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Article: Pathophysiology of canine diabetes.
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139. Yki-Järvinen H: Glucose toxicity. Endocr Rev 13:415, 1922
140. Young DA, Deems RO, Deacon RW, et al: Effects of amylin on glucose metabolism and glycogenolysis in vivo and in vitro. Am J Physiol 259:E457, 1990
141. Young AA, Mott DM, Stone K, et al: Amylin activates glycogen phosphorylase in the isolated solus muscle of the rat. FEBS Lett 281:149, 1991
142. Young AA, Wang M-W, Cooper GJS: Amylin injection causes elevated plasma lactate and glucose in the rat. FEBS Lett 291:101, 1991
143. Young AA, Carlo P, Rink TJ, et al: 8-37hCGRP, an amylin receptor antagonist, enhances the insulin response and perturbs the glucose response to infused arginine in anesthetized rats. Mol Cell Endocrinol 84:R1, 1992
144. Young AA, Cooper GJS, Carlo P, et al: Response to intravenous injections of amylin and glucagon in fasted, fed and hypoglycemic rats. Am J Physiol 264:E943, 1993
145. Young AA, Rink TJ, Wang M-W: Dose response characteristics for the hyperglycemic, hyperlactemic, hypotensive and hypocalcemic actions of amylin and calcitonin gene-related peptide-1 (CGRPalpha) in the fasted, anaesthetized rat. Life Sci 52:1717, 1993
146. Young AA, Gedulin B, Gaeta LSL, et al: Selective amylin antagonist suppresses rise in plasma lactate after intravenous glucose in the rat—Evidence for a metabolic role in endogenous amylin. FEBS Lett 343:237, 1994
147. Zaidi M, Shankar VS, Huang CL-H, et al: Amylin in bone conservation. Trends Endocrin Metab 4:255, 1993

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PATHOPHYSIOLOGY OF CANINE DIABETES

Margarethe Hoenig, DMV, PhD

PATHOGENESIS OF DIABETES MELLITUS

The term *diabetes mellitus* (DM) encompasses etiologically unrelated diseases and includes many different causes for disturbed glucose tolerance. Characteristic for all types of diabetes is the impairment of insulin release from the pancreatic beta cells. Because of major problems with nomenclature, a classification system was developed in 1979[43] and revised in 1985[58] in which diabetes was divided into four groups: (1) insulin-dependent diabetes mellitus (IDDM); (2) non–insulin-dependent diabetes mellitus (NIDDM); (3) gestational diabetes; and (4) diabetes associated with certain syndromes or conditions (secondary diabetes). In dogs, diabetes usually is divided broadly into IDDM and NIDDM. Because the pathogenesis and clinical picture in some stages of the disease are quite different, they are discussed separately. Only a few studies have examined the mechanisms involved in the pathogenesis of diabetes in dogs. Much of the information presented in this article, therefore, is based on studies in humans and other in vivo or in vitro models of diabetes with the hope that it will stimulate investigations into the pathogenesis of canine DM.

GENERAL PRINCIPLES

Insulin is produced in the beta cells of the islets of Langerhans in the endocrine pancreas. The islets also contain glucagon-secreting alpha

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cells, somatostatin-secreting delta cells, and PP or F cells, which secrete pancreatic polypeptide. Recently, insulin-like growth factor (IGF) 2 immunoreactivity has been found in association with beta cells, whereas IGF 1 immunoreactivity has been found in association with glucagon-secreting cells. Both are thought to influence islet function in a paracrine manner.[33] Other peptides have been detected in the dog pancreas, such as synaptophysin and peptide YY[6, 52], whose role in islet function currently is not known. Cosecreted with insulin is islet amyloid polypeptide (IAPP), also called amylin. This recently discovered polypeptide is the principal constituent of islet amyloid.[46] Islet amyloid is the principal lesion in the endocrine pancreas of diabetic humans and cats. Although canine IAPP possesses the amyloidogenic sequence similar to humans and cats, dogs do not develop islet amyloidosis because most diabetic dogs have experienced islet destruction at the time of diagnosis.

