



Diseases of the reptile pancreas

Scott J. Stahl, DVM, DABVP-Avian

Eastern Exotic Veterinary Center, 4001 Legato Road, Fairfax, VA 22033, USA

Diseases of the reptile pancreas are rarely documented in the literature and generally appear to be uncommon. As diagnostic capabilities improve more diseases of the pancreas will likely be documented and those currently known will become better understood.

For the clinician to approach the reptile patient with a pancreatic disorder a thorough understanding of basic anatomy and physiology will be necessary. This article will serve to review the normal reptile pancreas and discuss the common diseases that can affect this organ. Both endocrine and exocrine related disorders will be reviewed and diagnostic and therapeutic modalities discussed.

Gross anatomy

Lizards

The pancreas of lizards is more complex than snakes in that it is extended and trilobed (Fig. 1). One portion runs along the bile duct towards the gall bladder, one portion runs to the small intestine, and typically a thin limb with a distinct distal lobe runs to the spleen [1]. In some lizards a thin diverticulum of pancreas tissue extends anteriorly from the ventral portion of the pancreas and encircles the common bile duct. This is known as the hepatic portion, and may actually enter the hepatic parenchyma [2].

Snakes

The pancreas of snakes is consolidated and simpler, often pyramid shaped, and attached to the first portion of the duodenum. It generally lies posterior to the spleen, and may be in contact with the spleen. The pancreas

E-mail address: sstahldvm@aol.com (S.J. Stahl).



Fig. 1. The normal pancreas of a bearded dragon, *Pogona vitticeps*. This was a necropsy specimen. Note the complexity of the pancreas with several arms that move toward other organs. The light-colored pancreas (P) is suspended in the mesentery with the stomach (S) noted cranially, the spleen to the right, and the duodenum to the left. (Courtesy of Scott J. Stahl, Fairfax, VA, with permission.)

is usually posterior or adjacent to the gall bladder, and lies just posterior to the caudal tip of the liver. The association of the pancreas, spleen, and gall bladder is often referred to as the “triad”.

There are differences in the amount of pancreatic association with the spleen among species of snakes. In some snakes there is a limb of pancreas that runs forward to the spleen. In others, this limb is interrupted or there is no splenic limb at all. In some snakes the spleen and pancreas are adjoined [1].

Chelonians

In the painted turtle (*Pseudemys scripta*) the pancreas is attached to the mesenteric border of the duodenum starting at the pylorus region and ending by splaying out over the spleen (which is dorsal and more posterior). In the snake-headed turtle (*Chelodina longicollis*) the pancreas is associated with the proximal portion of the spleen but its proximal portion instead of its caudal portion as in painted turtles. Some turtles such as the South American side-necked river turtle (*Podocnemius uniflus*) lack an association between the pancreas and the spleen [1].

Crocodylians

In the alligator, *Alligator mississippiensis*, the ventral portion of the pancreas is between the limbs of the ventral duodenal loop. The body of the pancreas follows the dorsal portion of the duodenum and ends on the spleen, which is attached to the descending limb of the dorsal duodenal loop [1].

Exocrine pancreas

There are few differences in the histologic organization or ultrastructural cytology of the exocrine pancreas in reptiles when compared to mammals.

The exocrine parenchyma of the reptile pancreas consists of branching tubules rather than typical acini seen in mammals. The zymogen cells function similarly to mammals in the processes of protein secretion; granule formation, and granule discharge [1]. Histologically, eosinophilic zymogen granules are located in the apical portions of the darker staining exocrine cells. The nuclei of these exocrine cells are located in a basal position and they have a distinct prominent nucleolus. The positioning of these exocrine cells is with their bases along the capillary surface [1,3].

Endocrine pancreas

Lizards

Lizards have large islets usually confined to the dorsal lobe and localized primarily in the splenic portion of the pancreas [4]. Unlike mammals, birds, or fish there is no segregation of alpha and beta cells in lizards. These cells lie adjacent to each other in an alternating pattern along vascular spaces.

Monitor lizards (*Varanus* spp.), however, are similar to snakes, where the majority of their islet tissue is located in a distinct juxtasplic islet body distanced from the dorsal lobe of the pancreas and connected to it by a thin stalk. The presence of this elongated dorsal lobe of pancreas in monitor lizards is similar to that seen in the more primitive snakes, thus supporting an evolutionary link between the extended pancreas of lizards to the compacted pancreas of snakes [2]. Clinically, for a thorough histopathologic analysis of islet tissue in lizards, it is important to submit the dorsal lobe of the pancreas—and specifically the splenic or juxtasplic portion.

Snakes

The main islet tissue is found within a distinct juxtasplic islet body separate from the dorsal lobe of the pancreas and connected to it by a thin stalk. These large islets are composed of both alpha and beta cells distributed in a mixed pattern [2]. In the more advanced snake species

(family Colubridae), many islets of endocrine cells are found actually within the spleen [1].

To evaluate a snake's islet tissue on histopathology, it is important to submit the juxtasplic portion or even the spleen itself.

Chelonians

The pancreatic islets of turtles are not as large as lizards and snakes, and they are not confined to the splenic portion of the pancreas. In chelonians, there is a marked segregation of the alpha and beta cells—similar to fish, some birds, and mammals. The alpha cells are peripheral in their distribution as opposed to a mixed distribution in lizards and snakes [1].

Crocodylians

In the alligator, islet tissue is associated with first-order ducts at the periphery. Beta cells are often aggregated at the central portion of the islet, and alpha cells are clustered around the periphery as seen in humans [1].

