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Review

Blood Glucose in Birds: Another Way to Think About "Normal" Glycemia and Diabetes Mellitus in Animals

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Abstract: Birds exhibit naturally high blood glucose concentrations, a physiological trait that, unlike in mammals, does not lead to typical pathological consequences such as diabetes mellitus. This review explores the unique features of glucose metabolism in birds, with a particular focus on the anatomy and function of the avian pancreas, the roles of key hormones such as insulin and glucagon, as well as the distinctive mechanisms of glucose absorption and utilization. Evidence suggests a dominant role of glucagon over insulin, along with adaptations such as insulin resistance and antioxidant defenses, which may contribute to birds' apparent resilience to hyperglycemia-related complications. Despite these adaptations, cases of diabetes mellitus have been reported, primarily as secondary to other pathologies, including pancreatitis, hemochromatosis, infections, and toxicities. Diagnosis remains challenging due to interspecies variability and the lack of standardized assays. Treatment, mainly via insulin therapy, has shown mixed outcomes, often limited by the underlying disease severity. This review highlights the need for species-specific diagnostic tools and a deeper investigation into the pathophysiology of glucose regulation in birds, aiming to improve clinical outcomes, develop standardized therapies, and ultimately broaden the perspectives of comparative endocrinology.

Keywords: avian physiology; insulin; blood glucose regulation; avian pancreas; insulin resistance; glucagon; diabetes mellitus; hyperglycemia; comparative endocrinology

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1. Introduction

Birds exhibit a distinctive metabolic profile characterized by naturally elevated blood glucose levels that, in mammals, would typically be considered pathological [1]. Despite

this, they rarely exhibit the typical complications associated with chronic hyperglycemia, such as those seen in diabetic humans and mammalian animals [2]. This paradox has led researchers to consider birds as a "negative model" for diabetes mellitus, suggesting that their physiological adaptations may offer insights into resistance mechanisms against glucose-induced cellular damage [3–5].

The avian pancreas has unique anatomical and functional features, including a predominance of glucagon-secreting cells and limited responsiveness to glucose-stimulated insulin release [6–8]. Furthermore, birds often display insulin resistance, particularly in skeletal muscle, and rely more on glucagon and alternative metabolic pathways to regulate energy balance [9]. These metabolic adaptations are supported by enhanced antioxidant systems that mitigate oxidative stress, a major consequence of chronic hyperglycemia in mammals [1,9].

Although diabetes mellitus is relatively uncommon in birds, it has been documented across a wide range of avian orders, including Accipitriformes, Anseriformes, Columbiformes, Galliformes, Passeriformes, Piciformes, Psittaciformes, and Sphenisciformes [7,10–19]. Among these, psittacine birds (parrots) appear to be overrepresented in the literature, with macaws (*Ara* species), cockatiels (*Nymphicus hollandicus*), and toucans (*Ramphastos* species) reported most frequently. This overrepresentation is likely due to their popularity as companion animals and the increased likelihood of veterinary examination and diagnosis compared to wild avian species. Despite the taxonomic diversity reported, no clear sex or age-related predispositions have been observed. Overall, the prevalence of diabetes mellitus in birds remains low, and further research is needed to clarify species-specific susceptibilities and risk factors.

In birds, diabetes typically manifests secondary to other pathological conditions such as pancreatitis, hemochromatosis, or viral infections [4]. Diagnosis and treatment are further complicated by interspecies variability and the lack of validated diagnostic tools, underscoring the need for targeted species-specific approaches.

This review aims to explore the unique aspects of blood glucose regulation in birds, discuss the clinical presentation and challenges in diagnosing avian diabetes mellitus, and highlight the broader implications for comparative endocrinology.

2. Materials and Methods

Bibliographic Search Description

The literature search was conducted using leading research databases relevant to animal science and veterinary medicine, including "Web of Science", "PubMed", and "Google Scholar". The final selection of articles was completed by March 2025. The search employed various combinations of the following keywords: *diabetes mellitus*, *birds*, *pancreas*, *endocrine*, *disease*, *glucose*, *hyperglycemia*, and *regulation*. Initially, the relevance of each study was assessed based on its title. Articles deemed potentially suitable underwent a preliminary screening by evaluating their abstracts. This selection phase was independently carried out by two researchers with expertise in the field. Articles selected by both were automatically included in the next stage, while those chosen by only one researcher were reviewed jointly to reach a consensus. At this stage, 29 manuscripts were included in the review. In total, approximately 80 English-language publications were evaluated, from which 21 were found to be closely aligned with the focus of this paper. These selected studies were then categorized into two primary thematic areas: (1) anatomy, physiology, and pathology, and (2) clinical cases.

3. Anatomy of the Avian Endocrine Pancreas

In birds, as in other species, the pancreas, especially its endocrine component, plays a leading role in regulating blood glucose levels through the production of hormones such as insulin, glucagon, and somatostatin. However, it is not the only tissue with a significant influence on blood glucose regulation. The pancreas originates from the endoderm and, more specifically, from the anterior portion of the embryonic digestive tract. In birds, it develops from three papillae present in the wall of the primitive gut, one dorsal and two ventrolateral, located to the right and left [20] that appear approximately 56–67 h after the onset of embryonic development and begin to fuse around day 7 [21]. The dorsal papilla is the main source of insulin-, glucagon-, and somatostatin-secreting cells, while pancreatic peptide-secreting PP cells derive from the ventral papillae [20]. The exocrine component finally develops later in embryogenesis [22].