Beta cells comprise approximately 60% to 80% of the islet. In dogs, the endocrine cells are arranged in a nonrandom distribution. Beta cells form a central core surrounded by a mantle of the other three cell types; this is similar to other species including humans.[5, 25]

IDDM

The etiologic concepts outlined for IDDM in humans include the combination of genetic susceptibility and immunologic destruction of beta cells.[32] Similarly, in some diabetic dogs (e.g., in a line of Keeshounds) diabetes clearly is a hereditary disorder.[31] In most cases, however, a genetic cause is more difficult to prove. In one study, poodles were identified to be at increased risk for the development of diabetes among some other less popular breeds, whereas Cocker Spaniels, German Shepherd dogs, Collies, and Boxers were at decreased risk.[38]

The most common pancreatic lesion in canine DM is a reduction in the number and size of islets[19, 42] and hydropic balooning degeneration of beta cells. In severe cases, islets cannot be detected.[42] In fewer cases, islets are still numerous; however, the beta cells also show degeneration and degranulation. Approximately 75% of beta cells must be destroyed before hyperglycemia is observed.[51] Similar to neurons, beta cells have little regenerative capacity.[1] The decrease in beta cell mass is associated with a total decrease in insulin secretion, and in most diabetic dogs insulin can no longer be measured.[28, 37]

In human patients with IDDM, tolerance to the pancreatic beta cells is lost and cellular and humoral immune responses to beta cell antigens are activated, leading to beta cell destruction.[48] IDDM has been described as a classic organ-specific autoimmune disease in which beta cells are destroyed by T-lymphocyte–mediated mechanisms; circulating autoantibodies are considered markers of the ongoing disease process.[14, 36] However, there is evidence in spontaneous animal models of diabetes and prediabetic humans that a non–lymphocyte-dependent phase procedes beta cell destruction by cytotoxic T lymphocytes.[24, 47] It has been proposed that external or internal environmental factors (chemicals, virus, nutritional factors, and so forth), which can destroy beta cells, lead to the release of beta-cell proteins.[45] These proteins are taken up by antigen-presenting cells of the monocyte-macrophage dendritic cell line in the islets; this process begins the production and secretion of cytokines. The action of interleukin-1 which is potentiated by tumor necrosis factor α, interferon, and possibly other cytokines is important. These cytokines are cytotoxic to beta cells through the induction of free radicals. Beta cell proteins are damaged by free radicals and presented to the immune system in a more antigenic form, thus initiating a self-perpetuating cycle. Free radicals are known to produce DNA strand breaks, which are followed by poly(ADP-ribose)polymerase activation and nicotinamide adenine dinucleotide (NAD) depletion, ultimately resulting in cell death. The islet cytotoxicity seems to be highly dependent on the functional state of the beta cells. It has been suggested that during the IDDM disease process, as some beta cells are destroyed, the compensatory increased activity of the remaining beta cells increases their susceptibility to cytokine attack.[41] IDDM is a polygenetic disorder, and each of the pathogenic processes are under genetic control. Based on this information, it has been proposed that in human IDDM common alleles of normal genes recurring in unfavorable combinations confer susceptibility to IDDM by encoding a complex phenotype. This phenotype is characterized by efficient antigen presentation, unbalanced cytokine production, and poor beta cell defense mechanisms. The severity of the autoimmune attack may be the most important determinant of outcome; limited beta cell proliferative capacity may be of less importance in the pathogenesis of IDDM. The honeymoon period, a period of improved insulin secretion and decreasing needs for replacement shortly after onset of clinical disease, may nevertheless represent a regenerative effort to improve beta cell function and meet the insulin demands. It indicates that beta cells are able to repair themselves after damage,[16] but possibly only early in the disease process. Because honeymoon periods are not a feature of canine diabetes, this might be another indication that canine diabetes really is diagnosed very late in the disease process when beta cell destruction already has overcome restorative mechanisms within the cell.