General

Unlike mammals, most reptilian islet tissue lacks a sharp demarcation from exocrine pancreatic tissue. Islet tissue is usually associated with first-order exocrine ducts and tubules, and lacks a capsule. The pancreatic islets of lizards and snakes are larger than those of turtles and crocodylians [5]. The lizard islet is more centrally located than in the snake, which is more peripheral. Turtle islets are the smallest and are the most diffusely distributed, while crocodylian islets are highly branched.

Alpha and beta cells are equally proportioned in snakes, turtles, and crocodylians, but alpha cells are more abundant in lizards [5]. The high alpha cell predominance in lizards is not understood. A similar observation has been found in ducks, which also have high levels of alpha cells in the pancreas. In ducks and other avian species the alpha cells and elevated levels of glucagon are thought to play a very significant role in the maintenance of blood sugar [6]. However, more research is necessary to better understand the glucagon and insulin balance in reptiles, and the significance of alpha cells and glucagon in the lizard pancreas.

Studies on various species of reptiles have shown that there is a great deal of variation in the pancreatic islet morphology between different reptile orders [7]. Generally, four major cell types are present in the reptile endocrine pancreas: insulin (B), glucagon (A), somatostatin (D), and pancreatic polypeptide (PP or F) cells [4]. It appears that reptile insulin, glucagon, somatostatin, and pancreatic polypeptide crossreact with antisera raised against mammalian insulin, glucagon, somatostatin, and pancreatic polypeptide. The majority of studies done on the reptile endocrine pancreas utilized these mammalian-based antisera [4].

In another report the comparative morphology of the endocrine pancreas was studied in 11 species of lacertid lizards [8]. The study found that the endocrine islets always contain primarily three cell types: A-, B-, and D-cells, and only occasional F-cells. However, F-cells and D-cells were found to be much more abundant in the exocrine pancreatic parenchyma than A- and B-cells. These F- and D-cells were often associated with blood capillaries. The F- and D-cells may be influencing pancreatic exocrine function, therefore supporting the hypothesis that—as with other vertebrates—the reptiles' islet hormones may have a local action within the exocrine pancreas along with systemic action [8].

In two chelonian species and one species of lacertid lizard a complex reptilian gastroenteropancreatic endocrine system was described where glucagon-, insulin-, and somatostatin-containing cells were identified (immunocytochemically) in open-type gastroenteropancreatic cells of the digestive tract. In this study of the freshwater turtle *Mauremys caspica*, insulin-IR cells were found in both the gastric and intestinal mucosa. In the lizard *Lacerta lepida* insulin-IR cells were found in the large intestine [9]. As is evident from these studies, not all islet tissue may be present within the pancreas itself, and as more reptile species are studied, a great deal of variation will likely be found in the location of pancreatic islet tissue and the location and abundance of the specific endocrine cell types. Generalizations for species other than those studied should be made with caution.

Clinically, this information is valuable, as it indicates the importance of submitting the entire pancreas, spleen, and perhaps even portions of the gastrointestinal tract for histopathologic analysis to avoid missing the sites of islet concentration. Pancreatic biopsy may not be as useful a tool to evaluate islet presence or activity because the limited tissue available for ante mortem analysis may or may not be representative. In a case report involving a Chinese water dragon (*Physignathus cocincinus*), initial submission of pancreatic tissue revealed no endocrine islet tissue present [10]. The gross specimen was reevaluated and the splenic portion of the pancreas was submitted. Islet tissue was subsequently identified in this portion.

Diseases of the reptile pancreas

Hyperglycemia

Hyperglycemia is an uncommon clinical pathologic abnormality in reptiles. Presence of elevated blood glucose in reptiles has not been established as a consistent or specific indicator of pancreatic disease or diabetes mellitus. Elevations in blood glucose are more often related to other metabolic conditions, systemic diseases and physiologic variables. A better understanding of the reptile endocrine pancreas and continued research is necessary to determine the significance of hyperglycemia and its relationship to pancreatic disease.

Hyperglycemia versus diabetes mellitus

True diabetes mellitus has rarely been documented and is poorly understood in reptiles. Diagnosing diabetes mellitus in the reptile patient should be done cautiously. It is an uncommon condition, and there are metabolic and physiologic factors that can have a major influence on blood glucose. These factors must first be considered and ruled out. Persistent hyperglycemia is perhaps a better description for a reptile with elevated blood glucose values until further evaluation can determine possible etiologies.

Generally, diabetes mellitus results from a lack or deficiency of insulin, or an inability of insulin to transport glucose into cells. Reptile blood glucose appears to be regulated by insulin as it is in mammals. Therefore, the etiology for this disease in reptiles is most likely the result of the loss of pancreatic islet cells and thus insulin. Damage to the reptile pancreas from severe disease, trauma, or autoimmune disease are likely etiologies [3]. Campbell [11] believes that reptiles with a persistent marked hyperglycemia greater than 200 mg/dL with or without concurrent glucosuria are potential candidates for diabetes mellitus.

A diagnosis of diabetes mellitus in reptiles, according to Frye [3] and Mader [12], would start with persistent elevated blood glucose values above 300 mg/dL.

For the clinician to approach and assist the hyperglycemic reptile an understanding of the reptile endocrine pancreas and the influential factors that can affect glucose levels is imperative.

Variables that alter blood glucose in reptiles

Variations in blood glucose may be more common in reptiles due to variable metabolic rate, environmental influences and adaptations, and relative insulin resistance. Physiologic changes must also be considered, as they can seriously impact blood glucose levels. Of particular clinical importance in the reptile patient is stress-associated hyperglycemia, which is the result of glucocorticoid and epinephrine release. Stress-associated hyperglycemia has been reported in a number of reptile species [5,13–15].

