Lundehund Syndrome:
What we know about chronic gastrointestinal disease
in Norwegian Lundehunds

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Definitions and Nomenclature

There often is a lot of confusion as to what the correct terminology is when we talk about chronic gastrointestinal disease in Lundehunds.

Here are some definitions about the terms we are using:

Lundehund Syndrome (LS)

This term has first been used by Norwegian investigators in 1977, and can be found in several publications that deal with gastrointestinal (GI) disease in the Lundehund.[1,2,3,4]
A syndrome, by definition, describes a medical condition in which several symptoms, characteristics and/or diseases occur together.
In the case of Lundehunds, these are gastritis, intestinal lymphangiectasia (IL) and inflammatory bowel disease (IBD), which can all result in protein-losing enteropathy (PLE) (more about these later - see below).
It is important to recognize that Lundehunds can suffer from more than one GI disease at a time. It is not correct to refer to Lundehund disease only as IL or PLE, as is often done, because these are only components of what affects Lundehunds.

Clinical signs of LS can be:[1,2,3,5,6]

- Diarrhea
- Vomiting
- Weight loss
- Anorexia (loss of appetite)
- Lethargy, decrease in activity
- Ascites (fluid accumulation in abdomen)
- Subcutaneous edema (fluid accumulation under the skin)

Potential causes of these clinical signs can be:

- Chronic gastritis (inflammation of the stomach mucosa)
- Intestinal lymphangiectasia (IL)
- Inflammatory bowel disease (IBD)
- Protein-losing enteropathy (PLE)

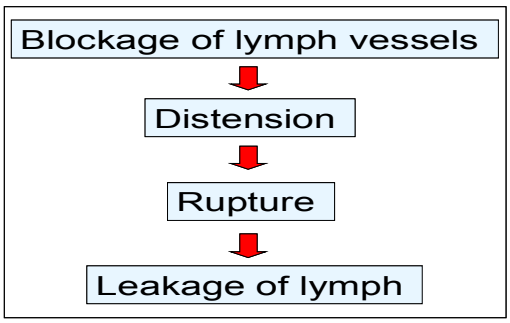
Chronic gastritis

Chronic atrophic gastritis is often found in affected Lundehunds. Gastritis is an inflammation of the stomach mucosa (inside lining of stomach). "Atrophic" means that it occurs with a loss of cells. Chronic gastritis leads to irritation, which can cause vomiting, a frequently seen clinical sign in Lundehunds affected by LS. In severe cases, the gastritis can produce ulcers and even gastric carcinomas (malignant stomach cancer).[3,4]
At this time, we do not know what the cause of gastritis in Lundehunds is. *Helicobacter* sp. is a type of bacteria that is often found to be the reason for gastritis and gastric cancer in people, and has also been detected in cats and dogs with gastritis.[7] We do not have enough evidence to say whether it is involved in LS or not. One investigation in Lundehunds did not find such bacteria in stomachs of Lundehunds,[3] but it may simply be that the methods used at that time (1994) were not equally effective to the ones we use today. More research needs to be done in order to see whether *Helicobacter* infection may be a cause of chronic gastritis in Lundehunds.

Intestinal Lymphangiectasia (IL)

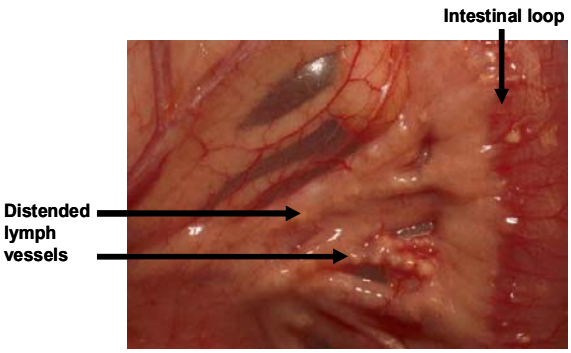
Lymphangiectasia simply means "distension of vessels that carry lymphatic fluid". There are two possible types of lymphangiectasia, primary and secondary, but they have a common mechanism:

Lymph vessels are blocked, which leads to distension and eventually rupture of the vessels. This results in leakage of lymph fluid (see chart to the right).

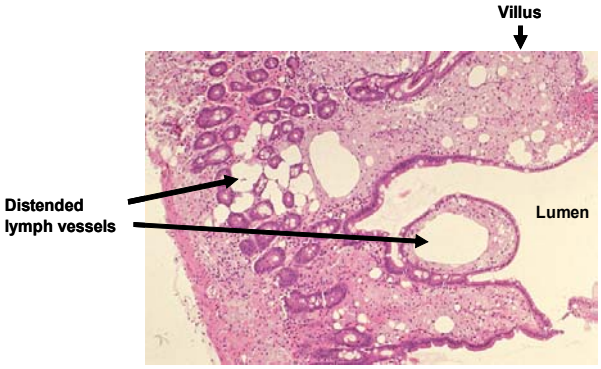


Primary IL is caused by a congenital (present at birth) defect in the lymphatic system which leads to the blockage of the lymph vessels.
Secondary IL is an acquired disease, and possible causes include inflamed tissue or tumors surrounding the lymph vessels (they exhibit pressure on the vessels and thus inhibit lymph flow). Another cause of secondary IL can be high blood pressure in the venous blood system (causes "back pressure" onto the lymphatic system), but that is unlikely to be the case in Lundehunds.