The pancreas is located within the mesoduodenum, positioned between the two segments of the duodenum that form the duodenal loop. It is generally pale in color, with shades ranging from yellow to pink. Its size varies across species, measuring approximately 140 mm in length in chickens, ducks, and geese, and around 80 mm in pigeons [6]. The avian pancreas is anatomically divided into three distinct lobes: dorsal, ventral, and splenic. Additionally, a fourth lobe, considered part of the ventral lobe, is identifiable exclusively in Galliformes, such as quails and chickens [8].

Due to its anatomical structure, the exocrine secretion produced by the pancreas is conveyed into the duodenal lumen through three distinct ducts [23].

The endocrine component of the pancreas consists of the islets of Langerhans, which, as in mammals, are composed in turn of α, β, δ, and PP cells, secreting glucagon, insulin, somatostatin, and pancreatic peptide, respectively. These islets of endocrine tissue are most concentrated in the splenic lobe [24]. Under microscopic observation, three types of pancreatic islets can be identified in birds: light (B-islets), dark (A-islets), and mixed islets, which differ in shape, size, and staining characteristics. Light islets appear clear following classical staining techniques (e.g., Heidenhain's iron haematoxylin) and are composed primarily of β- and δ-cells. Dark islets are generally larger and consist mainly of α-cells and δ-cells [23]. Some bird species do not exhibit a clear distinction between light and dark islets but instead possess mixed islets, which are composed predominantly of β-cells along with fewer α- and δ-cells. These mixed islets are randomly distributed throughout the pancreas and have been reported in several wild bird species, such as the Australian wedge-tailed eagle (*Aquila audax*) [25].

PP cells are located at the periphery of the pancreatic islets or scattered within the exocrine component, especially within the dorsal and ventral lobes. These cells secrete avian pancreatic polypeptide, which inhibits gastrointestinal motility as well as gallbladder and pancreatic secretions [26].

The unique characteristic of the avian pancreas is the numerical predominance of glucagon-secreting cells over insulin-secreting cells, with a ratio of approximately 2:1 [22]. Additionally, compared to the mammalian pancreas, somatostatin-secreting δ cells are also more abundant [24].

Previous studies have confirmed the presence of neuroendocrine cells secreting biotin, chromogranin, serotonin, and neuropeptide Y (NPY) [21,27].

The islet tissue in birds is highly vascularized, receiving arterial blood from the pancreaticoduodenal artery and draining through the pancreaticoduodenal vein [6]. Innervation, however, appears to be less pronounced in birds compared to mammals, with most nerve fibers targeting the exocrine acinar tissue rather than the endocrine component. Within the endocrine tissue, α cells are more innervated than β cells, and δ cells are more innervated than either of the other cell types [24].

4. Blood Glucose Regulation in Birds

4.1. Blood Plasma Glucose Levels

Birds exhibit a unique profile in glucose metabolism and regulation compared to other vertebrates. Glucose, a simple hexose monosaccharide, is the primary circulating carbohydrate in avian blood [2]. Unlike mammals, birds maintain physiologically elevated blood plasma glucose levels, which are, on average, 1.5–2 times higher than those observed in similarly sized mammals (e.g., rabbits: 76–148 mg/dL, rats: 50–135 mg/dL) [2,28]. Remarkably, this state of persistent hyperglycemia is not associated with pathological outcomes in birds, as it often is in mammals. In fact, hyperglycemia-related diseases are exceedingly rare in birds, leading some researchers to propose them as a negative model for diabetes [29].

Another distinctive feature of this class of vertebrates is the high inter-individual variability in blood glucose concentrations, even among individuals of the same species [30,31]. This wide range complicates both the diagnosis of disorders that may involve altered glucose homeostasis and the detection of glucose changes in response to dietary or pharmacological interventions.

4.2. Glucose Transporters (GLUTs)

In general, glucose is transported across cell membranes by specific glucose transporters (GLUTs), after which it is phosphorylated and metabolized through glycolysis and the Krebs cycle. Alternatively, it can be stored as glycogen in the liver and muscles or converted into fatty acids, primarily in the liver [6]. In the bloodstream, glucose circulates either freely dissolved in the plasma or transported into erythrocytes via GLUTs. However, in birds, erythrocytes progressively lose their ability to uptake glucose as they mature, and thus, in adults, nearly all circulating glucose remains dissolved in the plasma [32].

Before examining glucose uptake by various tissues and its regulatory mechanisms, it is essential to introduce the integral membrane proteins responsible for glucose transport in the bloodstream. Glucose transporters (GLUTs) are a family of facilitative transport proteins that mediate the bidirectional movement of glucose across cell membranes [33]. Phylogenetic analyses classify GLUTs into three classes: Class I (GLUT1–4), Class II (GLUT6, 8, 10), and Class III (GLUT5, 7, 9, 11) [34]. These transporters display tissue-specific expression and exhibit distinct kinetic and regulatory properties. In mammals, extensive research has defined the roles and distribution patterns of various GLUTs, and impairments in these glucose transporters have been linked to metabolic disorders such as insulin resistance and diabetes [34]. Studies have provided some insight into GLUTs' function in avian species; however, current knowledge remains incomplete [34]. Although most GLUT isoforms are expressed in birds, their specific physiological roles and tissue distribution are still not fully understood. Notably, chickens lack orthologs of mammalian GLUT4 and GLUT7 [2]. In particular, GLUT4 is one of the most important glucose transporters in mammals, as its function is insulin-dependent, and it plays a key role in glucose uptake by adipose and muscle tissue during the postprandial phase. However, until recently, its expression had not been identified in any avian species [2,34–40]. Genetic analyses suggest that the GLUT4 coding sequence is present in the avian genome but is located within a rapidly evolving region, where repeated guanine–cytosine sequences make its detection challenging [41]. In the same study, GLUT4 was identified in the muscle tissue of domestic chickens; however, its precise role and, in particular, its sensitivity to insulin remain to be elucidated [41].

