1. Universe of dogs and related sampling

Firstly in a total of 267 dogs that referred to Intestinal Permeability Mesaurmenet Center (İPÖM) and its related facilities at the University of Aydin Adnan Menderes, Faculty of Veterinary, Department of Internal Medicine in a certain period was under recorded. Out of 267 dogs, 149 were

diagnosed to have SIBO, in which were then participated/enrolled in two subclassfication were deemed available. Gastroentero-dermatological diseases, namely Group I involved n=95 dogs [at the age of 1.5 to 8 years, of both sexes (37 male, 58 female, 30 crosbred and other relevant 65 dogs from several dog breeds] and Group II other 54 relevant cases were deemed evolved [at the age of 1 to 11 years old of both sexes (30 male, 24 female) from several different dog breeds with solely gastroenteritis (without any dermatological reflection). The criteria involved triage; presentation of dermatological [alopecia, pruritus, hyperpigmentation, erythema, lichenification etc.] and/or gastroenterological signs [diarrhea/constipation, vomitting, abdominal bloat, hemotechezia, melena etc.] allowed the present author for group classification.

2.2. Demographic data set for diseased dogs

In a total of 267 dogs referred to İPÖM and its related facilities at the University of Aydin Adnan Menderes, Faculty of Veterinary, Department of Internal Medicine with special reference seaked for appointment on the authors practice of this manuscript, 95 (35.58%) (Group I) were diagnosed with gastroentero-dermatological diseases (Ural, Erdoğan, Erdoğan et al., 2021a; Ural, Erdoğan, Erdoğan et al., 2023; Ural, 2024; Ural, Erdoğan, Erdoğan et al., 2024), and other relevant 54 (20.22%) cases (Group II) with gastroenteritis. Therefore 149 out of 267 were detected to have SIBO

2.3. Inclusion criteria

The present research were entirely performed at İPÖM and its related facilities at the University of Aydin Adnan Menderes, Faculty of Veterinary, Department of Internal Medicine. Through presence of Sunvou Breath Analyzer, China (Turkish side distributor RDA Group, Istanbul, Turkey), selected researchers of this study were deemed available for detecting SIBO diagnosis. This breath analzyer was purchased by Aydin Adnan Menderes University, Research Funding (Unit ADÜ-BAP) Governed/Regimented Project (number VTF-24006) in which all contributors would like to thank for support. In 149 out of 267 dogs referred to İPÖM with gastroentero-dermatological or solely gastroenterological signs, entire physical examination, ultrasonography (Mindray VETUS 5Exp, China), serum biochemistry (Randox Clinical Chemistry Analyser, Ireland, hematological analytes (Mindray BC6000 Hematology Analyser, China), dermatological interpretation [DermLite DL 4 Dermatoscopy, USA, Callegari Soft Plus Epidermal Corneometric Analysis Device, Italy, Pet Quantum Bioresonance Scanning (China), Polycheck in vitro Allergy

Test (Germany), cytology etc.] and clinical findings were all recorded. As an inclusion criteria prior to breath anayzing by Sunvou Breath Analyzer, all dogs were required to be fed with the lowest carbohydrate food available. Another inclusion criteria was exclusion of any drug usage within the past 90 days. Prior to study, Aydin Adnan Menderes University Local Ethics Committee on Animal Research (ADÜ-HADYEK) approval was deemed available with no: 64583101/2024/90. Moreover written owner consent was available for each dog involved and participated.

2.4. Lactulose breath test (LBT) methodology

Hydrogen breath tests could be performed through usage of several different sugar probes like lactulose (as was preferred at shis study), glucose etc. As a well known matter of fact though quantitative culturing for jejunal aspirate has been suggested as a gold standard for SIBO diagnosis, hydrogen breath tests, in the face of their low sensitivity, frequently been used as a non-invasive technique. In this sense lactulose hydrogen breath test, synonym LBT (as was the used terminology in this study) coulbe used for both SIBO and estimation of oro-cecal transit time (Ghoshal, 2011).