The results are similar in both types: Lymph fluid rich in proteins and fat is lost into the surrounding tissue and the intestine. This can severely reduce the blood protein concentrations and lead to ascites and edema. We think that IL in Lundehunds is most likely primary and has a genetic background, because so many dogs are affected, but secondary involvement in addition to this is also possible (tissue inflammation caused by IBD could contribute to lymph flow impairment) and could aggravate a pre-existing condition.



Shown in this picture is small intestine of a Lundehund with IL. You can see the enlarged lymph vessels from the outside of the intestine.



This picture shows a section of intestine with IL. Note the large balloon-like lymph vessels inside the villi. In a healthy dog, these would not be nearly as big.

Inflammatory Bowel Disease (IBD)

The term IBD is generally used if an individual suffers from chronic intestinal inflammation, and most people are familiar with the two predominant types of IBD in humans: Crohn's Disease and Ulcerative Colitis. These are not exactly the same in dogs; in fact there is a lot of controversy regarding the proper diagnosis of IBD in dogs and whether we should be calling it IBD at all. There is even a special group from the WSAVA (World Small Animal Veterinary Association) composed of GI specialists who are trying to establish better guidelines for diagnosis of IBD/intestinal inflammation in dogs.
Nevertheless, due to a lack of a better definition at this time, we call the intestinal inflammation in Lundehunds IBD, specifically lymphocytic-plasmacytic enteritis (LPE). LPE simply describes the type of white blood cells (lymphocytes and plasma cells) that are predominantly found in intestinal biopsies from Lundehunds with IBD.
Intestinal inflammtion causes damage to the villi, which are very small finger-like extensions of the intestine that increase the surface area and are responsible for the absorption of nutrients. Therefore, if the villi are damaged (for example shortened or fused), malabsorption of nutrients can occur. This can lead to vitamin and other deficiencies, as well as protein loss (more on that later).

On these two pictures you can see normal villi from a healthy dog on the left, and damaged villi from a Lundehund with LS on the right.


Healthy villi


Damaged villi

Protein-losing enteropathy (PLE)

Protein-losing enteropathy (PLE) describes a condition in which there is abnormal loss of blood proteins into the intestine. PLE can have a variety of causes:

- Rupture of lymphatic vessels due to IL
- Intestinal inflammation (IBD)
- Intestinal cancer (lymphoma)
- Ulcers

In the Lundehund, we assume that there may be a combination of all of the above (not all Lundehunds develop intestinal cancer, but the risk is given).
PLE can lead to a decrease in blood protein concentrations (total serum protein (TSP), albumin and in some cases globulin) if the intestinal loss exceeds the production of proteins in the liver. In severe cases this can become life threatening.
The loss of protein is also the reason why ascites (fluid accumulation in the abdomen) and edema (fluid accumulation under the skin) develop: a certain concentration of proteins in the blood vessels is necessary in order to keep the fluid inside the vessels (called oncotic pressure). If there are not enough proteins left to hold the fluid inside, it starts "leaking" out of the vessels into the surrounding tissue or into the abdomen and accumulates there.
One important thing to know about PLE is that it is not a disease per se; it is a result of other disease processes, mainly the ones mentioned above. This is why it is incorrect to simply refer to Lundehund Syndrome as PLE – PLE is just a result, or a "symptom" of these other diseases, not a disease itself, though it brings more problems with it.

In summary:

- Lundehunds can suffer from several conditions which can lead to PLE.
- Because it is not a single disease, we refer to it as "Lundehund Syndrome" (a syndrome is "a set of symptoms or conditions that occur together and suggest the presence of a certain disease or an increased chance of developing the disease").
- Even more appropriate would be the term "Lundehund Gastroenteropathy" (but for simplicity's sake we will call it LS)

References:

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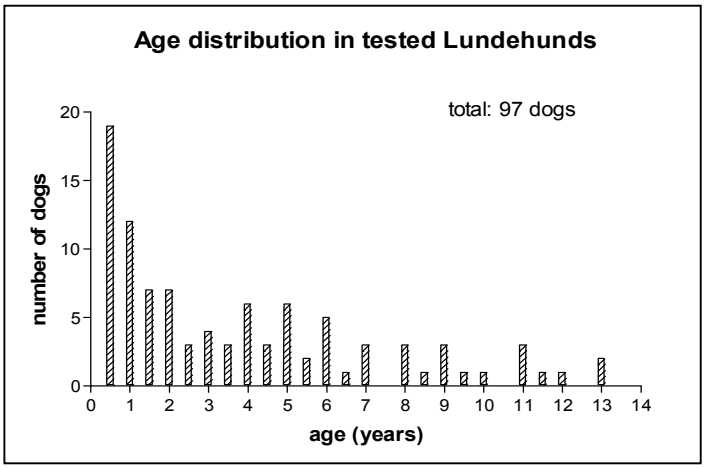
7. Pressel MA, Crandell JM, Jergens AE, Morrison JA, Baumgart M, Simpson KM: Fluorescence *in situ* Hybridization Confirms Eradication of Naturally-Acquired *Helicobacter gastritis* in the Dog and Cat. *J Vet Int Med* 2006;20:789 (abstract)

GI Lab study on the prevalence of PLE and chronic gastrointestinal disease in Lundehunds

From 2003 to 2006, we have collected data from more than 100 Lundehunds, and we have complete data sets from 97 of them (a complete data set consists of one serum sample and three fecal samples).

We were able to enroll dogs of all ages, with a median age of 3 years (ranging from 0.5 to 13 years).



Tests

We evaluated a variety of parameters in the serum samples as well as the fecal samples. These are the tests we did:

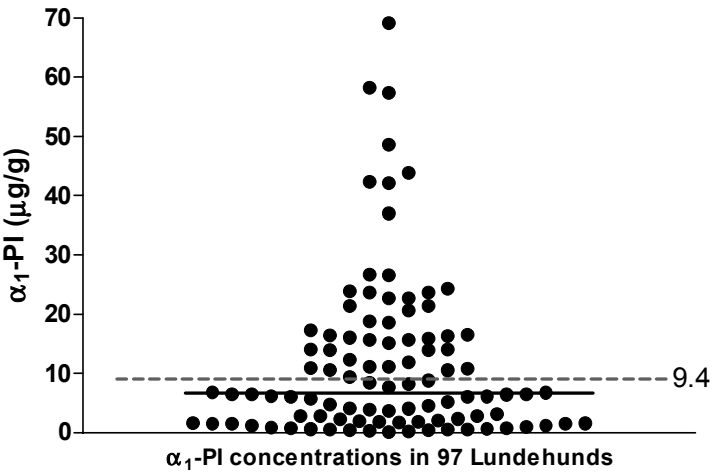
- Fecal samples
  - $Alpha_1$-Proteinase Inhibitor ($Alpha_1$-PI)
- Serum samples
  - Cobalamin (Vitamin B12)
  - Folate
  - Trypsin-like immunoreactivity (TLI)
  - Total serum protein (TSP)
  - Albumin
  - Globulin
  - C-reactive Protein (CRP)

Fecal $Alpha_1$-Proteinase Inhibitor

$Alpha_1$-PI is a test for the assessment of intestinal protein loss, or PLE. The diagnosis of PLE has always been difficult, because the blood proteins that are lost during PLE, like albumin, get degraded by enzymes present in the intestine (proteases, proteinases). Therefore, we cannot measure them anymore in a fecal sample. $Alpha_1$-PI is also a plasma protein and during PLE, it is lost into the intestinal lumen, similar to albumin. But due to its action as a "proteinase inhibitor", it inhibits the degrading enzymes and does not get digested. This enables us to measure it in fecal samples.
For the test we need three fecal samples from consecutive bowel movements. The reason we collect three samples and not just one is that there can be individual day-to-day variation in the amount of $Alpha_1$-PI

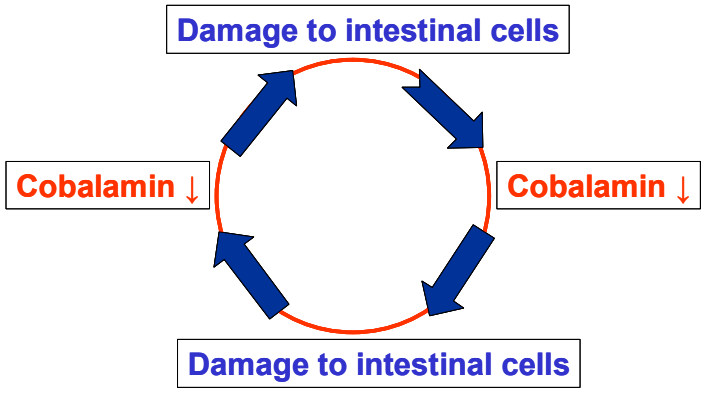
present in the feces. Even a dog with PLE can have single normal fecal samples. Thus, if only one sample was tested, and it happened to be in the normal range (0-5.7 µg/g feces), PLE would falsely not be diagnosed in that dog. Therefore, to ensure we make the proper diagnosis, we always collect three samples and then calculate the mean of the test results. If the mean is higher than 9.4 µg/g feces or one single sample is higher than 15 µg/g, we diagnose PLE, as values this high are not found in healthy dogs.