Clinically, a long asymptomatic period of beta cell autoimmunity, during which insulin secretory capacity is progressively lost, usually precedes the onset of IDDM.[15] This period, however, is characterized by the presence of autoantibodies that serve as predictive markers for the disease.[2, 4, 12, 15] Several islet cell autoantigens have been described that serve as targets for the islet autoimmune process in human IDDM and with improved techniques several more can be anticipated.[1, 4, 15, 45] The antibodies are directed against the cell surface, cytoplasmic beta cell components, or insulin. The multitude of antigens can be explained by the fact that beta cell proteins may not have been released from the beta cell in their native form but rather as denatured and more antigenic forms. The presence of more than one antibody greatly increases the risk of developing diabetes mellitus.

Little is known about pathogenic mechanisms in the dog that lead to the destruction of beta cells. It is likely that cytotoxic processes similar to those seen in other spontaneously diabetic animals and in human diabetes patients also play a role in canine diabetes. Anti-islet antibodies were first reported in dogs with diabetes and other endocrine diseases in 1985[20]; however, the tissue specificity was not tested at the time. In 1992, a qualitative assay for beta cell antibodies was described.[26] Using this assay, approximately 50% of diabetic dogs were found to have beta cell specific antibodies.[26] Although the antigen is unknown, it is not insulin. Even though antibody formation, which may imply that autoimmune phenomena, plays a role in the pathogenesis of canine diabetes, the infiltration of islets with lymphocytes rarely has been described in dogs.[19] This could be because of the fact that canine diabetes is not diagnosed as early as it is in man. Most cases of canine DM are presented with atrophy or fibrosis, both of which are observed as the endstage of IDDM in man. The diagnosis of diabetes in dogs usually is not made until the onset of symptoms with unequivocal hyperglycemia. In people, diagnosis may be made earlier, especially among first-degree relatives of individuals with IDDM, if they are tested for antibodies and alterations in insulin secretion on a regular basis. Recently, a dog with autoimmune hemolytic anemia also developed diabetes and was positive for beta cell antibodies.[17] Another case in which a dog developed antibodies to its own insulin and became diabetic has been studied by our group (unpublished data). Autoimmune mechanisms may be important factors in the development of canine diabetes. With an increased level of suspicion and awareness, early identification of canine diabetics may lead to the discovery of an autoimmune basis for the disorder.

NIDDM

NIDDM is a heterogeneous disorder characterized by hyperglycemia, insulin resistance, and impaired insulin secretion.[10] Of major importance in the genesis of diabetic hyperglycemia are beta cell function, hepatic glucose production, and insulin-mediated glucose uptake.[3, 10, 11] It remains controversial, however, whether insulin deficiency, insulin resistance, or a combination of the two represents the primary pathogenic process.[22] Deterioration of the early insulin response to glucose is a major feature of the transition from normal to impaired glucose tolerance. The extent to which this loss of insulin secretion reflects a major predisposing factor in the etiology of NIDDM is undetermined. It may also be secondary to glucose toxicity or amyloid accumulation.[22]

Frequently, NIDDM incorrectly is thought of as a disease with insulin hypersecretion and not impairment of insulin release. This is because early in the disease process (e.g., in obesity not complicated by glucose intolerance) there is indeed true hypersecretion of insulin, while glucose concentrations are still normal.[51, 57] As the disease progresses, however, insulin secretion becomes inadequate to control glucose concentrations and hyperglycemia ensues. If insulin secretion in NIDDM patients is measured they appear to hypersecrete insulin, especially during the sustained phase of release. When the insulin concentration is adjusted for the increase in glucose concentration, the insulin deficiency becomes obvious. This was demonstrated very elegantly by Ward et al who showed that when the acute response to the amino acid arginine was measured at different glucose concentrations in NIDDM patients and controls,[56] the insulin response was approximately eight-fold higher in the control compared with the NIDDM patient when the glucose was held constant at 350 mg/dL. If only the diabetic had been studied, one might have concluded that a greater amount of insulin was being released. It is now clear that hyperglycemia represents a way to compensate for the impaired islet function. As plasma glucose levels rise a greater stimulus is provided to the impaired islet in an attempt to overcome islet dysfunction.