Experimentally, an injection of glucose or epinephrine produces a prolonged increase in the blood glucose of lizards, snakes, tortoises, and caiman. Additionally, after these injections reptiles showed a much slower return to their normal blood glucose levels compared with mammals and birds [5].

More research is necessary to determine the roles of hormones from the pituitary, thyroid, and adrenal glands in the regulation of blood sugar in lower vertebrates.

A normal seasonal variation in blood glucose levels may occur in many species of reptiles [16].

Temperate reptiles generally have higher blood glucose levels during the breeding season [17]. When the peripheral blood glucose is higher during the breeding season the liver glycogen and the fat reserves are low. However, in the fall when most temperate species are increasing fat storage, peripheral blood glucose is low. Tropical reptiles, however, may not show seasonal blood glucose variations [17].

In a study involving captive Mediterranean tortoises (*Testudo graeca* and *T. hermanni*) blood glucose values were found to have a statistically significant peak in April and in May upon emergence from hibernation [18]. This sudden peak of glucose may act as a trigger for arousal, and may be associated with a rise in environmental temperature. This elevated blood glucose provides a readily available energy source for tortoises until they begin to feed again. In another study involving hibernating reptiles the level of glycemia in the winter was inversely correlated with the amount of glycogen stored in the liver [19].

Fresh-water turtles were found to show a marked hyperglycemia when diving, which is probably related to increased anaerobic metabolism [20].

Other studies indicate reptiles may exhibit hyperglycemia of several days' duration after a meal [21]. In a laboratory setting, 2 months of starvation at approximately 70°F (21°C) was necessary before blood-sugar levels become hypoglycemic [21].

In contrast, in a study on savannah monitors (*Varanus exanthematicus*) starvation altered B-cell constituents, resulting in a reduction in the biosynthesis of insulin-like material and subsequent hyperglycemia [22]. However, the other endocrine hormones of the pancreas were well conserved and seemingly unaffected. The changes found in the endocrine pancreas of these monitors were similar to the changes seen in animals treated with the drug alloxan [22].

Alloxan is a cytotoxic drug that specifically causes degeneration of B-cells, resulting in an experimental diabetic condition analogous to acute juvenile diabetes in humans.

In a study where several species of skinks were treated with alloxan electron microscopic observations of the pancreas showed similar changes to those seen with starvation in the above study in monitor lizards [21,23]. The changes included specific degenerative damage to B-cells characterized by rupture of the granular membrane and a subsequent reduction in the quantity of insulin-like material present followed by necrosis. In contrast, the A cells in these lizards were not affected. This may be clinically relevant in cases of sick reptiles that have been anorexic for extended periods. The inanition may result in damage to B-cells with a subsequent reduction in insulin and possible clinical hyperglycemia.

These research experiments have clinical significance because they show that many variables such as season, body and liver condition, and physiologic variables such as anaerobic metabolism and feeding can affect blood glucose values in reptiles. More research is needed to determine

whether feeding affects on glucose are related to the type of food, rate of digestion and absorption, variations of temperature at which these processes occur, or basic metabolic differences among reptiles.

Cases of hyperglycemia reported to the literature

In 35 years of practice Frye [24] found that the majority of spontaneous diabetes mellitus cases he was presented with exhibited similar histopathologic findings. The lesions most commonly seen included selective hydropic degeneration, amyloid deposition, or other noninflammatory destruction of pancreatic islets. In fewer cases he found postinflammatory endocrine and exocrine tissue fibrosis secondary to severe necrotizing pancreatitis. Frye [3] reported a red-eared slider (*Trachemys scripta elegans*) with blood glucose of 830 mg/dL. The turtle had been anorexic for 3 weeks, and presented in a semistupor. It was treated with NPN zinc insulin injections for 3 days, but the treatment failed to reduce the blood glucose level. The turtle died, and no histopathologic lesions were identified in the pancreas except there was granular degeneration and a reduction in islet tissue. In another slider with hyperglycemia that subsequently died, histopathology revealed a pancreas that lacked islet tissue and contained areas of fibrosis suggestive of previous severe inflammation and necrosis [3]. In a desert tortoise (*Xerobates agassizi*), Frye [3] described a severe granulomatous pancreatitis. No islet tissue could be identified, and the tortoise was found to have a primary gastrointestinal adenocarcinoma. In another case, Frye [25] was presented with a 12-year-old male red-eared slider turtle (*Trachemys scripta elegans*) in a moribund state. It had a history of progressive lethargy, anorexia (2 weeks duration), and muscle weakness. It lived with other turtles but was stunted in size. Physical exam findings were unremarkable except for a severely weakened state. Radiographs were normal. The blood glucose was dramatically elevated at 610.7 mg/dL. Supportive care was provided, but the turtle died several hours after admission. Gross necropsy revealed the total absence of visceral or omental fat and a markedly enlarged pale gray, friable liver. The histopathologic diagnosis included pancreatic islet atrophy, hepatic hydropic degeneration with reduction of reserve glycogen, and chronic glomerulonephritis. Based on these findings a diagnosis of spontaneous diabetes mellitus was made. The diabetic state in this turtle was advanced with a concomitant hepatopathy and nephropathy.

Another case of persistent hyperglycemia was reported in a 4-year-old male Chinese water dragon (*Physignathus cocincinus*) [10]. The dragon had a reduced appetite, weight loss, and mandibular symphyseal bone exposure and osteomyelitis. The blood glucose value was 794 mg/dL. Additionally, this lizard had a profound glucosuria on a urine sample that was collected by cystocentesis (3+; >10,000 g/L; 1000 mg/dL) and proteinuria (4+; >20,000 g/L; >2000 mg/dL).