Overall, it is important to note that, as in mammals, protein expression, including that of GLUT transporters, is dynamic and can vary over time. Although the role of insulin-dependent GLUT4 in birds remains unclear, studies in Galloanserae (chickens, ducks,

turkeys) have shown that GLUT1 and GLUT12 expression increase in response to rising insulin levels [42,43]. However, a similar correlation has not yet been reported in Neoaves (house sparrows and mourning doves).

4.3. Intestinal Glucose Absorption

Glucose absorption in the avian intestine is mediated by specific transmembrane transport proteins. The Sodium-Glucose Linked Transporter 1 (SGLT1) plays a central role in actively co-transporting sodium and glucose from the intestinal lumen into enterocytes. Once inside the cells, glucose is transported across the basolateral membrane into the bloodstream via the facilitative transporter GLUT2 [44–53].

From a nutritional standpoint, glucose represents the primary dietary sugar and is absorbed in the small intestine both through membrane transporters and via paracellular diffusion pathways [54]. Interestingly, the reliance on these mechanisms varies with body size among bird species. In smaller birds (<180 g), paracellular glucose absorption is more prominent [55] and appears to compensate for their relatively shorter intestinal tracts compared to non-flying mammals [56], offering an energy-efficient strategy for nutrient uptake. Conversely, larger birds, which have proportionally larger gut sizes, rely more on transporter-mediated absorption and less on paracellular pathways [57]. Supporting the role of paracellular uptake in small birds, studies have shown that inhibitors of facilitated transport, such as flavonoids, do not significantly alter blood glucose concentrations in these species [56].

In summary, the avian gastrointestinal tract is relatively short compared to that of mammals of similar size [4], with a low volume to help minimize body weight for flight. As a result, birds consume small amounts of food frequently and rapidly extract energy and nutrients to sustain their high metabolic rate [26]. To meet these physiological demands, they compensate for the reduced intestinal transit time and the smaller surface area available for nutrient absorption through a predominant reliance on passive paracellular glucose absorption, a mechanism particularly evident in small passerines, as demonstrated by several studies [56,58–66].

4.4. Glucose Utilization by Tissues

In birds, as in mammals, glucose serves as a critical energy source for various tissues, with the brain exhibiting particularly high rates of glucose utilization [6]. Indeed, glucose is the primary energy source for mammalian brains, which consume significantly more glucose than other tissues relative to their mass [67]. In birds such as the mourning dove (*Zenaida macroura*), brain tissue has been shown to consume more glucose compared to other tissues, although, unlike mammals, birds may have different mechanisms of glucose utilization [38]. In birds, glucose uptake in nervous tissue occurs primarily via the GLUT1 and GLUT3 transporters [2,35,36,68]. Moreover, cerebrospinal fluid, in accordance with the high glycemic levels, contains a very high concentration of glucose, even higher than that found in mammals [69]. Additionally, astrocytes in the brain are capable of accumulating glycogen as a form of energy reserve [70]. Several studies have also demonstrated marked utilization of glucose by brain tissue for processes such as learning and memory [71,72], similar to the glucose utilization observed in mammals [73].

During fasting or intense flight, glycogen serves as an important energy source for skeletal muscle [74–77]. Supporting this, higher blood glucose levels have been observed in migratory birds compared to sedentary ones [78]. However, despite these elevated blood glucose levels, during endurance flight, the primary energy source for muscle metabolism shifts to fatty acids [79,80]. Other studies have shown marked resistance to insulin-dependent glucose uptake in skeletal muscle tissue, leading many to consider birds

as insulin-resistant [4]. In contrast, in mammals, skeletal muscle tissue represents one of the major sites of glucose uptake, due to the presence of an abundant pool of GLUT1 transporters, which are constitutively expressed in the sarcolemma, and GLUT4, which are translocated to the cell membrane in response to food intake or exercise [81–83]. Unlike mammals, in birds, muscle glucose uptake is mediated by GLUT1 transporters located at the tissue barrier in contact with the bloodstream [35,36,39,68,84,85].

4.5. The Role of Insulin in Avian Glucose Regulation

The role of insulin in regulating blood glucose levels in birds has been investigated in several studies, which generally report a hypoglycemic effect in both Galloanserae and Neoaves [4]. However, this may be an oversimplification, as other research suggests that the insulin response is also influenced by the age of the animal. For instance, a hypoglycemic effect was observed in adult mourning doves, although it was not associated with increased glucose uptake by skeletal muscle [38]. In contrast, an in vitro study on skeletal muscle cells from 1-day-old chicks showed increased glucose uptake in response to insulin [36]. This suggests that insulin can stimulate cellular glucose uptake under certain conditions, probably related to the species and age of the birds considered. However, the underlying mechanism remains debated, as birds appear to lack insulin-dependent GLUT4 transporters [2,34–37,39,85].

Satoh [9] hypothesized that insulin resistance evolved in theropods (a subgroup of bipedal, primarily carnivorous dinosaurs) during the Mesozoic era as an adaptive response to a hypoxic atmosphere. Interestingly, birds, modern descendants of theropod dinosaurs, have developed several adaptations to low-oxygen environments, including the development of air sacs to enhance respiratory efficiency, nucleated erythrocytes, and the ability to increase hemoglobin concentration under hypoxic conditions. The evolution of insulin resistance could have allowed these animals to survive more effectively in oxygen-deprived environments by sustaining high metabolic rates and optimizing oxygen utilization for the oxidative phosphorylation of glucose [9]. In fact, maintaining high blood glucose levels reduces the need for insulin availability, as the resulting concentration gradient facilitates glucose uptake by cells.