In our study, we found that 42 of 97 dogs (43.3%) had Alpha1-PI concentrations higher than 9.4 µg/g.
Out of these, 19 dogs (19.6%) had concentrations above 20 µg/g, which is considered severe PLE.
These results suggest that PLE is present in at least 43% of all Lundehunds, and therefore has a very high prevalence.

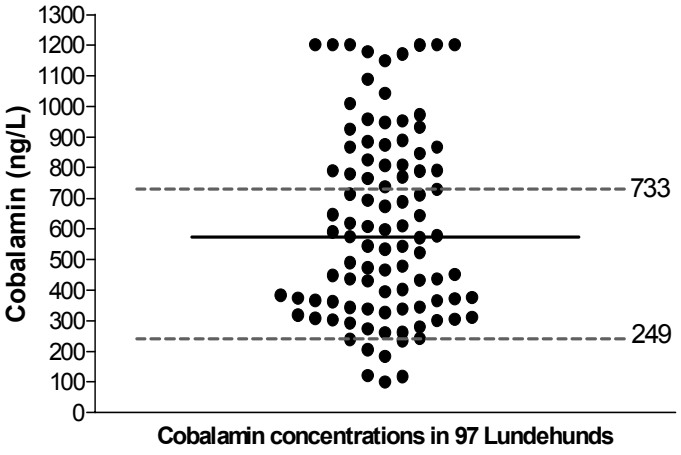


Cobalamin

Cobalamin (Vitamin B_{12}) is a water-soluble vitamin that is important for many biochemical processes throughout the body and essential for the proper function of intestinal cells. A decrease in serum cobalamin concentrations is often seen in chronic gastrointestinal disease. Cobalamin undergoes a complicated method of absorption in the intestine, and a disturbance of this mechanism at any point can result in cobalamin deficiency. In addition to several necessary factors, it is absorbed only in one section of the small intestine. Therefore, anything that disturbs the integrity of that section (e.g. inflammation) can produce a deficiency. This can then become a vicious cycle, as the deficiency leads to more damage to the intestinal cells, which in turn makes the deficiency worse and so on.



The reference range (normal range) for serum cobalamin in dogs is 249-733 ng/L.



We found eight Lundehunds (8.2%) with subnormal cobalamin concentrations (<249 ng/L) and quite a few dogs with cobalamin concentrations above the reference range. This was initially surprising, as we would have expected a larger percentage of dogs to be cobalamin deficient. But, we need to keep in mind that many Lundehunds receive cobalamin supplementation on a regular basis, which could falsify these results. For obvious reasons, we could not ask you to stop treating them, as this may have worsened the condition of the dogs, so we can only guess as to what the actual number of dogs with cobalamin deficiency is.

Cobalamin deficiency is a real threat to Lundehunds with GI disease; therefore we encourage regular check-ups to test the cobalamin concentrations and to initiate supplementation as soon as a decrease is detected. Cobalamin is not expensive, thus cost should not be a limiting factor.

Briefly, we recommend treating Lundehunds with the following schedule:

Body weight	***Dose of cobalamin***
< 5 kg (< 10 lb)	250 µg/dog
5-15 kg (10-30 lb)	500 µg/dog
Time regime for supplementation	
Weeks 1-6	once per week
Weeks 7-12	once every two weeks
Week 16	one additional injection
Week 20	recheck serum cobalamin concentration

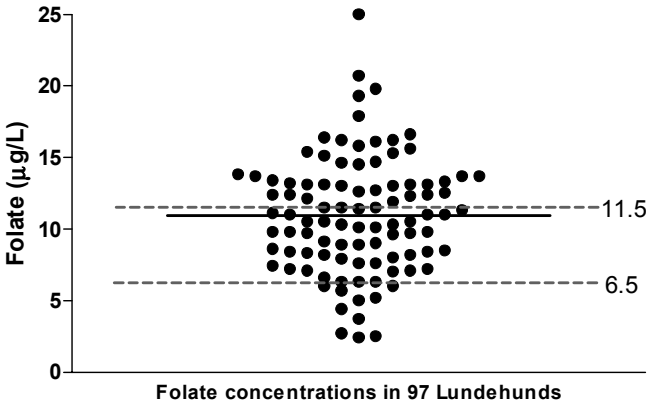
Cobalamin must be given as an injection (subcutaneously), because the absorption after oral supplementation is compromised. It should always be given as pure cobalamin (for example cyanocobalamin), and not as B-complex. B-complex often does not contain sufficient amounts of cobalamin and can also be irritating at the injection site, whereas pure cobalamin does not cause any reactions. Most cobalamin injection solutions have a concentration of 1 mg (= 1000 µg) per mL, so you would give about 0.25 – 0.5 mL per dog. But there are also higher concentrated solutions, so please make sure you check the dosage and discuss it with your veterinarian. As cobalamin is water-soluble, an overdose should not cause any harm, because it gets excreted with the urine (urine may look reddish/brown when cobalamin is given), but it is unnecessary to give more than is required.

