Pancreas Functions

- The pancreas is a compound organ with both **EXOCRINE** and **ENDOCRINE** functions.
- The **exocrine pancreas** is composed of glandular epithelium that forms acinar lobules comprising about 80% of the pancreas.
- **Endocrine cells** are concentrated in the islets of Langerhans and secrete hormones.

Source: Faculty.Cord.edu
THE EXOCRINE PANCREAS
The primary function of the exocrine pancreas is the synthesis and secretion of digestive enzymes.

These enzymes include,

- **Proteases** that are stored in acinar cell zymogen granules and secreted as **inactive proenzymes** (e.g., trypsinogen, chymotrypsinogen, proelastase, and procarboxypeptidases),
- **Lipase**, which hydrolyzes lipids,
- **Amylase**, which hydrolyzes starches.

The inactive proenzymes become activated by enzymatic cleavage of a small peptide.

- Normally, trypsinogen is cleaved by enterokinase in the intestine to form trypsin and trypsinogen activation peptide (TAP); trypsin then activates other proenzymes.
- Unlike the proteases, **amylase** and **lipase** are secreted in active form.
Two major disorders of the exocrine pancreas can be detected by laboratory evaluation.

1. **Pancreatits**: It is the injury of the pancreatic parenchyma. It is recognized most commonly in dogs and cats, and may be acute or chronic.
   - Inflammation may result in the premature activation and leakage of pancreatic enzymes into the pancreatic interstitium, peritoneal cavity, and vasculature.

2. **Exocrine pancreatic insufficiency (EPI)**: It is a disorder resulting in insufficient production and secretion of pancreatic enzymes. EPI is due to loss of pancreatic acinar cells, and results in inadequate digestive function (maldigestion).
   - The clinical signs are similar to malabsorption.
The Exocrine Pancrease

- The diagnosis of pancreatitis is particularly difficult in chronic and mild cases.
- Although vomiting and abdominal pain are frequent in dogs with acute pancreatitis, these symptoms are rarely seen in cats.
- Cats seem to develop chronic pancreatitis more frequently.
- Recent studies have reported chronic pancreatitis more frequently in both dogs and cats.
The Exocrine Pancrease

- There are various **risk factors**.
  - Miniature schnauzers, Yorkshire terrier
  - Hyperlipidemia
  - Obesity
  - High fat diet
  - Zinc toxication, hypercalcemia
  - Trauma, ischemia, cholestasis
  - Neoplasia, infectious agents
  - Large intestine and bilier duct inflammations

- Due to non-specific and highly variable clinical manifestations,
  - Laboratory testing + Imaging + Biopsy may be required.
Pancreatic Lipase Immunoreactivity (PLI)

- It is measured by species-specific immunoassay techniques (such as RIA or ELISA).
- There is also a rapid in-clinic test available for PLI.
- Sensitivity in dogs is ~65-95%.
- Sensitivity in cats is ~54-100%.
  - In cats, Cobalamin and folate levels should also be considered in cases of chronic pancreatitis complicated with small intestine diseases.
- Nowadays, it is the most reliable parameter for diagnosis of pancreatitis.
Pancreatic Lipase Immunoreactivity (PLI)

- The best sample for analysis is the serum collected after 12 hours fasting.

- Reference ranges:
  - Cat : < 3.5 µg/L
  - Dog : < 200 µg/L

- The evaluation of test is different in cats and dogs.
### Pancreatic Lipase Immunoreactivity (PLI)

#### CATs

<table>
<thead>
<tr>
<th>CATs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3,5 µg/L</td>
<td>It is unlikely that the cat has pancreatitis. Investigate for other diseases</td>
</tr>
<tr>
<td>3,6 - 5,3 µg/L</td>
<td>It is increased. The cat may have pancreatitis and fPLI should be reevaluated in two weeks if clinical signs persist. Investigate for other diseases that could cause observed clinical signs.</td>
</tr>
<tr>
<td>≥ 5,4 µg/L</td>
<td>It is consistent with pancreatitis. The cat most likely has pancreatitis. Consider investigating for risk factors and concurrent diseases (e.g., IBD, hepatitis, Diabetes mellitus). Periodic monitoring of fPLI may help assess response to therapy.</td>
</tr>
</tbody>
</table>