In summary, birds evolved several adaptations to survive in oxygen-deficient environments. However, as atmospheric oxygen concentrations increased over time, the primary threat to their survival shifted to the heightened production of reactive oxygen species (ROS). To address this challenge, birds have developed a progressive upregulation of antioxidant metabolic pathways, including the constitutive activation of Nuclear factor erythroid 2-related factor 2 (Nrf2), a key factor involved in the regulation of transcription for antioxidant proteins [9].

4.6. Pancreatic Function and Hormonal Regulation

Over time, several studies have utilized pancreatectomy to assess the precise role of the pancreas in blood glucose regulation. In mammals, this procedure typically leads to significant hyperglycemia and diabetes mellitus due to insulin deficiency [26]. However, the outcome is different for birds. Instead of developing sustained hyperglycemia, only a transient increase in blood glucose is observed, which quickly returns to physiological levels [86–89]. In chickens, partial pancreatectomy has shown that the remaining pancreatic tissue compensates for the lost portion by increasing in volume [90]. In the carnivorous species *Bubo virginianus* (great horned owl), pancreatectomy appears to induce a state of hyperglycemia that rapidly leads to death of the animal [91]. In contrast, in geese, partial pancreatectomy results in hyperglycemia and hypoinsulinemia, along with a transient reduction in glucagon levels. This condition eventually progresses to hyperglucagonemia [92].

Additionally, it has been observed that some granivorous birds, such as mallard ducks, become hypoglycemic rather than hyperglycemic following total pancreatectomy [93].

These findings have led some researchers to propose that insulin plays a less prominent role in glucose regulation in granivorous birds than in mammals. They further suggest that diabetes mellitus in granivorous species may not be caused by abnormalities in plasma insulin levels [94].

In two recent studies, intravenous insulin and radiolabeled glucose were administered to measure tissue uptake in response to insulin stimulation. In the first study, porcine insulin was administered to 8-day-old *Gallus gallus* chicks. This resulted in a slight reduction in blood glucose, with increased glucose uptake in skeletal muscle and liver, while uptake was reduced in the brain [95]. In the second study, however, the administration of *Gallus gallus* insulin to adult mourning dove (*Zenaida macroura*) specimens showed no significant effects. Although there was a slight decrease in blood glucose, there was no notable glucose uptake in the muscle, liver, heart, kidney, brain, or other tissues [38].

To date, it is certain that insulin levels in the blood of chickens are approximately one-tenth of those found in rats, suggesting a possible scarcity of β-cells in the pancreas and reduced insulin production [96]. Additionally, the avian pancreas is resistant to glucose-induced stimulation of insulin production. According to Hazelwood [8], exposure to 27.5 mM glucose is required to induce a transient release of insulin in isolated pancreatic tissue, which lasts approximately 15–30 min.

Glucagon concentrations in the avian pancreas are approximately 8–10 times higher than those found in mammals, per unit mass, and its release is inhibited by glucose exposure [4]. Insulin appears to play a key role in the perception of glucose levels by α-cells, as exposure to both glucose and insulin leads to the inhibition of glucagon secretion [8].

In birds, glucagon plays a dominant role, as tissues are more responsive to its stimulation, leading to increased blood glucose levels through the activation of hepatic glycogenolysis, as well as the release of triglycerides, glycerol, and circulating fatty acids [8]. As in mammals, somatostatin produced by δ-cells in birds inhibits the release of both insulin and glucagon, while also slowing nutrient absorption [97].

In birds, the insulin/glucagon ratio is also regulated by somatostatin release, and it is approximately half the value observed in mammals [98]. This ratio determines whether a catabolic or anabolic state is maintained in the animal. In birds, the ratio generally favors a catabolic state, ensuring a constant supply of expendable energy to support their high metabolism, particularly during stressful conditions such as egg laying, fasting, and migratory flight [7].

4.7. Hyperglycemia and Oxidative Stress Resistance

Birds appear to defy prevailing theories of aging, as they often outlive mammals of comparable size despite exhibiting high blood glucose concentrations [2], elevated body temperatures, and exceptionally high metabolic rates [99,100]. Additionally, birds possess dense mitochondria and reach maturity later in life [100,101]. In many vertebrates, circulating glucose concentrations are negatively correlated with longevity; however, birds seem to have evolved adaptations that mitigate the potential oxidative stress associated with high blood glucose levels, thereby contributing to their extended lifespans [4].

Research has demonstrated that birds exhibit a strong resistance to oxidative stress, allowing them to prevent much of the cellular damage associated with their high metabolic activity [101,102].

In a study examining 325 species of birds from 18 different orders, no correlation was found between metabolic rate and longevity [103]. This discrepancy between the high rate of oxygen consumption for metabolic reactions and the relatively low amount of reactive

oxygen species (ROS) produced has been referred to as the "Bird Paradox" [9]. Several studies support this paradox, showing that although birds generally produce less ROS relative to their metabolism, they maintain higher concentrations of antioxidant factors. These include superoxide dismutase, glutathione peroxidase, vitamins E and C, and uric acid [103–109].

Volatiles also seem to exhibit a reduced rate of protein glycosylation, which in turn leads to a lower formation of advanced glycation end products (AGEs). AGEs are proteins or other molecules, such as lipids, that become glycosylated when exposed to high concentrations of glucose [29,100].

5. Diabetes Mellitus

Diabetes mellitus is an endocrine disorder characterized by a state of marked hyperglycemia, along with symptoms such as polyuria, polydipsia, and glycosuria [110]. The term "mellitus" originates from the Latin word for "honey-sweet," reflecting the sweet taste of urine that occurs when blood glucose levels rise and exceed the renal threshold for reabsorption, leading to glucose spilling into the urine [111].