For more information about cobalamin supplementation, also for your veterinarian, please see the cobalamin information on the website of the GI Lab: http://www.cvm.tamu.edu/gilab/cobalamin.shtml.

Folate

Folate (folic acid) is also a water-soluble B-vitamin and is involved in a variety of metabolic pathways in the body, some of them similar to cobalamin. It is possible to see decreased or increased serum concentrations of folate in dogs with gastrointestinal disease:
Folate deficiency due to a deficient diet is very unlikely, because most diets are rich in folate. Therefore, it is more likely to be a result of malabsorption. Folate is absorbed in the upper part of the small intestine, and chronic gastrointestinal disease can lead to a decrease in folate concentrations if this part of the intestine is affected.
An increase in folate can be observed when there is an imbalance in the intestinal microflora. Certain species of bacteria are able to produce folate, so if there are a large number of them, it could lead to high folate concentrations. This is often called small intestinal bacterial overgrowth (SIBO), although today it is being discussed whether we should rename this condition, as bacterial overgrowth in dogs is difficult to characterize and diagnose, and high folate may represent the presence of different bacteria, rather than an overgrowth of bacteria.

The reference range for folate is 6.5-11.5 µg/L.
In this study, 13 of 97 dogs (13.4%) had serum folate concentrations that were lower than normal (<6.5 µg/L).
40 of 97 dogs (41.2%) had serum folate concentrations above the reference range (>11.5µg/L).
This shows that there are a number of dogs that have folate deficiency because of intestinal damage, but also a few dogs that showed a higher than normal folate concentration. It may be useful to treat these dogs with an antibiotic if they are showing clinical signs of gastrointestinal disease. You should discuss these options with your veterinarian in this case.



Trypsin-like immunoreactivity (TLI)

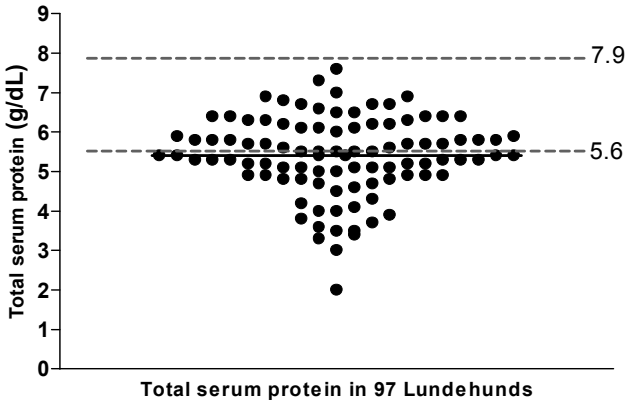
TLI is a test for exocrine pancreatic insufficiency (EPI), a condition in which the pancreas does not produce enough enzymes. This can cause malabsorption and can lead to alterations in cobalamin and folate concentrations similar to those seen in LS. While EPI is not common in Lundehunds, we still run this test on all our Lundehund samples, just to rule out that this is the cause for vitamin abnormalities.
The TLI test was normal in all Lundehunds tested for our study.

Total serum protein (TSP), albumin and globulins

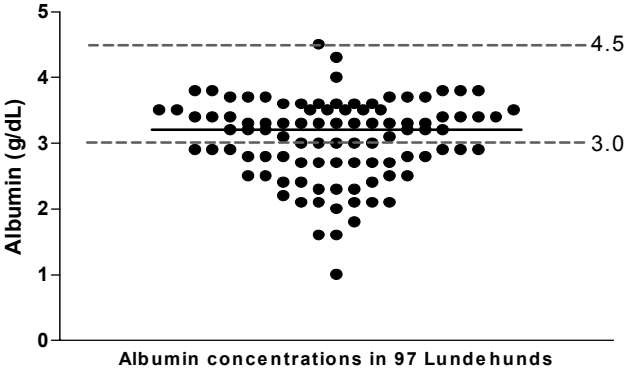
Albumin is part of the TSP and is usually the first blood protein to be lost when PLE occurs. Globulins are also part of the blood proteins and include antibodies (immunoglobulins). Because PLE has such a high prevalence in Lundehunds, we measured albumin, globulin and TSP concentrations in all dogs. Low albumin (hypoalbuminemia) and low TSP (hypoproteinemia) can have devastating effects on the health of affected dogs and are indicators for PLE, if other causes of low protein can be ruled out.

The graphs to the right show the results of our tests for the protein concentrations in Lundehunds.