Efforts to treat the dragon with regular insulin using five times the feline dosage, 0.0971 IU intramuscularly, did not reduce the hyperglycemia. Glipizide, given orally at 0.25 mg and then subsequently 3 mg, and then octreotide acetate at 6 mg did not appear to have an effect on the hyperglycemia. The water dragon died, and histopathology revealed severe diffuse hepatic lipidosis and moderate cortical tubular lipidosis of the kidney. Pancreatic islets were found to be indistinct, so additional sections were obtained from the splenic portion of the pancreas. In this portion, islet tissue was identified in the more centralized pancreatic tissue. The islets appeared to have random, minimal cell pyknosis, and immunohistochemical stains specific for human insulin failed to discern the presence of insulin.

Autoimmune disease

A case of autoimmune pancreatitis resulting in clinical hyperglycemia and suspected diabetes mellitus has been described in a western pond turtle, *Clemmys m. marmorata* [24]. A wild-caught adult male Pacific pond turtle presented for acute lethargy and anorexia. Bloodwork indicated dramatically elevated blood glucose of 842 mg/dL. No insulin was administered to this turtle, which subsequently died. Histopathology revealed that a wide cuff of lymphoplasmacytic leukocytes and the occasional large histiocytic macrophage surrounded every pancreatic islet [24]. No normal pancreatic islet tissue could be found. The hyperglycemia in this case was thought to be due to the absence of any intact and functioning islets in the pancreas. The nature of the cellular infiltrate in this case would support an immune-mediated etiology for the destruction of the islets, and thus the likely inability for this turtle to secrete insulin.

Functional islet cell tumor

A single report of a functional pancreatic glucagonoma in a rhinoceros iguana *Cyclura c. figgensi* has been published [26]. In this case, an adult female Great Exuma Island ground iguana was presented for depression and reluctance to bear weight on its rear limbs for a 2-week duration. Blood work was obtained at presentation and hyperglycemia was found (987 mg/dL). Along with supportive care a single dose of regular zinc insulin (1 unit) was given intramuscularly. The iguana died the second day after presentation. Necropsy findings included degenerative arthritis of the left-tibial articulation and thickening of the small bowel mucosa.

On histopathology examination of hematoxylin- and eosin-stained pancreatic tissue revealed round to irregularly shaped islets with edges bordered by fine fibrovascular stroma. The stroma separated the islets from the pancreatic exocrine cells, which possessed a coarser granular cytoplasm.

Immunohistochemical staining of these tissues with specific antiglucagon reagents from monoclonal antirabbit glucagons revealed variable-sized

islands of pancreatic endocrine cells. A diagnosis of an alpha-cell glucagonoma was made based on clinical hyperglycemia and the morphologic and specific immunohistochemical staining characteristics of the pancreatic islet cells of this iguana.

Paraneoplastic syndrome

Several cases have been published where a persistent hyperglycemia was associated with neoplasia. Paraneoplastic syndrome may exist in association with certain neoplasms and/or certain organ pathology. Any associations may become more evident as more cases are reported.

A case of hyperglycemia was reported in a bearded dragon with hepatocellular carcinoma [27]. In this case, a 6-year-old female inland bearded dragon (*Pogona vitticeps*) presented for lethargy and anorexia and persistent hyperglycemia. Several blood glucose samples were drawn several weeks apart (604 mg/dL, 576 mg/dL). A canine/feline insulin radioimmunoassay was performed on this lizard after it presented with the second persistent elevated glucose. The plasma insulin result was 1.8 ng/dL. A control sample was drawn from a clinically normal female bearded dragon in the same owners collection. The plasma insulin result for this lizard was 13.1 ng/dL. The author made a tentative diagnosis of diabetes mellitus based on persistent hyperglycemia and a low plasma insulin result [27].

This dragon was taken to surgery and a firm 2–3-mm nodule was noted in the pancreas and the liver contained a firm 5–7-mm spherical mass of the right ventral liver lobe. Biopsies of these abnormalities were taken at surgery but the lizard died 24 hours after surgery and necropsy revealed several more masses involving the liver. Histopathology revealed a pancreatic hyperplasia characterized by proliferating exocrine acini and fibrovascular stroma. Pancreatic acini were lined by well-differentiated pancreatic epithelium containing numerous zymogen granules with no evidence of neoplasia. Multifocal hepatocellular carcinoma was the diagnosis for the extensive liver masses.

Immunoperoxidase staining for insulin, glucagon, somatostatin, chromogranin, and neuron-specific enolase was performed on multiple sections of the liver and pancreas. The liver carcinoma did not show any positive staining, but the pancreatic islets contained cells that stained positive for insulin, glucagon, and somatostatin.

The author concluded that diabetes mellitus and a paraneoplastic syndrome were the two most likely causes of the hyperglycemia in this case [27]. No insulin therapy was initiated in this patient to confirm an insulin deficiency.

In another case in a desert tortoise (*Xerobates agassizi*) that died with hyperglycemia, a severe granulomatous pancreatitis was found at necropsy and histopathology. In this case, no islet tissue could be identified in the pancreas and the tortoise was also found to have a primary gastrointestinal adenocarcinoma [3].

Approach to the hyperglycemic reptile patient

Historical presentation and clinical signs

Because blood glucose values in reptiles can be affected by physiologic and environmental factors it is important to obtain a complete history. Husbandry information obtained should include housing, lighting, heating, diet, vitamin and mineral supplementation, and feeding history. Any recent changes in the environment, previous medical history, and treatment with any drugs should also be reviewed.