Ref.: [GILab Texas A&M](http://www.gilab.tamu.edu)
## Pancreatic Lipase Immunoreactivity (PLI)

<table>
<thead>
<tr>
<th>DOGs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200 µg/L</td>
<td>Result within the reference interval.</td>
</tr>
<tr>
<td>201 - 399 µg/L</td>
<td>Questionable range. This patient may have pancreatitis and serum cPLI should be reevaluated in 2-3 weeks. Also, the patient should be evaluated for other differential diagnoses.</td>
</tr>
<tr>
<td>≥ 400 µg/L</td>
<td>Consistent with pancreatitis. Treatment can be monitored by repeated serum cPLI analysis.</td>
</tr>
</tbody>
</table>

Ref.: [GiLab Texas A&M](#)
Trypsin-Like Immunoreactivity (TLI)

- Trypsinogen is synthesized only in the pancreas and transforms into active trypsin in the intestine.

- It is measured by species-specific immunoassay techniques (such as RIA or ELISA).
  - Both trypsinogen and trypsin are measured together. Therefore, it is called TLI.

- Today, there are routine tests for cats and dogs.

- In healthy animals, a small amount of trypsinogen leaks into the extracellular space and then diffuses via the lymphatics into the blood. Therefore, the normal serum concentration of TLI is a good indicator of sufficient amount of trypsinogen produced by the pancreas.
Trypsin-Like Immunoreactivity (TLI)

- Increased levels is associated with pancreatitis.
  - Due to damaged acinar cells, it is leaked to blood. However, trypsinogen is removed by glomerular filtration. So, if there is a problem that result in decreased GFR, TLI levels may increase in serum.
  - On the other hand, activated trypsin is blocked by protease inhibitors and removed by mononuclear phagocytic system.
  - The sensitivity of increased serum TLI concentration for diagnosis of pancreatitis in dogs and cats is less than PLI.

- As a result, TLI is now principally applied to diagnosis of Exocrine Pancreatic Insufficiency (EPI).
Trypsin-Like Immunoreactivity (TLI)

- The best sample for analysis is the serum collected after 12 hours fasting.

- **Reference Ranges**
  - Dog: 5.7 - 45.2 µg/L
  - Cat: 12.0 - 82.0 µg/L

- **In Dogs,**
  - <2.5 µg/L are diagnostic for EPI.
  - 3.5 - 5.7 µg/L are rarely if ever associated with signs of EPI but may reflect subclinical pancreatic disease.
    - Such as subtotal pancreatic acinar cell destruction secondary to on-going immune-mediated lymphocytic pancreatitis. Progression of the disease may ultimately lead to EPI.
  - 2.5 - 3.5 µg/L are sometimes (but rarely) associated with clinical signs due to EPI. Assay should be repeated after one month paying particular attention to ensuring that food is withheld for 12 to 15 hours before the blood sample is collected.
Trypsin-Like Immunoreactivity (TLI)

- In cats,
  - ≤ 8.0 µg/L are diagnostic for EPI.
  - 8.0 - 12.0 µg/L being equivocal. Repeating the assay one month later (fasting level) should be considered.

- Serum TLI values above 50.0 µg/L (dogs) and 100.0 µg/L (cats) are consistent with either acute or chronic pancreatitis or decreased renal excretion due to severe renal insufficiency (rare).
  - It is increased in approximately 30-40% of cats and dogs with pancreatitis; it is important to recognize that normal test results do not rule out the possibility of pancreatic inflammation. If pancreatitis is suspected, a PLI test should be performed.
  - In cats increased serum TLI is often also observed with small intestinal disease. In these cases serum concentrations of cobalamin and folate should be determined for evaluation of the small intestine.
Serum Lipase Activity

- Enzymatic test methods can not distinguish lipase from pancreas or other tissues. Thus, increased activity may not be specific for the pancreas.

- Serum activity is usually normal in cats with pancreatitis. Therefore, it is not a useful parameter for cats.