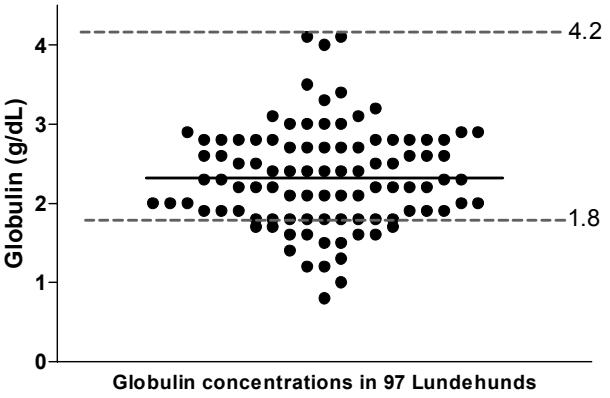
The reference range for **TSP** is 5.6-7.9 g/dL.
In our study, we found that 55 of 97 dogs (56.7%) had TSP concentrations below 5.6 g/dL, and were therefore hypoproteinemic (median TSP = 5.4 g/dL; range 2.0-7.6 g/dl).



The reference range for serum **albumin** is 3.0-4.5 g/dL.
38 of 97 dogs (39.2%) in our study had albumin concentrations lower than 3.0 g/dL, and were thus hypoalbuminemic (median albumin = 3.2 g/dL; range 1.0-4.5 g/dl).



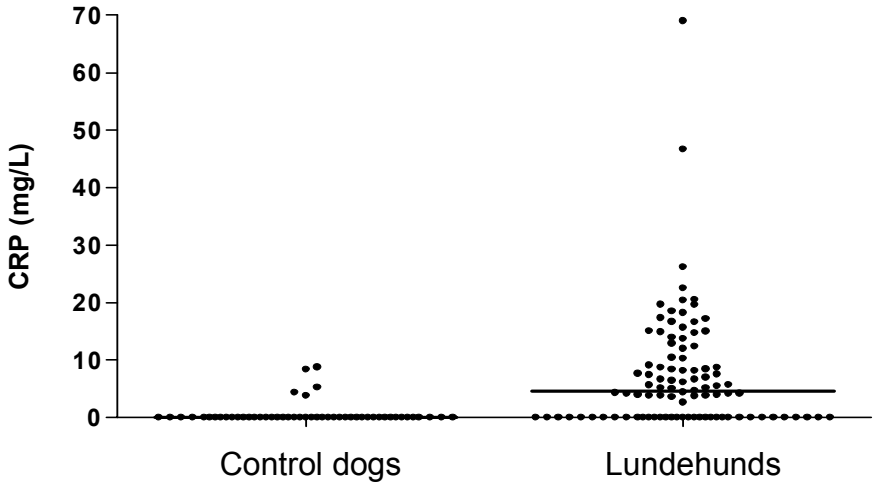
The reference range for serum **globulin** is 1.8-4.2 g/dL.
14 of 97 dogs (14.7%) had globulin concentrations below the reference range, and were hypoglobulinemic (median globulin = 2.3 g/dL; range 0.8-4.1 g/dl).
All dogs with hypoglobulinemia also had low total protein and albumin.



These results clearly show that a large number of Lundehunds have low albumin and/or low TSP and globulins, which is consistent with the finding of PLE in many of these dogs.
In fact, there was a correlation of TSP and fecal Alpha$_1$-PI concentrations, supporting that there is a relationship between blood protein concentrations and fecal Alpha$_1$-PI, as one would expect, because Alpha$_1$-PI is an indicator of protein loss.
Based on these results, it is very important to monitor the blood protein concentrations in affected Lundehunds.

C-Reactive Protein (CRP)

CRP is a general marker of inflammation and it is not specific for intestinal inflammation. Nevertheless, it can be used to evaluate whether there may be an inflammatory process in a patient with GI disease. In human medicine, it correlates with disease activity in Crohn's Disease patients, and similar results have been found in dogs. We tested CRP concentrations in all Lundehunds and compared them to a group of healthy control dogs. This graph shows the result of that comparison:



The reference range for CRP is 0-7.6 mg/L.
While almost all of the 51 control dogs had undetectable CRP concentrations (the highest was 8.8 mg/L), many of the Lundehunds had CRP levels well above that.
In fact, 34 Lundehunds (35.1%) had CRP concentrations above the reference range.

These results indicate that inflammatory disease is present in many Lundehunds. Unless there is another reason for inflammation (for example arthritis, surgery), we can probably assume that this is due to intestinal inflammation (IBD).