Seasonal cycles including hibernation and reproduction, both past and present, are important variables that may reflect on blood glucose and thus should be noted.

Reptiles with hyperglycemia are often presented for a variety of nonspecific clinical signs, including anorexia, weight loss, lethargy, and severe depression. Polyuria and polydipsia may be present, but is not a consistent clinical sign [3].

Physical examination

Physical examination findings may also be nonspecific as described for the clinical signs above, but may include loss of muscle mass, weakness, loss of righting reflex, stupor, and severe depression. Some reptiles may present overconditioned or obese.

Blood glucose sampling

As was previously discussed in this article, external factors will influence the blood biochemistry of reptiles more so than mammals and birds. These factors must be considered when attempting to interpret results of blood sampling. Plasma glucose values for normal reptiles varies among species and by nutritional status, season, age, sex, and environmental conditions [11]. Additionally, there are few controlled studies to establish the meaning of specific changes in the biochemical profile of reptiles. Thus, interpretation of reptilian clinical chemistry values has not yet achieved the level of accuracy that is seen in small mammals and avian patients [11].

In general, blood glucose values for normal reptiles are between 60–100 mg/dL [3,11,12]. In one study, a range of blood glucose values in various species of normal appearing reptiles was found to be between 30–205 mg/dL, with average values usually in the range of 90–100 mg/dL [5].

A blood sample may reveal an elevation in blood glucose, but because there are a number of external variables that can affect blood glucose values, one elevated value may have limited clinical significance in the sick reptile. However, multiple sampling and or serial sampling can be valuable in confirming true hyperglycemia, establishing general trends, and helping to determine the clinical progression of the reptile patient. Also, if other reptiles of the same species, in the same collection—and kept under similar

environmental conditions—could be sampled, it would help to establish a baseline for reptiles in this group. These values would be more valuable and specific to this patient than published reference ranges.

Glucosuria

Glucosuria may be noted in reptiles with persistent hyperglycemia [10].

Reptile urine is typically not sterile, as it is exposed to contents of the proctodeum and coprodeum, and in many species, it is actually held within the terminal colon before being released. More research is needed to understand the effects of fecal contamination on urine and urate testing for the presence of glucose.

Blood insulin

Blood insulin levels may prove to be useful in an attempt to differentiate between diabetes mellitus and other causes of hyperglycemia.

More research is necessary to establish normal values for reptiles and to validate the use of mammalian insulin radioimmunoassays in reptiles. However, it appears that reptile insulin has a high affinity for human and mammalian insulin receptors, and may favorably react with mammalian radioimmunoassays. Specifically, in one study it was found that the affinity of python insulin for human insulin receptors was very similar to that of human insulin [28]. Furthermore, a mammalian insulin radioimmunoassay was used with apparent success in a hyperglycemic bearded dragon [27].

Further research has revealed that there may be specific physiologic factors, such as inanition or starvation, that may result in a reduction of immunoreactive insulin content in the pancreas of reptiles. A study in savannah monitors (*Varanus exanthematicus*) found that prolonged starvation resulted in a reduction of immunoreactive insulin content in the pancreas [22]. It is not clear, though, if this decreased immunoreactivity of insulin specifically or directly correlates with hypoinsulinemia and hyperglycemia.

Ketosis

Ketoacidosis is a concurrent clinical condition seen commonly with diabetes mellitus in mammals. This condition may or may not be present in reptiles; however, experimentally, total pancreatectomy resulted in an increase in ketone production. One study in lizards found a significant rise in ketone bodies 3 weeks after pancreatectomy, and continued to elevate through the eighth week when the experiment ended [29].

Pancreatic biopsy

Pancreatic evaluation and biopsy at exploratory surgery or during celioscopy may prove to be a useful tool for diagnosing pancreatic disease ante mortem (Fig. 2). Unfortunately, in most cases of persistent hyper-

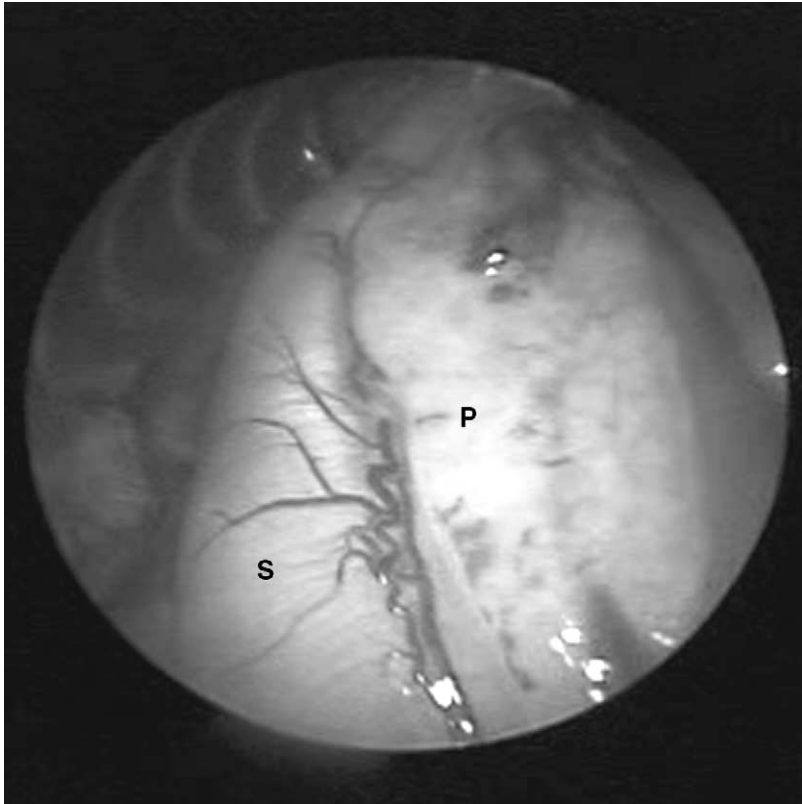


Fig. 2. Endoscopic evaluation of a normal pancreas in the green iguana, *Iguana iguana*. Note the Stomach (S) on the left and the lighter colored Pancreas (P) on the right. Endoscopic biopsy may have its limitations when diagnosing specifically endocrine disease of the pancreas, as the islet tissue tends to be found in focal areas that may not be readily accessible. (Courtesy of Stephen J. Hernandez-Divers, Athens, GA, with permission.)