Principals of gas dynamics and hydrogen formation with LBT

Table 1. SIBO diagnosis and H2 detection by use of lactulose breath test. Reference ranges were deemed available within the previous descriptions

Intestinal gas dynamics	**Hydrogen (H_2)**	
SIBO diagnosis	$H_2 \geq$ 20 ppm	A baseline value without substrate (lactulose) ≥ 20 ppm or an elevation ≥ 20 ppm from baseline during testing

SIBO: Small intestinal bacterial overgrowth H_2:hydrogen

Kaynak: Rezaie et al 2017, Gasbarrini et al 2009

Anarobic bacteria, resided within the healthy large bowel and diseased small bowel both exhibit hydrogen, through fermentation of oblivious carbohydrates. Even if few concentrations of hydrogen has been exhibited through selected concentrations of oblivious carbohydrate reaching the colon, greater hydrogen concentrations might be exhibited, whether if there existed carbohydrate malaborption within the small intestine. The latter condition occures even if allowance of larger amount reaching the colon or in case of SIBO. Exhibited hydrogen via the bacteria is preoccupied via small/large intestinal wall. The hydrogen-composed blood drives into the lungs where releases hydrogen and be exhaled in the breath where it might be analyzed (Ghoshal, 2011). At the present study LBT (Figure 1) was deemed positive taking into account the

North American Consensus Guidelines. Moreover table 1 below showed criteria for positive test results.

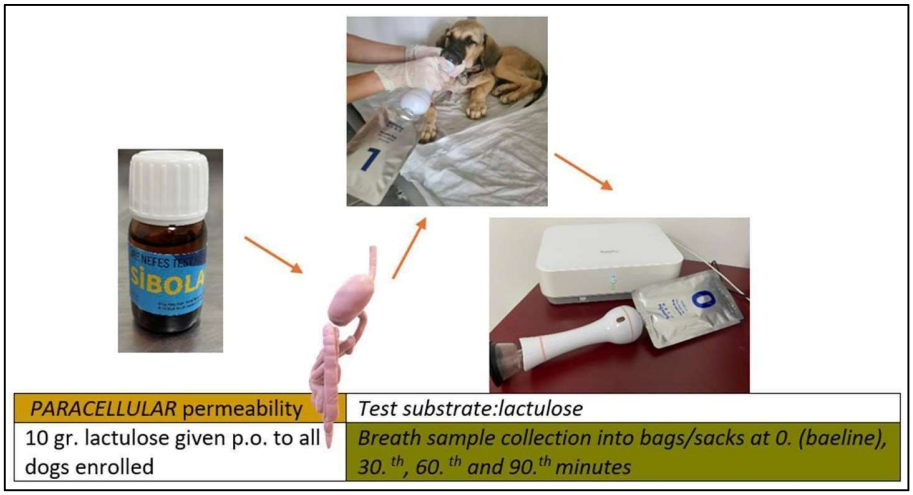

Figure 1. Schematic represantation of lactulose breath test (LBT).

2.5. Sunvou Breath Analyzer

All 149 dogs, with presence of gastrointestinal and/or gastroentero-dermatological signs were subjected to lactulose breath test (LBT) (brief methodology shown in figure 1) based on inclusion criteria. Even if any dog was showing evidence of fractional exhaled nitric oxide leves ≥ 10ppb (as detected by Sunvou-CA2122 Analyzer (NOS), with other name Nano Coulomb Breath Analyzer CA2122), China, the dog was presumed to be SIBO positive, in which than was forwarded to LBT. If a dog was a candidate for SIBO LBT, then the owners were adviced to subject their dogs to 12 hours fasting, without any drug usage and at least 24 hours low residual diet. Water was not restricted. All diseased dogs were prescribed with the procedure as was shown in figure 1., i.e. test substrate 10 gr. lactulose (SIBOLAC by RDA Group Istanbul) administration followed by baseline sampling at minute 0, ii) and other relevant breath samples collected to Sunvou Breath Bags for retesting on 30., 60. and 90.th Breath analysis protocole, involved stabilization of normal breathing into one of two close fitting anesthesia face mask with a one way valve through at least 30 cc volume of end expiratory air was collected into Sunvou Breath Bags. Exhaled air withdrawn immediately at available temperature to those of special bags were then analyzed through Sunvou Breath Analyzer catching hydrogen/methane/CO_2/O_2 in air. Data were then immediately transferred into analyzer were then calculated automatically by software at computer connection were analyzed in parts per million. Table 1 below showed test interpretation. The authors would like to thank Aydin Adnan Menderes University Reserach Funding Unit (ADUBAP) for supporting ADUBAP Governed Project no: VTF-24006.