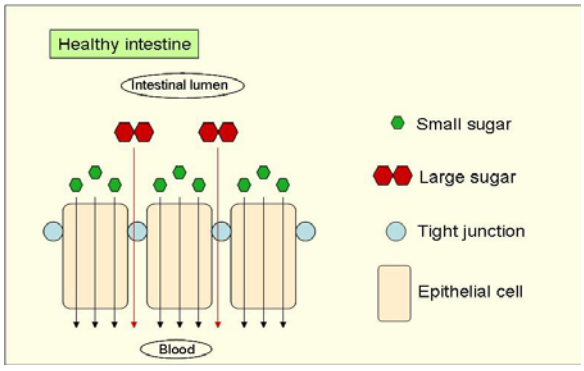
GI Lab study on intestinal permeability and absorptive capacity in Norwegian Lundehunds

The intestines have several important functions. First, and most obvious, is the uptake of nutrients from food. But another very important role is providing a barrier against "unwanted" and potentially harmful molecules and bacteria that can be present in the gut. This barrier is formed by the intestinal wall. The inner "lining", the mucosa (the layer that faces the inside of the intestine), regulates what the body absorbs/takes up.

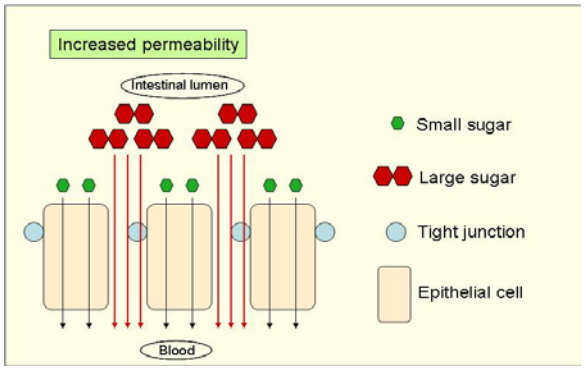
One important term in this context is permeability. Permeability describes the extent of what the mucosa allows to pass through. An increase in permeability, as we describe it, means that larger molecules/particles are able to enter the intestinal wall and therefore the body. To a certain extent this is normal and happens in all of us daily, as our intestine deals with the food that enters the GI tract. But if this mechanism gets out of control we talk about increased intestinal permeability.

Increased intestinal permeability can have the following effects:

- It can cause uptake of substances that should not enter the body; and it can potentially lead to leakage of fluid into the intestine
- It can cause hypersensitivity/allergic reactions and inflammation
- It can trigger disease processes
    - This has been found to be the case in Diabetes mellitus and Celiac Disease in humans; possible others?



In a dog with healthy intestines, the connections between the cells, called tight junctions (TJ), are intact and prevent large molecules from passing through. Therefore, more of the small sugar will be taken up by the intestine and only a small amount of the large sugar will enter the body.



If the TJ's are not functioning properly due to damage from intestinal disease, "gaps" between the cells can occur and we see an increase in permeability. This means that more of the large sugar will be able to enter the blood stream, which we will then be able to measure.

Another important mechanism is what we refer to as absorptive capacity. As the name implies, absorptive capacity is a measure of how well the mucosa absorbs nutrients.

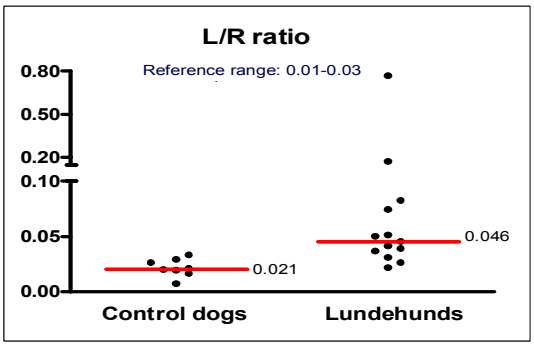
Intestinal disease can cause an increase in intestinal permeability as well as changes in absorptive capacity. These can be determined by the use of different sugar probes:
Permeability can be measured with
- Lactulose (large sugar molecule) and rhamnose (small sugar molecule)
- These are expressed as a ratio of lactulose to rhamnose (L/R ratio)

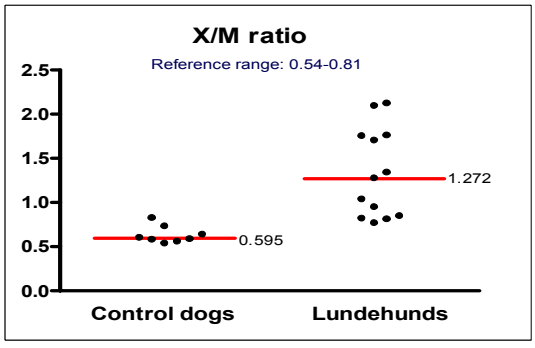
Absorptive capacity can be measured with
- Xylose and methylglucose
- These are expressed as a ratio of xylose to methylglucose (X/M ratio)

In a healthy dog, we would expect to find a low L/R ratio (low permeability) and a high X/M ratio (high absorptive capacity).

The principle of the sugar test is as follows:
- A baseline blood sample is taken (before the test is started)
- The dogs are then given a solution containing the sugar mixture (L, R, X and M) via stomach tube
- Further blood samples are taken at 60, 90 and 120 minutes after dosing
- All samples are then frozen, shipped to the GI Lab and analyzed.