glycemia reported, a biopsy was not performed due to the moribund nature of the patient.

An important consideration when using a pancreatic biopsy as a diagnostic tool is to be aware of the location of the islet tissue in the pancreas. For example, in the savannah monitor all of the islet tissue is concentrated in the splenic portion of the pancreas. This localized concentration of islet tissue in some reptiles may make it difficult to assess islet tissue on an ante mortem biopsy alone.

Necropsy and histopathology

Because of the severity of the reptile's condition at presentation, most documented cases of persistent hyperglycemia in reptiles have been investigated at necropsy.

A review of the anatomy of the pancreas and the primary location of islet tissue in reptiles is important to ensure the evaluation of the pancreatic islet tissue on the gross necropsy and histopathology. For example, in the more advanced snake species (family Colubridae) the majority of endocrine cells are actually found within the spleen [1].

As more reptile species are studied, a great deal of variation will likely be found in the location and abundance of pancreatic islet tissue and specific endocrine cell types. Thus, generalizations should be made with caution. To be clinically thorough it is imperative to submit the entire pancreas for histopathologic analysis.

On histopathology there are characteristic lesions seen in cases of suspected pancreatic insulin deficiency. Typically, the islets of Langerhans may display atrophic characteristics or may be entirely absent. When present, the islets of insulin-producing cells may reveal hydropic degenerative changes, hyalinization, amyloid deposition, and a loss of intracytoplasmic granulation of beta cells [3,24]. In reviewing the cases of persistent hyperglycemia described in the literature, some similarities in changes or involvement of other organs is apparent. The liver appears to play a significant role in many of these cases. The diagnosis of liver disease is becoming more common in reptiles with the use of improved and more specific diagnostic tools including bile acid values, ultrasonography, and endoscopic biopsy. As more cases of liver disease are documented and described, it may become evident that liver pathology may play a primary role in influencing hyperglycemia. Liver histopathologic changes associated with persistent hyperglycemia in reptiles include hydropic degeneration, hepatocellular lipidosis, and centrilobular necrosis [3]. Hepatic lipidosis is commonly associated with diabetes mellitus in mammals. Hepatic lipidosis is a common condition seen in reptiles, and has been associated with persistent hyperglycemia. However, it has not been shown to have a consistent association with persistent hyperglycemia in reptiles [3,10,12,24,30]. Histopathologic changes associated with hyperglycemia have also been found in the kidneys of reptiles, and typically include chronic glomerulonephritis and interstitial nephritis or nephrosclerosis [3,10]. The diagnosis of kidney disease is also becoming more common in reptiles with the use of improved and more specific diagnostic tools including ultrasonography and endoscopic biopsy. As more cases of renal disease are described, it may become evident that kidney pathology may influence glucose levels in reptiles.

Management of hyperglycemia

Due to the multifactorial causes of hyperglycemia, management of the syndrome is both difficult and poorly documented. Anecdotal reports on individual cases exist, but very little information on clinical treatment is available. Indeed, no controlled clinical studies have been published, and all treatments are empirical at this time. Reported cases and treatment in the

literature are summarized, as well as academic research. Rough guidelines can be extrapolated from this information to initiate treatment.

Experimental research

Total pancreatectomy in the tegu lizards, *Tupinambis teguixin* and *Tupinambis rufescens*, caused an initial hypoglycemia lasting approximately 2 weeks, and was followed by an intense and permanent diabetic hyperglycemia [29]. In the false viper snake (*Xenodon merremii*) a total pancreatectomy resulted in an initial hypoglycemia that lasted 3–4 days, followed by a permanent intense hyperglycemia [29,31].

Similar to some reptiles, ducks were observed to have a marked hypoglycemia following total pancreatectomy [6]. Hypoglycemia in birds has been attributed to the suppression of glucagon, which would typically keep blood glucose at a normal level. More work needs to be done with reptiles, however, to firmly establish that neutralization of glucagon causes hypoglycemia and neutralization of insulin causes hyperglycemia.

Research indicates that compared with mammals and birds, reptiles respond very slowly to the administration of mammalian insulin [5].

Reptiles, especially lizards, seem to tolerate larger doses of mammalian insulin than mammals and birds. In one study, lizards were treated with insulin at 5–10 IU/ kg body weight. No deaths occurred at this dose, and only one lizard died after receiving an injection of 100 IU/kg [29]. This insulin resistance in lizards is most likely due to insulin stimulating the central nervous system, which may have both direct and indirect effects on regulation of carbohydrate metabolism [5].

In another study, lizards were experimentally pancreatectomized to induce hyperglycemia. Three weeks later they were injected with 100 IU/ kg body weight of insulin. The lizards showed a decrease in blood glucose of 150 mg/dL below the initial diabetic level 3 days after the injection. Recovery of the hyperglycemic level was established on the seventh day [5].