2.6. Serum zonulin detection

Sandwich ELISA (at the facilities of RDA Group Istanbul), similar to previous methodlogy (Alıç Ural, 2022a,b,c; Alıç Ural, 2023; Alıç Ural, Ural, Erdoğan et al., 2021; Alıç Ural, Erdoğan, Erdoğan et al., 2021; Alıç Ural & Ural, 2023) by use of commerically available test kits (My Biosource Canine Zonulin Test Kits purchased by RDA Group, Istanbul) and interpretation reference ranges (Ural, Erdoğan, Balıkçı et al., 2021).

3. RESULTS

Demographic distrubution of disease phenotypes and relevant co-morbitidities in dogs with SIBO as was shown in table 2 below. Out of 95 dogs enrolled at group I, 25 dogs exhibited Pyo+CafR followed by IBD+Ad (n=17) and IBD+CafR (n=13) as top 3 co-morbidities. Group II involved 54 dogs with gastroenteritis subclassified to 3 sharp co-morbidities as IBD (n=28), inf (n=16) and poisoning (n=10). LBT H_2 dynamics were shown below at table 3. In both group I and II, initial LBT H_2 values were significantly different in contrast to 90. minutes test results

Table 2. Demographic distrubution of disease phenotypes and relevant co-morbitidities in dogs with SIBO.

		Disease phenotypes in dogs with SIBO	**Serum zonulin concentrations (ng/DL)**
Group I	Gastroentero-dermatological diseases (n=95)	IBD+Ad (n=17) IBD+CafR (n=13) LBd+Sm (n=11) Pyo+CafR (n=25) inf+CafR (n=9) Liv+ CafR (n=4) Liv+Ad (n=6) Gu+CafR (n=2) IBD+Sm (n=3) IBD+Dm (n=5)	10.9->20
Group II	Gastroenteritis (n=54)	IBD (n=28) İnf (n=16) Poisoning (n=10)	8.4->20

IBD: Inflammatory Bowel Disease, Ad: Atopic dermatitis, CafR: Cutaneous adverse food reaction, LBd: Large bowel diarrhea, Sm:sarcoptic mange, m:demodectic mange, Gu:gastric ulceration, Liv:liver disease, SIBO:small intestinal bacterial overgrowth Pyo:pyoderma

Table 3. LBT and relevant gas dynamics. Samples were collected at baseline (0.min) and thereafter every 30 minutes till 90th minutes. Different letters at the same row, denoted statistical significance

Group	**LBT H_2 gas dynamics**			
	0. min	**30. min**	**60. min**	**90. min**
I-Gastroentero-dermatological diseases (n=95)	23.13 ± 3.09[a]	25.72 ± 1.71[b]	24.40 ± 2.18	28.36 ± 2.13[b]
II-Gastroenteritis (n=54)	34.25 ± 5.16[a]	33.65 ± 3.72	30.58 ± 2.48	28.44 ± 2.42[b]
P value	0.003	0.009	0.005	0.312

LBT: Lactulose breath test

4. DISCUSSION

In the present study as to the present author's knowledge, first time in the veterinary literature disease phenotypes and co-morbidities (associated primary/secondary disease conditions) were reported to those of dogs with SIBO (as detected by LBT and Sunvou Breath Analyzer) and presumed leaky gut [(determined by zonulin levels (zonulin levels ≥ ng/mL)] were determined. This should have helped future/close studies directed at 'gut-brain-skin axis' for better assuming and interpretation. Moreover even if a veterinary surgeon has to make interventional approach, this co-morbidty list should have to be taken into consideration.

In the present study regarding disease phenotypes Group I involved dogs with gastrointestinal diseases of several selected conditions. Out of 95 ill dogs, disease phenotypes were Pyo+CafR (n=25), IBD+Ad (n=17), IBD+CafR (n=13) and LBd+Sm (n=11), as the vast majority along with other ones (table 1). On the other hand in comparison group II (n=54) enrolled dogs with gastroenteritis in which IBD (n=28), inf (n=16) and poisoning (n=10) were evident. Regarding Group I with gastroentero-dermatological diseases [this definition has been use previously by (Ural, 2024; Ural, Erdoğan, Adak et al., 2019; Ural, Erdoğan, Erdoğan et al., 2021; Ural, Erdoğan, Balıkçı et al., 2021; Ural, Erdoğan, Erdoğan et al., 2023)] IBD and CafR were evident with the vast majority of population. It should not be unwise to draw a brief explanation from this study might be that gastroentero-dermatological diseases are intertwine. To this context 'gut-brain-skin axis' (Ural, 2024; Ural, Erdoğan, Adak et al., 2019; Ural, Erdoğan, Erdoğan et al., 2021; Ural, Erdoğan, Balıkçı et al., 2021; Ural et al., 2023)] should be taken into consideration for both diagnsosis and treatment applications.