For our study, we tested 13 Norwegian Lundehunds and eight healthy control dogs of various breeds for comparison. We found differences between the Lundehunds and the control dogs for both, intestinal permeability and absorptive capacity:





The results show that Lundehunds had both, a higher median L/R ratio and a higher median X/M ratio compared to the control dogs (medians are shown next to the red line in the graphs).
The high L/R ratio is consistent with the finding of intestinal disease in Lundehunds, and while this was not as pronounced in all of them, it indicated that Lundehunds in general may have a higher chance of having increased intestinal permeability.
Lundehunds also had a higher mean X/M ratio. This was unexpected, as a high ratio would tell us that the dogs have a high absorptive capacity, which

would likely not be the case in intestinal disease. However, this is based on the assumption that the absorption of methylglucose is relatively constant and does not change much, even in diseased dogs, and a high X/M ratio would result from a high absorption of xylose. In this case, though, the elevated X/M ratio in the Lundehunds results from a decreased absorption of methylglucose, rather than increased xylose absorption.
This is unusual, and currently we are not sure about what the cause of this is. It could be hypothesized that there may be damage to intestinal glucose carrier system, but further studies are needed to investigate the exact mechanisms of xylose and methylglucose absorption and the cause of the decrease in methylglucose absorption in Lundehunds.

Conclusions

Based on the literature and all our test results from recent years, we can conclude that:

- Lundehunds can suffer from a variety of conditions, including
  - Gastritis
  - Intestinal lymphangiectasia
  - Inflammatory bowel disease
  - PLE and increased intestinal permeability
- Our results show that at least 50% of Lundehunds are affected by intestinal disease
- Follow-up data available from some dogs indicate that the actual number may be a lot higher than that, probably closer to 100%
  - Many dogs that tested normal at initial tests showed abnormal test results later on (e.g. PLE based on $Alpha_1$-PI, cobalamin deficiency etc).
  - Even dogs that appear healthy for a long time may get sick.
  - No Lundehund is "safe" from LS!

Recommendations

- These results again show how important regular testing is for any Lundehund, including those that seem healthy, but especially those that are showing clinical signs (e.g. vomiting, diarrhea, weight loss) or have done so in the past.
- We recommend monitoring your Lunde's health from an early age and retesting at regular intervals (i.e. every six months or annually).
- If your dog is sick or has been sick before, more frequent checks may be necessary (for example to monitor the blood proteins and verify treatment success).
- Remember that the earlier LS is detected, the better the chance that it can be treated.

- In some dogs, lifelong treatment may be necessary (for example cobalamin substitution).
- There is no excuse for not having your dog tested!
    - Currently, the GI Lab still offers free testing to all Lundehunds.
    - The only cost you will incur is for your vet performing the blood draw.
    - For ordering a free test kit with instructions, contact me at nberghoff@cvm.tamu.edu or (979) 458 2293.

Outlook

Further studies in which Lundehunds can be enrolled are currently ongoing:

In one study, we are trying to evaluate intestinal biopsies from Norwegian Lundehunds. If your dog is having biopsies done for diagnosis of IBD, for example, please have your vet contact us. We would be happy to receive samples and include them in our research. Also, while we know it is difficult to think about this – if your Lunde is very sick and you and your vet decide she needs to be put to sleep, please consider donating biopsy samples which your vet can obtain at the time of euthanasia. Those biopsies are extremely valuable for Lundehund research and may help many other Lundes in the future. We would be very grateful if you gave this some consideration.

In another study we are testing the effect of a new trial drug on intestinal permeability in dogs with intestinal disease. The drug acts locally in the intestine and is reducing permeability by closing the gaps at the Tight junctions (TJ's). It has been found to be very safe - toxicity studies were done with much higher doses (250 times higher) than what we are using and side effects have not been found.
The actual study will cover a total of three months (95 days). Dogs enrolled in the study will undergo a health check, an initial permeability test and then receive the drug for three months. At the end of the study, the permeability test is repeated to record any possible changes (see outline of the study below).
There are no costs associated with this study for the owner, as all veterinary costs are billed directly to the GI Lab.

- **Day 1** – Health check
- **Days 2-4** – Collection of 3 fecal samples
- **Day 5** – 1st Sugar permeability test
- **Days 6-95** – Dogs receive drug 2x/day
- **Days 12-14** – Collection of 3 fecal samples
- **Days 92-94** – Collection of 3 fecal samples
- **Day 95** – 2nd Sugar permeability test

We still need Lundehunds, preferably with known GI disease, to participate in this study! If you are interested in more information, please contact me at nberghoff@cvm.tamu.edu or call (979) 458 2293 and I will be happy to send you more

information and discuss the study with you! There is no obligation, so please don't hesitate to contact me.

Last, but not least: Thank you very much for all the support you have shown in the past! We will continue to include Lundehunds in as many projects as possible in order to help find out what is causing GI disease in these sweet dogs.

Sincerely,

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