In yet another study, experimentally induced hyperglycemic lizards were treated with intracelomic injections of insulin to determine the effect. As the dose of insulin was increased it caused a greater reduction in blood glucose, but also the larger dose caused a more prolonged effect. A dose of insulin of 10 IU/ kg body weight resulted in a reduction in the blood glucose of 43 mg/ dL below the initial level. This effect lasted for 3 days before the blood glucose returned to the initial elevated value. A dose of insulin of 20 IU/kg body weight caused a decrease in blood glucose of 80 mg/dL below the initial level in 2 days, with a recovery of the initial level on the third day. A dose of insulin of 100 IU/kg body weight caused a decrease of 93 mg/dL below the initial level on the third day after the injection, and the normal level was not recovered until the seventh day. No deaths occurred [29].

Based on published research, turtles and snakes seem to be much more sensitive to insulin than lizards. If 1–2 IU/kg body weight of mammalian

insulin is administered to turtles or snakes, hypoglycemia of several hours duration usually occurs [32].

Alligators tend to be more like lizards, and are less sensitive to insulin. In one study, the minimum blood glucose-affecting dose for alligators was approximately 10 IU/kg body weight [5,33].

One unusual finding from using high insulin doses was an initial increase in glucose followed eventually by the expected decrease [29].

Although lower doses of insulin in reptiles did not elicit a hyperglycemic phase before the hypoglycemic response, larger doses—10 IU/kg in chelonians [5], 100 IU/kg in the crocodilians [33], and more than 100 IU/kg in lizards [5]—consistently did. The exact mechanism for these initial hyperglycemic responses are not well understood. Factors unrelated to the pancreas, such as an adrenal medullary response, direct or indirect nervous system effects, or other endocrine effects may be responsible.

Treatment

Initially, management should focus on making a diagnosis of what may be causing the persistent hyperglycemia. Is it related to underlying metabolic disease, neoplasia, physiologic circumstances, or true diabetes mellitus?

The clinician must evaluate the entire patient, review all the variables that may affect blood glucose levels, and rule out these influences. Physical examination, biochemical analysis, radiology, ultrasonography, endoscopy, and surgery are all modalities that can be used.

Persistent hyperglycemia should be established using serial sampling, and attempts made to rule out underlying diseases and environmental or physiologic influences prior to the use of insulin or other glucose regulating drugs.

Based on the clinical evaluation supportive care including hydration, alimentation, liver support, and other appropriate chemotherapeutics as indicated should be initiated.

Even with a review of the clinical cases and published research, much work is still needed to provide clinically relevant information. To date, no clinical trials or even long-term management of individual cases with the use of mammalian insulin or other glucose-regulating agents has been reported in reptiles. Variables such as dosage, frequency of dosing, dramatic physiologic differences among reptiles, and their unique adaptations to their environments (xeric, tropical, aquatic, etc.) will make it difficult to establish standardized dosing regimens for reptiles.

If all factors indicate that the patient is truly a strong candidate for diabetes mellitus—an uncommon diagnosis in reptiles—and the clinician feels some glucose-regulating agent must be initiated, then a *starting point* for regular mammalian insulin may be:

Lizards and crocodilians 5–10 IU/kg body weight IM
every 24–72 hours

Snakes and chelonians 1–5 IU/kg body weight IM
every 24–72 hours

These doses are empirical, and should be adjusted based on response to therapy and continued serial sampling of blood glucose. Clinicians must be aware that intracelomic injections often took 24–48 hours before any response was seen, so a change in a dosing regimen should be considered only after looking at serial sampling for several days. Clinicians must continue to document and report cases of persistent hyperglycemia, treatment regimens, and responses to therapy to improve the clinical management of these cases.

Other diseases of the pancreas

Pancreatitis

Pancreatitis is defined as inflammation of the pancreas, and in reptiles is typically the result of the presence of bacteria or metazoan parasites. Pancreatic damage results in the release of pancreatic enzymatic secretions into the glandular parenchyma and subsequent auto digestion [3].

Unfortunately, in reptiles the diagnosis is usually made at necropsy. Frye [3,24] has found that lesions are typically characterized by an intense inflammatory reaction with a focal to diffuse mixed inflammatory infiltrate into one or more lobules of the pancreas. The inflammatory cells may center on the pancreatic ducts, or they may be randomly distributed around the glandular parenchyma of the pancreas.

Acute necrotizing pancreatitis

Similar to the disease seen in other animals, this is the result of severe necrotizing inflammation of the pancreas caused by the escape and activation of digestive pancreatic enzymes. Acute necrotizing pancreatitis in reptiles has been associated with trauma to the pancreas, abscesses or pyogranulomatous conditions, migrating helminthes, and obstruction of the pancreatic outflow ducts by masses or calculi. Depending on the location and severity of the inflammation, both the exocrine and the endocrine portions of the pancreas may be involved [3].

Clinical signs for acute pancreatitis and pancreatic necrosis may include indications of pain in the coelomic cavity such as stinting and holding the coelom off the ground, anorexia, lethargy, and depression. Clinical signs associated with hyperglycemia may also be seen if there is significant damage to endocrine tissue. Diagnosing this disease may be difficult, as

clinical signs may be vague and specific diagnostic tests are not well established. Elevations in the white blood cell count may or may not be seen.

Clinical chemistry values would be expected to show evidence of severe pancreatic damage, and may include elevations of lipase and amylase. Unfortunately, the validation of lipase and amylase has not been established for reptiles. In one study in the green iguana (*Iguana iguana*), amylase was found in high concentration exclusively in the pancreas; however, they found a very wide range of plasma values in the study, concluding that its clinical application may be limited [34]. More research needs to be done to determine the potential reliability of these enzymes. Hyperglycemia may also be found if the islet tissue is damaged.