The gut–skin axis, still novel paradigma and underlying probable reason for pathology of several chronic/inflammatoric disorders. The latter axis has been linked to interaction between gastrointestinal health influencing cutaneous homeostasis/allostasis. This interconnection is between metabolic, immune and nervous systems (O'Neill, Monteleone, McLaughlin et al., 2016; Salem, Ramser, Isham et al., 2018). On the other hand gut microbiome has been well recognized as a prime influencer of the gut–skin axis through a collaborative interplay between the gut microbiome and host immüne system (Forbes, Van Domselaar & Bernstein, 2016; O'Neill et al., 2016; Salem et al., 2018). Disturbance of the gut microbiota could perturbate immune respond both at systemic and intestinal mucosal levels. Moreover leaky gut, exhibited through elevated gut permeability, intestinal dysbiosis, and altered immune mucosal defense, has entirely been linked to chronic inflammatory disorders (Forbes et al., 2016). In the present study elevated leaky gut biomarker serum zonulin levels (no healthy control group as deemed available, which was out of the purpose of the study, however previous experience, pHd thesis and unpublished researches with healthy control dogs exhibited very low zonulin levels in contrast) and intestinal gas dynamics (elevated H_2 gas dynamics as detected by LBT in both group of dogs enrolled) all indicated possible low grade systemic

inflammation [(fractional exhaled nitric oxide leves ≥ 40 ppb as detected by Nano Coulomb Breath (Sunvou)-Analyzer CA2122, data was not necessary to show)], linked to SIBO. Regarding intestinal gas dynamics, with special reference to H_2, LBT results were deemed available with Sunvou Breath Analyzer, China. At Group I with gastroentero-dermatological diseases, H_2 baseline values (23.13±3.09 ppm) were statistically significant for initial and tentative diagnosis for SIBO, which inturn elevated at 90 th minutes values (28.36 ± 2.13 ppm), possessing an increase. Moreover at group II with solely gastroenterological diseases initial baseline values (34.25 ± 5.16 ppm) were diagnostic (Gasbarrini, Corazza, Gasbarrini et al., 2009; Rezaie, Buresi, Lembo et al., 2017). At 90th minutes of LBT H_2 values (28.44 ± 2.42) were still indicative of SIBO. During LBT there were also statistical difference regarding inter- group comparison during timeline; at 0.to 60. minutes (p=0.003, 0.009 and 0.005, respectively).

Someone might criticise available data herein obtained. Moreover it should be a criticism of solely usage of LBT, instead of bacterial colonization for diagnosis. In a prior study SIBO was detected by quantitative bacterial culturing from duodenum via endoscopy to those 41 out of 80 dogs exhibiting chronic gastrointestinal issues (Rutgers et al., 1995). On the other hand H_2 is the vast majority prevalent gas exhibited via resident bacteria at colon, which has been assembled only by bacterial fermentation of non– digestible substrates located at colon (Naito, Kashiwagi, Takagi et al., 2018). Subsequently breath H_2 analytes are primarily available for determining carbohydrate malabsorption or SIBO. Metabolic process following fermentation via gut microbiota manufacture huge amount of H_2 gas (up to 1L of H_2 might be existing in a day), in which the amount of gas could subsequently iniate clinical signs (Gasbarrini et al., 2009; Strocchi & Levitt, 1992). The vast majority of relatively abundant genus responsible for H_2 manufacturing through the colon are *Bacteroides/Ruminococcus* and *Roseburia* (Duncan, Hold, Barcenilla et al., 2002). In the present study LBT was preferred as a diagnostic tool for SIBO. In a fresh meta-analysis reported a sensitivity and specificity of 42.0% and 70.6%, respectively, for LBT (Losurdo, Leandro, Ierardi et al., 2020). In comparison a previous reserach indicated 31% and 86%, sensitivity and specificity for LBT in comparison to traditional culture for jejunal aspirate (bacterial colony count ≥ 10^5 CFU/mL) recognized as gold standard (Ghoshal, Ghoshal, Das et al., 2006). All aformentioned data belongs to human literature, whereas veterinary literature is lacking.

5. CONCLUSION

İn conclusion herein for the first time a large dog population was subjected to LBT was capable of SIBO detection by Sunvou Breath Analyzer. It should also needed to be addressed that other relevant disease phenotypes along with co-morbidities showed at this study indicated probably changing diagnostic and treatment protocoles.

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