- In dogs, it can be useful for diagnosis of pancreatitis and is usually included in the biochemistry profile test, but its sensitivity is low.
  - Generally, increases of serum lipase activity of greater than 3–5 fold the upper reference limit are interpreted as suggestive of pancreatitis in dogs, and should prompt further evaluation, such as cPLI, imaging and biopsy.
Serum Lipase Activity

- In dogs, serum lipase activity may also increase due to non-pancreatic conditions.
  - **Decreased GFR:** Dogs with azotemia can have increased serum lipase activity due to decreased renal excretion and/or inactivation of lipase. Thus, serum levels increase (2-5 fold)
  - **Corticosteroid administration:** Dexamethasone can cause increased serum lipase activity (2-5 fold)
  - **Neoplasia:** A variety of neoplasms involving the pancreas, liver, gastrointestinal tract and heart have been associated with increased serum lipase activity.
  - **Liver diseases:** Hepatic necrosis and fatty degeneration have been associated with increased serum lipase activity
  - **Acute enteritis:** Increases up to 5 fold.
Serum Amylase Activity

- Enzymatic test methods cannot distinguish amylase from pancreas or other tissues. Thus, increased activity may not be specific for the pancreas.

- Although serum amylase activity is readily available on standard biochemical profiles, its utility for the diagnosis of pancreatitis is limited.

- Cats with spontaneous or experimental pancreatitis typically have normal to minimally increased serum amylase activity, even decreased activity may be detected. Therefore, serum amylase activity is not useful for diagnosis of pancreatitis in cats.
Serum Amylase Activity

- In dogs, increased serum amylase activity is neither sensitive nor specific for pancreatitis, and generally considered inferior to serum lipase activity as a screening test.

- Increases of 3-5 fold may be interpreted as suggestive of pancreatitis, prompting further evaluation (cPLI, imaging, biopsy).

- However, in dogs without pancreatitis many of the same conditions that cause increased serum lipase activity (discussed earlier) can also cause increased canine serum amylase activity.
  - The main exception is corticosteroid administration, which does not increase serum amylase activity and may actually decrease it.
Investigation of Peritoneal Fluid Amylase and Lipase Activities

- Measurement of amylase and lipase activities from the peritoneal fluid in animals with suspected pancreatic injury may also be useful for diagnosis.

- In active pancreatic injury, these enzymes leach into the peritoneal cavity and activity in the fluid increases.

- Especially, if the activity in the peritoneal fluid is higher than the serum activities, it is evaluated as compatible with pancreatic damage.
  - It should not be forgotten, however, that non-pancreatic causes may be the reason of increase in peritoneal fluid; e.g. duodenal perforation.
Other Laboratory Tests

- Other test parameters may also be correlated with pancreatic injury.

- The presence of several of abnormalities in addition to physical findings suggestive of pancreatitis should prompt further evaluation using more sensitive and specific tests (cPLI, imaging, etc.).

**Complete Blood Count (CBC/Hemogram)**

- It is normal in cats, especially in chronic pancreatitis.
- 55% of dogs may show signs of inflammation (leukocytosis, neutrophilia).
- Pain can cause stress and this can lead to lymphopenia.
- Vomiting and inadequate fluid intake may increase HCT, Hgb and RBC.
- Mild anemia can often be seen in cats and dogs.
Other Laboratory Tests

- **Azotemia**
  - Usually prerenal, is common in severe cases of pancreatitis and is caused by a combination of factors, including dehydration and hypovolemia that result in decreased GFR.
    - Urine specific gravity is usually high.

- **Hyperglycemia**
  - It is common in animals with acute pancreatic injury and, acutely, is the result of increased serum concentrations of corticosteroids, epinephrine, and glucagon.
  - In patients with chronic or recurring pancreatitis, hyperglycemia may be caused by diabetes mellitus resulting from islet cell injury.

- **Hypoglycemia**
  - Mild to moderate hypocalcemia is inconsistently present in animals with pancreatic injury.
Other Laboratory Tests

- **Increased serum leakage and induced liver enzymes**
  - ALT, AST and ALP, GGT.
  - Hepatocytes can be affected as a secondary to leakage pancreatic enzymes.
  - Biliary obstruction may develop due to inflammation of the pancreatic tissue.