Radiology, ultrasonography, endoscopy (celioscopy), and exploratory celiotomy are other modalities that may be useful in diagnosing pancreatitis. Biopsy of the affected pancreatic tissue followed by histopathology may be the only way to truly diagnose this disease ante mortem (Fig. 2). Disease progression is often rapid, severe, and may be fatal. Most cases of pancreatitis reported in reptiles have been diagnosed and described at postmortem examination. Gross lesions noted at necropsy will vary with the severity of the condition and the duration of the process, but may include evidence of pancreatic digestion of surrounding tissues. Associated fatty tissue that comes in contact with these released pancreatic lipases will appear soapy in appearance as saponification of the fat occurs. Other tissues may also be damaged by digestion from the released and activated pancreatic proteases resulting in autodigestion. Adhesions may be evident between the damaged pancreas and adjacent damaged viscera.

On histopathology, a severe leukocyte response is typically found that is exudative, and consists of a mixed population of heterophils and mononuclear cells [3].

Pancreatic fibrosis

Pancreatic fibrosis or chronic fibrosing pancreatitis is a common histopathologic finding in reptiles [3]. A variety of inflammatory and other acquired conditions can lead to damage of pancreatic exocrine or endocrine tissue. The damage typically results in the movement of fibrocollagenous connective tissue into the parenchyma of the pancreas where lesions can be focal or diffuse. Clinical signs for chronic fibrosing pancreatitis will be associated with the amount of damage to the pancreas and whether there is involvement of exocrine and endocrine tissue. Physiologic chemistry findings may provide evidence for loss of endocrine or exocrine function. Diarrhea or gastrointestinal signs may be noted with the loss or damage of exocrine tissue. Hyperglycemia could be noted with endocrine tissue involvement. On histopathology, the disease is characterized by fibroblasts and fibrocytes invading the interlobular septa. An inflammatory leukocyte component may be present if there is still active pancreatitis.

Specifically in snakes a chronic fibrosing pancreatitis has been reported with an undetermined etiology [35].

Clinical management of acute and chronic forms of pancreatitis would include supportive care such as fluid therapy, assisted alimentation, antimicrobials, and pain management. Unfortunately, due to the difficulty in diagnosing these cases the disease is often not identified until necropsy and subsequent histopathology. However, with the use of improved diagnostic tools to evaluate the pancreas including radiology, ultrasonography, and endoscopic evaluation with biopsy, the ability to make an ante mortem diagnosis may allow opportunities to better understand and apply effective therapeutic regimens.

Pancreatic ductal calculosis

Complete obstruction of the ductal outflow of a portion of the pancreas may result in either atrophy or auto digestion and resulting necrosis. Frye [3] describes two specific cases, one in a northern diamondback terrapin (*Malaclemys t. terrapin*) where complete obstruction of the interlobular ducts by amorphous crystalline material resulted in a loss of pancreatic tissue including islet tissue. In another case involving a Pacific rattlesnake (*Crotalus viridis oreganos*) the majority of the pancreatic duct system was occluded, which resulted in chronic pancreatitis followed by pancreatic fibrosis [3]. No islet tissue was found during the microscopic examination of the step-sectioned pancreas in this case. Based on these histopathologic findings, endocrine related deficiencies would have been expected in this patient, but no demonstration of hyperglycemia was made in this snake prior to death.

Pancreatic parasitic diseases

Pancreatic helminthiasis

Trematodes and nematodes have occasionally been found to migrate into pancreatic tissue, and are typically seen at histopathology [3]. Generally they appear to cause minimal damage to the pancreas. Occasionally associated pathology involving micro-organisms such as bacteria may be seen with aberrant migration of these parasites, and may result in damage to both exocrine and endocrine tissue. Typically these organisms will be walled off and phagocytized. The diagnosis is usually made at necropsy and histopathology by finding the helminthes or their characteristic ova on cross section.

Endoscopic biopsy could also be utilized to identify these organisms if lesions were noted during a celioscopic exam.

Pancreatic coccidiosis

Cryptosporidiosis involving the pancreas and biliary ducts has been reported in corn snakes (*Elaphe guttata*) [36].

Another report described intranuclear coccidiosis in two radiated tortoises (*Geochelone radiata*) with histopathologic evidence of pancreatitis. Nephritis, hepatitis, and enteritis with similar intranuclear coccidiosis were also found in these tortoises [37].

Pancreatic viral diseases

Intracytoplasmic inclusion bodies in snakes consistent with the boid inclusion body disease virus are often found on histopathology in the pancreas of snakes affected with this retroviral disease [35,38].

Pancreatic neoplasia

Pancreatic neoplasia is uncommon in reptiles. Pancreatic adenocarcinomas have been reported in snakes, and are typically carcinomas or adenocarcinomas of the acinar or ductular epithelium [39,40]. A Komodo dragon (*Varanus komodoensis*) was reported to have a pancreatic islet cell tumor along with several other neoplasms including a colonic carcinoma, a metastatic adenocarcinoma involving the spleen, and a thyroid adenoma [41].

A single report of a functional pancreatic glucagonoma in a rhinoceros iguana *Cyclura c. figgensi* has been published [26] (see above in hyperglycemia associated cases).

Summary

A great deal of research is still needed to better understand the reptile pancreas especially with regard to diagnosis and treatment. However, vigilant clinicians and pathologists have important roles to play in expanding our knowledge base in this field, and are encouraged to share their findings through publications and presentations.

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