There are two forms of diabetes mellitus:

- Type I (insulin-dependent) diabetes: This form results from the autoimmune-mediated destruction of pancreatic β-cells, leading to an absolute deficiency of insulin production. Genetic predisposition and environmental factors contribute to this process, causing a significant reduction in insulin secretion and subsequent hyperglycemia [112].
- Type II (insulin-independent) diabetes: This form is characterized by insulin resistance, which occurs when peripheral tissues fail to adequately respond to insulin [113]. Despite elevated blood glucose levels prompting increased insulin secretion, the tissues do not efficiently uptake glucose, resulting in sustained hyperglycemia. Insulin secretion is accompanied by the release of islet amyloid polypeptide (IAPP), also known as amylin. In humans, the aggregation of IAPP into amyloid deposits within the islets of Langerhans has been implicated in β-cell dysfunction and the progression of diabetes mellitus [114]. However, the presence of amyloidosis is not a prerequisite for diagnosing diabetes [115]. To date, pancreatic amyloidosis has not been reported in birds. Nonetheless, factors such as a high-fat diet, obesity, and genetic predisposition may predispose birds to developing diabetes mellitus [5].
- In addition to these two primary types of diabetes, there are at least two other recognized forms in humans: MODY (Maturity Onset Diabetes of the Young) and LADA (Latent Autoimmune Diabetes in Adults), with minor incidence [116].

As previously discussed, several physiological characteristics of birds make the development of diabetes mellitus relatively uncommon. Birds are naturally adapted to maintaining high blood glucose levels, which makes the onset of this condition less likely in this class of vertebrates. When diabetes occurs, its pathogenesis is often unclear [7]. In particular, the role of insulin in birds, especially granivorous species, appears to be limited in regulating blood glucose levels. As a result, insulin is considered to play only a minor role in the development of diabetes in these animals [9].

Currently, the classification of diabetes based solely on the presence or absence of insulin secretion is being progressively replaced. Instead, increasing attention is given to the insulin-to-glucagon (I/G) ratio, which is now considered a more accurate indicator of the disease in birds [117].

5.1. Etiopathogenesis

As in other animals, diet plays a key role in the development of diabetes mellitus in birds, particularly in parrots. Although birds naturally exhibit a certain degree of insulin

resistance, obesity resulting from a diet that does not meet the species' specific nutritional needs can be a significant predisposing factor [117].

The pathogenesis of diabetes mellitus in birds remains largely unclear, with most of our current understanding derived from a limited number of documented cases. In some of these reports, histopathological changes have been observed in the endocrine portion of the pancreas, suggesting that structural abnormalities may play a role in the development of the disease. For example, in an African Gray parrot specimen with a diagnosed lymphocytic pancreatitis, histopathological analysis revealed infiltration of lymphocytic cells within the islets of Langerhans, causing significant damage and leading to a marked reduction in circulating insulin levels [18]. Similarly, in a red-tailed hawk that exhibited clinical signs suggestive of diabetes, a post-mortem anatomopathological examination revealed cellular vacuolization within the islets of Langerhans, further supporting the potential involvement of pancreatic endocrine disruption in the disease process. Additionally, a case of pancreatic neoplasia has been reported in a cockatiel, highlighting another possible pathological trigger for diabetes in birds. In other cases, the development of diabetes has been associated with conditions involving intracellular iron accumulation. Specifically, diffuse hemochromatosis has been identified in both the liver and pancreas; however, the exact pathogenetic mechanism linking iron overload to the onset of diabetes remains unclear and warrants further investigation [15]. In a particularly well-documented case, a definitive form of type I diabetes was diagnosed. Histopathological examination revealed not only the presence of a lymphocytic infiltrate consistent with pancreatitis but also the complete absence of both α- and β-cells within the islets of Langerhans, confirming severe endocrine pancreatic damage [11].

It is also important to consider that infectious diseases may contribute to the onset of diabetes in birds. For instance, avian influenza has been shown to affect the pancreas, leading to varying degrees of tissue degeneration. Similarly, infection with *Chlamydophila psittaci* may also result in pancreatic damage. Supporting this hypothesis, a study involving 28 turkeys experimentally infected with two low-pathogenic avian influenza virus strains revealed the presence of mild to severe pancreatic lesions upon histopathological examination [118].

In this context, Phalen et al. [13] reported a case of diabetes mellitus in a cockatiel, in which post-mortem examination revealed a herpesvirus infection that had caused chronic pancreatitis, ultimately leading to the development of diabetes.

Beyond infectious causes, toxicological factors such as heavy metal poisoning may also play a role in the onset of diabetes. For example, zinc poisoning has been implicated in a case involving a domestic goose [14]. Excess zinc appears to interfere with the exocrine function of the pancreas, leading to degeneration and atrophy of the organ [119,120].

These findings overall suggest that, in avian species, diabetes mellitus often develops secondary to an underlying pathological process, with pancreatic inflammation or damage potentially playing a more significant role in its pathogenesis compared to mammals.

The current literature indicates that the conventional classification of diabetes mellitus into type I and type II, as applied in mammals, does not adequately reflect the disease presentation in avian species [121]. Birds have unique physiological mechanisms for glucose regulation, relying more on glucagon and somatostatin than on insulin, which complicates the application of traditional mammalian diabetes classifications. Although some avian cases may exhibit features resembling type I or type II diabetes mellitus, similar to those observed in dogs and humans, accurate classification remains difficult. Therefore, understanding the underlying pathophysiological mechanisms driving persistent hyperglycemia is ultimately more important than assigning a specific diabetes mellitus type when formulating treatment strategies [121].