- **Hypercholesterolemia** and **Hypertriglyceridemia**
  - Plasma is usually lipemic in dogs with pancreatitis.
  - The variable function of lipoproteins and cholestasis are thought to play a role in the pathogenesis.
  - Hypertriglyceridemia in cats is rare, hypercholesterolemia is more common.
Other Laboratory Tests

- **Serum and plasma protein concentrations**
  - Variable in patients with pancreatitis.
  - Ex. If leakage occurs in the peritoneal cavity, serum concentration decreases. If there is a dehydration, it tends to increase serum protein concentration.

- **Disseminated intravascular coagulation (DIC)**
  - It can be a sequela to acute pancreatitis.
  - Bile acids are required for the absorption of fat-soluble vitamins.
  - If pancreatitis-induced obstruction blocks the flow of bile acids, absorption of vitamin K in particular will be insufficient. As a result, hemostasis is affected and abnormal coagulation test results are obtained.
THE ENDOCRINE PANCREAS
The Endocrine Pancreas

- It consists of Langerhans islets. Islets contain different types of cells involved in the secretion of different hormones.
  - \( \alpha \)-Cells: Glucagon
  - \( \beta \)-Cells: Insulin
  - \( \delta \)-Cells: Somatostatin
  - PP-Cells: Pancreatic polypeptide

- Most of the functional anomalies of the endocrine pancreas are related to \( \beta \)-cells (60-80%).

- Both deficient and excessive insulin production may result in serious abnormalities of glucose metabolism.
The Endocrine Pancreas

- Many factors in addition to the endocrine pancreas play key roles in glucose metabolism.

- It is extremely important to know the factors that cause hypoglycemia or hyperglycemia in order to assess glucose metabolism by applying laboratory tests.
Normal Glucose Metabolism

- **Sources of Blood Glucose**
  - Intestinal absorption
  - Hepatic production (Glycogenolysis, Gluconeogenesis)
  - Renal production (Gluconeogenesis)

- **Regulation of Blood Glucose Concentration**
  - Dependent on multiple interacting factors, including time since meal, hormonal influences, use of glucose by peripheral tissues (e.g. Skeletal muscle)
  - **Hormones that affect blood glucose concentration**
    - Insulin
    - Glucagon
    - Glucocorticoids
    - Catecholamines
    - GH
    - Extreme physical activity
# Normal Glucose Metabolism

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Action</th>
<th>Effect on blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td>Promotes tissue glucose uptake&lt;br&gt;Inhibits gluconeogenesis&lt;br&gt;Promotes glycogen synthesis</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Glucagon</strong></td>
<td>Promotes gluconeogenesis&lt;br&gt;Promotes glycogenolysis&lt;br&gt;Inhibits glycogen synthesis</td>
<td>Increase</td>
</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td>Promotes gluconeogenesis&lt;br&gt;Promotes glucagon release&lt;br&gt;Inhibits tissue glucose uptake</td>
<td>Increase</td>
</tr>
<tr>
<td><strong>Catecholamines</strong></td>
<td>Promote glycogenolysis&lt;br&gt;Inhibits insulin secretion&lt;br&gt;Stimulates growth hormone release</td>
<td>Increase</td>
</tr>
<tr>
<td><strong>Growth hormone (GH)</strong></td>
<td>Inhibits tissue glucose uptake&lt;br&gt;Inhibits insulin action&lt;br&gt;Promotes glucose production</td>
<td>Increase</td>
</tr>
</tbody>
</table>
Causes of Hypoglycemia

- **Drugs**
  - Therapeutic insulin overdose.
  - Sulfonylurea medications (glipizide and glyburide).

- **Extreme exertion**
  - Hunting dogs and endurance horses.

- **Glycogen storage diseases**

- **Hepatic insufficiency or failure**
  - Resulting from the loss of >70% of functional hepatic mass may cause hypoglycemia due to decreased gluconeogenesis and glycogenolysis.
  - Hypoalbuminemia, decreased BUN, increased serum bile acid concentration.
Causes of Hypoglycemia

- **Hypoadrenocorticism**
  - Gluconeogenesis is decreased due to cortisol deficiency.
  - Insulin-mediated uptake of glucose is increased by muscle tissue.

- **Hypopituitarism**
  - Lack of ACTH secretion.

- **Juvenile and neonatal hypoglycemia**
  - Especially common in pigs.
  - Juvenile hypoglycemia is a syndrome that usually is seen in toy breed puppies younger than 6 months.
  - Inadequate storage pools of glycogen and protein probably play an important role in this syndrome. Inadequate levels of hepatic enzymes for gluconeogenesis also may contribute.
Causes of Hypoglycemia

- **Lactational Hypoglycemia**
  - Also known as spontaneous bovine ketosis.
  - In cattles, it is especially seen during peak stage of lactation.
  - Hepatic gluconeogenesis is unable to meet the demand for glucose production.

- **Pregnancy Hypoglycemia**
  - In dogs and sheep, it can be seen together with ketonemia during late pregnancy.
  - Also known as pregnancy toxemia in sheep.

- **Neoplasia**
  - Insulinomas are the most common tumors. It have been reported in dogs, cats and ferrets.
Causes of Hypoglycemia

- **Sepsis**
  - Most often associated with endotoxemia.

- **Starvation or malabsorption**
  - Decreased glucose absorption from the intestine is a rare cause of hypoglycemia.
  - Hypoglycemia only occurs after long-term starvation or malabsorption, because gluconeogenesis helps to maintain a normal blood glucose concentration at the expense of other substances, principally protein.

- **Xylitol toxicosis**
  - It is strong promoter of insulin release in dogs.
Causes of Hyperglycemia

- **Drugs or Toxins**
  - Ethylene glycol, glucocorticoids, glucagon, IV glucose, ketamine, morphine, progestins, thyroxine, xylazine
  - They are associated with transient mild hyperglycemia.

- **Physiologic**
  - Diestrus, exertion, excitement, pain, postprandial, stress response.
  - Cats frequently exhibit transient hyperglycemia related to struggling during blood collection; the magnitude of the hyperglycemia may reach 300 mg/dL or greater, and it may persist for 1.5–2 hours.
Causes of Hyperglycemia

- **Diabetes mellitus**
  - Diabetes mellitus is caused by a deficiency of insulin production or an interference with the action of insulin in target tissues, thereby resulting in abnormal glucose metabolism.
  - Diabetes is typically associated with the greatest degrees of hyperglycemia. Altered protein and lipid metabolism also occurs in diabetes mellitus.
  - Animals with diabetes mellitus usually have blood glucose concentrations greater than the renal threshold resulting in glucosuria.
  - Diabetes mellitus has been classified according to the underlying cause as either **type 1** or **type 2**, and by the dependence of the affected animal on insulin therapy as either **insulin dependent (IDDM)** or **noninsulin dependent (NIDDM)**.
  - These two classification schemes overlap, causing confusion regarding the types of diabetes mellitus occurring in animals.
Causes of Hyperglycemia

- **Type 1 Diabetes mellitus (T1DM)**
  - T1DM results from immune-mediated destruction of pancreatic $\beta$ cells, and animals with type 1 diabetes mellitus are insulin dependent.
  
  - It is the most frequent cause of diabetes in dogs.
  
  - Insulin dependent diabetes mellitus can also occur secondary to other disease.
  
  - E.g. Pancreatitis, $\beta$ cell hypoplasia (in Keeshond dogs), juvenile pancreatic atrophy in greyhounds.
Causes of Hyperglycemia

- **Type 2 Diabetes mellitus**
  - Type 2 diabetes mellitus is characterized by a sluggish insulin response to hyperglycemia (i.e., decreased capacity to produce insulin) and a poor tissue response to insulin (i.e., insulin resistance).
  
  - Animals with type 2 diabetes mellitus may be either insulin or noninsulin dependent.