5.2. Reporting

To date, it is not possible to define a typical clinical presentation of diabetes in birds, as the existing case reports involve a very limited number of individuals, which is insufficient to establish reliable statistics. Furthermore, no studies have been conducted to determine whether factors such as sex, age, genetic predisposition, or species may influence susceptibility to the disease in birds [7].

5.3. Clinical Signs

In birds exhibiting polyuria, polydipsia, weight loss, and polyphagia, diabetes mellitus should always be considered as a potential differential diagnosis. Additional signs such as depression, regurgitation, and anorexia may also be present, often in association with other underlying conditions [117].

It is particularly important in avian patients to distinguish between diarrhea and polyuria, as the two are often confused. Polyuria refers to an increased volume of urine and is frequently noted by the owner, who may observe that the bird is wetting the bottom of the cage more rapidly than usual. In contrast, diarrhea involves an increase in the liquid component of the feces, resulting in poorly formed droppings or droppings in which feces, urine, and urates are not clearly distinguishable [7].

5.4. Diagnosis

An initial indication of diabetes mellitus in birds can arise from clinical symptoms, which were discussed in detail in the previous section, as well as the presence of clinical signs such as hyperglycemia and glycosuria [117].

In birds, normal blood glucose levels typically range from 9.9 to 19.4 mmol/L (180–350 mg/dL). However, levels exceeding this range are not necessarily diagnostic of diabetes, as stress can also cause transient hyperglycemia. It is generally only extremely elevated values, such as those above 44 mmol/L (800 mg/dL), that are strongly suggestive of diabetes mellitus [117,122]. At these concentrations, the renal threshold for glucose reabsorption is surpassed, resulting in the presence of glucose in the urine, which can be detected using reagent strips [7]. Therefore, when both hyperglycemia and glycosuria are present simultaneously, primary renal glycosuria can be ruled out, and a diagnosis of diabetes mellitus becomes more likely [123].

Another notable diagnostic clue is the presence of ketone bodies, which are typically absent in the urine of healthy birds. The detection of ketonuria, therefore, provides additional support for a diagnosis of diabetes mellitus [7].

The use of additional diagnostic tests, commonly employed in mammals, such as blood assays for insulin, glucagon, fructosamines, and β-hydroxybutyrate, has also been reported in the literature. However, hormone assay results can be highly variable. This variability likely reflects differences in the pathogenesis of the disease across bird species and even among individuals within the same species.

These challenges complicate the establishment of standardized reference ranges for diagnosing more complex forms of diabetes. Nevertheless, the information obtained from these tests can still be valuable in guiding treatment decisions, particularly when choosing between insulin therapy and oral hypoglycemic medications [117].

Fructosamines are formed through the glycosylation of serum proteins, and their concentration reflects the average blood glucose levels over the lifespan of these proteins. In dogs and cats, this corresponds to a period of approximately 1–3 weeks, making fructosamines a useful indicator of glycemic control over that time frame [117]. In birds, however, the turnover of serum proteins is much faster, with an average lifespan of about three days. As a result, while the principle remains the same, fructosamine levels in birds

reflect blood glucose concentrations over a much shorter period. According to Gancz et al. [15], the physiological range of fructosamines in birds is between 113 and 238 µmol/L.

According to the same authors, β-hydroxybutyrate levels in healthy parrots range from 450 to 1422 µmol/L. The measurement of this metabolite, alongside fructosamines, has been used to assess the effectiveness of insulin therapy. However, it is important to note that the commercial kits used for measuring these hormones and metabolites have not yet been validated for avian species. Therefore, results should always be interpreted with caution.

Finally, since diabetes mellitus can be caused by other underlying conditions, it is important to accompany the previously mentioned assays with a thorough diagnostic evaluation. This includes a complete blood count, serum biochemistry, radiographic imaging, viral screening, and assessment of blood zinc levels. These tests can help identify or rule out other diseases that may be contributing to the development of diabetes [7]. In some cases, a pancreatic biopsy may be necessary. If pathological changes are observed, further investigation using immunohistochemical staining can help determine which pancreatic cell populations are affected [7]. This comprehensive approach not only allows for a definitive diagnosis of diabetes mellitus but also offers insight into its possible underlying causes.

5.5. Treatment

Management of diabetes involves not only insulin therapy but also the use of hypoglycemic drugs, appropriate dietary changes, maintaining a healthy body weight, and, when relevant, stopping medications that may contribute to elevated blood glucose levels [117].

5.5.1. Insulin Therapy

Evidence from various case reports [15,17,124] has shown that insulin therapy can be effective in birds. The treatment protocols are adapted from those used in mammals, with smaller bird species generally requiring higher doses relative to their body weight compared to larger birds [117].

In birds that appear depressed, dehydrated, anorexic, or exhibit vomiting, initial treatment should focus on stabilizing the patient through fluid therapy and assisted feeding. Once stabilized, any underlying conditions that could interfere with diabetes management should be identified and addressed as necessary [7].

Insulin therapy, either intramuscular or subcutaneous, should be initiated during hospitalization to closely monitor the patient's response. Ideally, a glucose curve should be measured, with blood glucose levels taken before treatment and every 2 to 3 h thereafter for up to 24 h to assess the patient's condition [7,123]. Gancz et al. [15] reported the successful use of porcine and bovine protamine-Zn insulin, which effectively controlled clinical symptoms associated with hyperglycemia for extended periods. Initial insulin administration should begin with a minimum dose of 0.1 to 0.2 IU/kg. Blood glucose levels should then be regularly monitored, and the dosage should be adjusted as needed to maintain glucose concentrations within a near-physiological range [7]. Once the patient is stabilized, long-acting insulin can be introduced, and with proper monitoring, this therapy can be continued at home.

In cases of diabetes without complicating pathological conditions, it may be appropriate to start treatment with long-acting insulin immediately. However, hospitalization is still recommended, even if the patient's initial clinical condition does not require it, as this allows for close monitoring of blood glucose levels [7].

The effective dosages described in the literature vary widely, ranging from 0.002 U/bird to 3 U/kg administered intramuscularly every 12 to 48 h, depending on the glycemic curve [125].

For very small dosages, it is recommended to dilute insulin in injectable water-based preparations, which can be stored in a refrigerator for up to 30 days.

Once the initial phase of treatment is complete and the patient is discharged, insulin therapy should be continued by the owner, provided they are compliant. The injections may be given at varying intervals, sometimes every 12 h, or with days between administrations. The goal of treatment is to eliminate the clinical signs and symptoms of diabetes, such as polyuria, polydipsia, and polyphagia.

For home-based monitoring of blood glucose levels, urine reagent strips can be used. In this case, therapy should aim to maintain mild hyperglycemia to prevent hypoglycemic crises and ensure that glucose remains detectable in the urine [7]. It is also recommended to test the urine a few times a day and closely observe the patient for signs of hypoglycemia, such as weakness, lethargy, and seizures. Additionally, all diabetic individuals should be monitored for the development of bacterial or fungal infections [117], as altered immune function has been observed in mammals with diabetes mellitus.

In the end, insulin therapy has shown variable results in the literature, which can be attributed to the wide range of underlying causes for the development of diabetes in birds. In some cases, it may even be suggested that any apparent "cure" is more likely due to the resolution of the primary disease process causing hyperglycemia or transient diabetes, rather than the insulin itself.

Furthermore, the use of various forms of insulin and differing dosages complicates the ability to make meaningful comparisons regarding the effectiveness of different treatment protocols.

5.5.2. Oral Hypoglycemic Therapy

As an alternative to insulin, glipizide, a hypoglycemic drug, may be considered for the treatment of diabetes. While this medication is commonly used for managing type II diabetes in humans and cats, its use in birds has shown highly variable results, with the desired outcomes being rarely achieved [7,14,16]. Glipizide works by stimulating insulin secretion from pancreatic beta cells; however, for this to be effective, the beta cells must still be functional [117]. In cats, glipizide is typically used only in cases of uncomplicated or mild diabetes [126].

Treatment protocols for birds typically involve doses of glipizide ranging from 0.3 to 0.5 mg/kg, orally, twice a day [16], 1 mg/kg, orally, twice a day [13,14], or even a 10 mg tablet dissolved in drinking water [7].

The objective of these treatment protocols is the same as that of insulin-based therapies: to reduce or eliminate the clinical symptoms and signs associated with diabetes mellitus.

As an alternative to glipizide, two cases in the literature describe the use of a synthetic somatostatin analogue to inhibit glucagon release from pancreatic alpha cells. However, in both cases, the desired outcomes were not achieved [12,124].

5.5.3. Adjustment of Dietary Regimen

As with mammals, dietary adjustments are also recommended for birds with diabetes mellitus. Feeding foods that are high in fiber and low in sugar and fat can help reduce body weight and minimize postprandial blood glucose fluctuations [7,123].

In two reported cases [15,19], transitioning to an iron-poor diet appeared to reduce the insulin dosage needed for effective disease management, though the underlying mechanism remains unexplored.

6. Discussion

In almost all cases, diabetes mellitus in birds is associated with damage to the pancreas. Due to the natural physiological insulin resistance in birds, the development of type II diabetes is less common compared to mammals.

While the available data are limited and insufficient to provide reliable statistics, it appears that smaller parrots are more prone to diabetes than larger species. Additionally, cases seem to be more frequent in granivorous or frugivorous birds than in carnivorous species.

An inadequate diet, particularly one with a high carbohydrate intake, is often a common factor in the development of diabetes. However, rather than being a direct cause, it is more of a predisposing factor.

In birds, diabetes is typically a secondary condition that arises due to other underlying diseases. These can include infectious diseases, neoplasms, heavy metal poisoning, or any other conditions that affect organs such as the pancreas and liver, which play key roles in blood sugar regulation.

In cases where biopsies or post-mortem examinations were performed, several types of alterations have been observed that could be linked to the secondary onset of diabetes, including:

- Lymphoplasmacytic pancreatitis
- Pancreatic adenocarcinoma
- Hepatic and pancreatic hemochromatosis
- Pacheco's disease (herpesvirosis in psittacines)
- Elevated hepatic zinc concentrations.

In only two reported cases in the literature [15,16], no significant lesions were found in the pancreas, which makes it even more challenging to understand the potential etiology and pathogenesis of diabetes.

The most common finding by far is lymphoplasmacellular infiltration, which is often sufficient to explain the onset of the disease. This infiltration is frequently associated with a depletion of the endocrine component and can be attributed to a form of pancreatitis, the underlying causes of which remain unclear. In this context, one of the most likely hypotheses is that pancreatitis develops as a result of an infection originating elsewhere in the body. *Chlamydophila psittaci* is frequently cited as a potential infectious cause, but PCR tests have consistently returned negative results. Other bacterial and viral infections could potentially lead to a similar clinical presentation, but once again, PCR testing has generally been negative, except for one cockatiel, in which herpesvirus associated with Pacheco's disease [13] and *Ara severa* [15] were found to be positive for herpesviruses.