  - This is the most common type of diabetes mellitus in cats (approx. 70%).
    - A consistent finding in over 90% of diabetic cats is deposition of islet amyloid, derived from islet amyloid polypeptide.
    - Obesity is considered a major risk factor for diabetes mellitus in cats.
Causes of Hyperglycemia

• The pathophysiology of type 2 diabetes mellitus (T2DM) also intersects with thyroid dysfunction.
  • Studies in humans and animals have shown that thyroid hormone abnormalities also play a role in the development of T2DM. The most likely mechanism leading to T2DM in thyroid dysfunction,
    • Physiological deviations causing glucose impairment and muscle spillage,
    • Hepatic glucose synthesis is excessive and
    • Splanchnic is thought to be impaired in exerting a number of genes with an increase in glucose absorption.
  • These factors undoubtedly contribute to insulin resistance. Therefore, both hyperthyroidism and hypothyroidism have been associated with insulin resistance, which is reported to be the most important cause of impaired glucose metabolism in T2DM.
Causes of Hyperglycemia

- In the case of hypothyroidism, it has been determined that there is a decrease in stimulation of gluconeogenesis. In hyperthyroidism, it increases.
- T_3_ stimulates gluconeogenesis, especially in the case of hyperthyroidism, and hypothyroidism is associated with decreased gluconeogenesis.
- In particular, the regulation of phosphoenolpyruvate carboxykinase (PEPCK), which is the rate-limiting step in gluconeogenesis, has critical importance for glucose homeostasis.
- In hyperthyroidism, hepatic glucose output increases due to increased gluconeogenesis. Therefore, the rates of insulin-stimulated glucose excretion in peripheral tissues should be altered to preserve normoglycemia.
Causes of Hyperglycemia

- **Hepatocutaneous Syndrome**
  - It is seen in dogs and characterized by liver disease in combination with superficial necrolytic dermatitis. Hyperglycemia is common, but the pathogenesis is not clear.

- **Hyperammonemia**
  - Hyperglycemia may occur in horses and cattle with hyperammonemia that is unrelated to liver disease.

- **Metabolic Syndrome**
  - Serum glucose concentrations may be increased or normal in horses with metabolic syndrome which is a complex disorder that mimics Cushing’s disease. Affected horses are typically obese and insulin resistant, and are prone to develop laminitis.
Causes of Hyperglycemia

**Milk Fever**
- Hyperglycemia, along with hypocalcemia and hypophosphatemia, is often present in cattle with milk fever.
- Hypocalcemia suppresses insulin release; catecholamine and/or corticosteroid release in “down” cows may also contribute to the hyperglycemia.

**Moribund Animals**
- Usually ruminants. Likely causes include catecholamine and/or corticosteroid release, and decreased peripheral use of glucose.

**Neoplasia**
- Pituitary adenomas (acromegaly in cats), glucagonoma, adrenal neoplasia, pituitary hyperplasia.
Causes of Hyperglycemia

- **Pancreatitis**
  - Underlying cause in up to 30% of canine IDDM cases.

- **Proximal duodenal obstruction**
  - Cattle with proximal duodenal obstruction may have marked hyperglycemia, up to 1000 mg/dL.
  - The proposed pathogenesis is a combination of stress and decreased peripheral glucose utilization.
  - By contrast, cattle with abomasal volvulus have a much milder hyperglycemia, usually attributed to stress.
Laboratory assessment of glucose metabolism

- **Blood Glucose Concentration**
  - *It is the initial step.* After detection of either hyperglycemia or hypoglycemia, tests for more specific evaluation of glucose metabolism may be required.
  
  - It can be performed in serum or plasma.
  
  - It should be separated by centrifugation within 30 minutes. There is a 10% loss per hour. If it is not possible to separate during this time, NaF-blood tubes should be used.
  
  - Reference laboratories, in-house clinical chemistry analyzers or portable blood glucose meters (PBGM) are available.
Laboratory assessment of glucose metabolism

- In most cases (but not all), glucose concentrations determined by PBGMs are lower than those determined by reference methods. Therefore, it is important to consider test methodology.

- Because blood glucose concentrations in monogastric animals are increased for 2–4 hours postprandially, glucose concentrations should be measured after fasting.

- Dogs and cats should be fasted for 12 hours before sampling to avoid postprandial influences. Potentially hypoglycemic animals should not be fasted before sampling.