From an etiological standpoint, it is difficult to pinpoint the most likely causes of diabetes in birds. However, it can be concluded that any condition capable of damaging the pancreas or liver may also contribute to the onset of diabetes.

In birds, an important question arises regarding the underlying cause of diabetes: given the predominance of glucagon over insulin, could an excess of glucagon be responsible for diabetes, rather than the typical insulin deficiency seen in mammals? In the three case reports that have investigated this issue, insulin levels were found to be below the lower limit of the physiological range [16,18,19]. However, in one of these cases, glucagon was also measured, and it was found to be similarly low, matching the insulin levels. This information does not rule out the possibility that hyperglycemia in cases of diabetes could be due to an excess of glucagon, as it was measured in only one individual. Therefore, although assay methods for these hormones are not yet validated or widely available for these species, the available data suggest that, regardless of glucagon levels, insulin concentrations are often reduced in individuals with diabetes.

Further in-depth studies in this area may help clarify this aspect, enabling us to better understand the hormonal imbalances that contribute to the onset of diabetes in birds.

Recently, even in mammals, the traditional classification of diabetes based on insulin deficiency or non-insulin deficiency is being increasingly replaced by the assessment of the insulin/glucagon (I/G) ratio [127].

While the etiopathogenesis of diabetes in birds remains open to interpretation, the diagnostic process itself is now well-defined.

During clinical examinations, the primary clinical signs of diabetes can be identified, including:

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Lethargy

Laboratory tests typically include:

- Hematocrit and complete blood count (CBC)
- Hematobiochemical analysis (with special attention to blood glucose levels, liver enzymes, and amylases, among others)
- Measurement of β-hydroxybutyrate
- Urinalysis to evaluate glycosuria and ketonuria
- Measurement of insulin and glucagon levels
- Endoscopy and pancreatic biopsy for histological examination

To establish an etiological diagnosis, specific molecular tests, such as PCR, can be used to detect the presence of pathogen genomes, whether bacterial or viral, that may be responsible for the disease.

These steps are not always essential for diagnosis; in most cases, clinical signs, blood glucose levels (which can be measured with a standard digital glucometer), and urinalysis using reagent strips are sufficient to confirm a diagnosis of diabetes.

If further investigations are possible, they can provide valuable additional information not only for confirming the diagnosis but also for selecting the most appropriate treatment protocol and assessing the patient's prognosis.

It is important to remember that other endocrine disorders can also cause clinical signs and hyperglycemia similar to diabetes. Therefore, additional tests are necessary to rule out other potential diseases.

Once diabetes is diagnosed, an appropriate treatment plan must be determined.

The value of endoscopic diagnostics becomes clear, as it enables biopsy samples to be taken to assess the pancreas's condition alongside insulin dosing. If these investigations cannot be performed, a hypoglycemic treatment approach can still be attempted, though one must anticipate the possibility of failure due to the drug's mechanism of action.

In the literature, the use of hypoglycemic medication has been reported in four cases [13–16]. In all four cases, the treatment was ineffective: one bird was euthanized, one died, and the other two passed away after subsequent attempts with insulin therapy. A necropsy was performed on two of these subjects, revealing significant pancreatic changes that likely explained the ineffectiveness of the hypoglycemic therapy [13,14]. In contrast, no major lesions were found in the other two subjects.

Insulin therapy, while effective in cases of both insulin deficiency and glucagon excess, is more complex and potentially dangerous when administered intramuscularly. Errors in dosing can lead to a fatal hypoglycemic crisis. Moreover, the insulin dosage is not fixed; it starts at a minimum and is gradually increased to control blood glucose and manage

diabetes symptoms. This process requires significant time and close monitoring, making it particularly challenging for pet owners to manage effectively.

Despite its potential, insulin therapy has not consistently shown positive results in the literature. In fact, the majority of investigated subjects do not survive, probably because they had significant pathological changes, often affecting not only the pancreatic tissue, which complicated diabetes management and impeded their survival [15].

If avian-specific insulin formulations were available, it is possible that treatment effectiveness and management could be greatly improved.

Ultimately, prognosis and success depend on the underlying cause of diabetes. The more severe the primary disease, the less likely it is that the individual will survive.

7. Conclusions and Future Directions

In the future, a more comprehensive understanding of the mechanisms behind blood glucose regulation in birds, along with the wider availability of accurate and reliable methods for insulin and glucagon assays in these species, will provide a clearer insight into the etiopathogenesis of diabetes.

More broadly, endocrine disorders in birds are generally rare and of limited relevance in daily clinical practice. However, diabetes presents a notable exception. According to the current literature, no case of primary diabetes has been identified in birds to date, which is not surprising given their unique physiological characteristics. Instead, the occurrence of diabetes appears to be consistently associated with other pre-existing conditions. This point is particularly significant because the search for an optimal treatment protocol, including the potential availability of an avian insulin product, may not be sufficient in these complicated cases. In fact, the treatment of diabetes cannot be viewed in isolation from addressing the underlying pathology that caused it. As seen in the cases reported in the literature, identifying the primary pathology is not always straightforward, and even when it is, its progression is often too advanced, with lesions too severe to be treated effectively. Consequently, in many cases, diabetes treatment was only temporarily effective, and the bird was either euthanized or died naturally.

This review underscores the necessity for a comprehensive approach, where the focus is not only on determining the ideal treatment protocol for diabetes but also on expanding our knowledge and improving diagnostic procedures to better identify conditions that may contribute to the development of the disease. In this context, and in alignment with modern scientific tools, transcriptomic data could be invaluable for elucidating the molecular mechanisms underlying glucose regulation and insulin signaling pathways in birds, offering insights into the development of metabolic disorders in avian species [128,129].

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