- Artifactual hypoglycemia may occur due to in vitro consumption of glucose in cases of extreme leukocytosis and marked erythrocyte parasitemia with hemotropic mycoplasmas.
Laboratory assessment of glucose metabolism

- **Urine Glucose**
  - Glucosuria occurs when the blood glucose concentration exceeds the renal threshold, which varies by species.
  - Renal thresholds are between 180 and 220 mg/dL in dogs, 200 to 300 mg/dL in cats, 30–180–200 mg/dL in horses, 60 and 100 mg/dL in cattle.
  - Concurrent measurement of blood glucose is important when interpreting glucosuria; diabetic animals typically have both persistent hyperglycemia and glucosuria.
  - Glucosuria can occur in the absence of hyperglycemia if the renal glucose threshold is decreased.
    - Proximal tubular abnormalities (acquired or congenital).
Laboratory assessment of glucose metabolism

- **Serum Insulin**
  - Insulin levels can be determined in serum or heparinized plasma.
  - Immunoassays are used.
  - Using antibodies developed to detect porcine or human insulin, but there is good cross reactivity with canine insulin; assays should be validated for the species of interest.
  - Serum insulin is stable for a week if kept refrigerated, and for several months if frozen.
  - Insulin levels are most frequently measured in hypoglycemic animals when insulinoma is suspected.
  - Normally, insulin concentrations should be very low when glucose concentrations are low. In dogs with a blood glucose <60 mg/dL, detection of insulin concentrations that are above the reference interval (usually >20 µU/mL) is strong evidence for insulinoma.
Laboratory assessment of glucose metabolism

- Measurement of insulin levels in diabetic animals could help to classify their disease as IDDM or NIDDM.

- Practically, however, this has not proved to be very useful.

- The vast majority of dogs have IDDM with low serum insulin concentrations.

- Most cats with type 2 diabetes mellitus (insulin resistant) also have low serum insulin and require insulin therapy, although some only transiently.
Laboratory assessment of glucose metabolism

- **Fructosamine**
  - Fructosamine is a general term that refers to any glycated protein.
  - It is formed when glucose is linked irreversibly to amine groups of albumin and other proteins in the blood.
  - The serum fructosamine concentration is an indicator of blood glucose concentrations during the previous 2–3 weeks.
  - It provides more reliable information regarding the long-term state of glucose metabolism than the blood glucose concentration, which may be transiently increased in some situations.
  - Fructosamine, therefore, has potential in establishing the diagnosis of diabetes mellitus and in monitoring therapy for diabetics.
  - Serum fructosamine assays are available at reference laboratories. Fructosamine appears to be quite stable in serum kept refrigerated (~10 days) or frozen (~30 days).
  - Hemolyzed samples may give erroneous results, and should be avoided.
  - Hypoproteinemia may cause false decrease. In this case it is necessary to correct the results.
    - **Dog:** Corrected Fructosamine = Fructosamine x (Normal albumin:patient albumin)
    - **Cat:** Corrected Fructosamine = Fructosamine x (Normal total protein:patient total protein)
Laboratory assessment of glucose metabolism

- **Glycated Hemoglobin (HbA1C/GHb)**
  - Glycated hemoglobin (GHb) is formed in erythrocytes by an irreversible reaction between carbohydrates (especially glucose) and hemoglobin.
  - The amount of GHb that is formed is proportional to the blood glucose concentration during the life span of the erythrocyte.
  - The blood GHb concentration reflects glucose status during a longer period of time than does the serum fructosamine concentration, because of relatively long erythrocyte life spans (approximately 110 days in dogs, 70 days in cats, 150 days in cattle and horses).
  - Glycated hemoglobin can be used in the same situations as fructosamine. However, fructosamine concentrations change faster with changes in blood glucose concentrations, which may be an advantage in many situations.
  - Glycated hemoglobin is measured in EDTA-anticoagulated whole blood. Their levels are affected by anemic and polycythememic animals.
Laboratory assessment of glucose metabolism

- **Serial Glucose Curve**
  - In diabetic animals receiving initial insulin therapy, measurement of blood glucose concentrations at 1–2 hour intervals throughout the day helps to assess the efficacy and appropriateness of the insulin dosage.
  - In diabetic dogs, the goal is to keep glucose concentrations between 100 and 250 mg/dL. In diabetic cats, the goal range is 100–300 mg/dL.
  - Ideally, the blood glucose nadir should be 100–125 mg/dL for both dogs and cats.
  - Many factors must be taken into account when interpreting serial glucose curves, including the type and duration of insulin being administered, time of feeding, and stress and/or excitement induced by hospitalization during the procedure.
  - Portable blood glucose meters are sometimes used by owners of diabetic pets to generate serial glucose curves at home, under the supervision of their veterinarian, to avoid the effects of stress or excitement.
Laboratory assessment of glucose metabolism

Well-controlled, ideal blood glucose curve.
Laboratory assessment of glucose metabolism

- **Continous Glucose Monitoring**
  - CGMS: Continous glucose monitoring system.
  - By using subcutaneous sensor and up to 24 hours.

- **Glucose Tolerance Test**
  - Oral or IV glucose tolerance tests can be performed.
  - Provide more information about glucose metabolism in suspected animals.
  - These test are labor and time intensive and rarely used in clinical small animal practice, but are occasionally performed in horses that are suspected to have metabolic syndrome and are used in research settings.
Laboratory assessment of glucose metabolism

- **Oral Glucose Tolerance Test (OGTT)**
  - Mostly preferred in dogs.
  1. Fasting blood sample is collected
  2. The glucose is then orally administered to the animal at a dose of 4 g/kg, and a blood sample is taken every 30 minutes for the next 3 hours.
  3. Serums should be separated as soon as possible and delivered collectively in the cold chain to the laboratory.
  4. If it is not possible to take a sample every 30 minutes, a single sample can be taken after 2 hours of glucose administration.
Laboratory assessment of glucose metabolism

- **Intravenous Glucose Tolerance Test (IVGTT)**
  - It is the test used as the gold standard in animals.
  1. After an overnight fasting, the first blood sample is collected in the morning.
  2. 0.5 mg/kg glucose is then IV infused over 30 seconds in the form of a 50% sterile solution.
  3. The test starts at 15 seconds following infusion. Blood samples are then collected at 5, 15, 25, 35, 45 and 60 minutes.
  4. Collectively sent to the laboratory in the cold chain for glucose analysis. A total of 7 samples are assayed.
Laboratory assessment of glucose metabolism

- Combined Glucose/Insulin Test to diagnose Equine Metabolic Syndrome
  
  - Fast the animal overnight and begin the test at about 9am.
  
  1. Take basal blood sample and measure glucose with handheld glucometer.
  
  2. Inject bolus of glucose (150mg/kg); use 40% or 50% glucose.
  
  3. Immediately after glucose administration, give 0.1IU of soluble Insulin/kg.
  
  4. Collect blood samples and analyze with glucometer at the following times after completion of Insulin administration: 1, 5, 25, 35, 45, 60, 75, 90, 105, 120, 135, 150 minutes.
  
  - Then the serum is separated and sent to the laboratory together with the basal sample.
  
  - A total of 14 glucose analyzes are performed. Samples with Sodium Fluoride are recommended.
Laboratory assessment of glucose metabolism

- **Other laboratory abnormalities associated with diabetes mellitus**
  - **Hemogram (Complete blood count):** HCT/PCV may increase. Leukogram may indicate stress or inflammation.
  - **Azotemia, dilute urine:** Diabetic cats and dogs can have glomerular lesions. In glucozo-uric animals, the density is generally lower. If dehydrated, prerenal azotemia can occur. Serum phosphorus level can increase.
  - **Pyuria, hematuria, proteinuria:** Diabetic animals often have urinary tract infections. This is reflected in urinalysis.
  - **Ketonuria:** Acetoacetate, BHBA and acetone
  - **Electrolyte abnormalities**
  - **Metabolic acidosis**
  - **Increased anion gap**
  - **Increased hepatic and pancreatic enzyme activities**
  - **Increased serum bilirubin concentration**
  - **Hyperlipidemia**
Your Questions?

Send to serkan.sayiner@neu.edu.tr
References

- Gastrointestinal Laboratory, Texas A&M University.
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