Recently, it has been shown that with insulin, proinsulin and proinsulin-like peptides are cosecreted. In routine insulin assays both proinsulin and proinsulin-like peptides cross-react strongly with insulin and one has to be cautious in the interpretation of "hyperinsulinemia." With the development of specific assays[53, 54] it is possible to show that in the insulin-resistant patient without impaired glucose tolerance all hormones are increased and their proportions are maintained; however, the ratio of proinsulin and proinsulin-like molecules to insulin increases as the disease progresses. As plasma glucose concentrations rise, processing of des 32,33 split proinsulin to insulin becomes rate-limiting. It has been suggested that there is a fundamental impairment of insulin processing in NIDDM.[21] Some investigators propose that des 32,33 split proinsulin may measure the degree of exposure of beta cells to glucose.[22] In fact, the total concentration of proinsulin-like molecules in plasma from NIDDM subjects is one third to two thirds of the total concentration of insulin–like molecules.[23] Measuring the relatively biologically inactive proinsulin-like molecules as "insulin" could lead to the erroneous conclusion that a diabetic patient was insulin resistant rather than insulin deficient.

Different organs are important players in the pathophysiology of diabetes. The beta cell is one of them. Not only has it been shown that insulin processing is altered in NIDDM, it also has been shown that the beta cell glucose-sensing device is altered in NIDDM. Because the insulinotropic action of glucose depends on its capability to be metabolized in the beta cell to a step beyond pyruvate, NIDDM could be caused by a variety of defects. Five major candidates for altered beta cell glucose metabolism have been identified[34]: (1) site-specific defects may exist in either the transport of glucose across the plasma membrane of the beta cell[55]; (2) defective phosphorylation of glucose by glucokinase[7]; (3) an increase in dephosphorylation of glucose[29]; (4) a deficiency of mitochondrial enzymes, such as glycerophosphate dehydrogenase[18]; and (5) glycogen accumulation in response to high glucose concentrations.[35] It also has been proposed that alterations in fatty acid metabolism are important in the pathophysiology of NIDDM.[40]

Insulin regulates glucose homeostasis mainly by acting on the liver and muscle. In NIDDM, the impairment of insulin secretion together with insulin resistance at these target tissues causes reduced clearance of glucose and reduced suppression of glucose production. It has been suggested that impaired insulin release, hepatic insulin resistance, hyperglucagonemia, and an increase in free fatty acids all act on the liver to promote gluconeogenesis.[8] The increase in gluconeogenesis causes an increase in hepatic glucose production. As plasma glucose levels rise there is a compensatory increase in insulin secretion that must be great enough to overcome the insulin resistance. The poorer the islet function, the greater the degree of hyperglycemia that is necessary to compensate for insulin resistance. Impaired suppression of hepatic glucose production is a main contributing factor to hyperglycemia.

Based on insulin secretion studies after a glucose load, NIDDM is rare in dogs.[27] Most cases of NIDDM in dogs are observed with severe obesity.[39] In fact, a study examining the response to an intravenous glucose load in 35 obese dogs with fasting normoglycemia, found that increasing obesity correlated with the degree of deterioration of glucose tolerance.[39]

SECONDARY DIABETES

Diabetes caused by other conditions or found in increased frequency with other conditions (implying an etiologic relationship) constitutes a third subclass of diabetes: *secondary diabetes* (1). Conditions most frequently seen in dogs with this subclass of diabetes are endocrine disorders, such as hyperadrenocorticism[49, 50]; and progesterone-induced growth hormone abnormalities.[13, 44] These hormones oppose the action of insulin and cause insulin resistance. The glucose intolerance occurring secondary to endocrine disorders usually is of moderate degree and occasionally can be reversed by the treatment of the underlying disease. Hyperinsulinemia is characterized by a disproportionate increase in proinsulin; therefore, insulin measurements are not a reliable indicator of true insulin levels.[9] Diabetes secondary to acute pancreatitis is described in about 15% of all cases.[30] It is thought that the diabetes is caused by progressive destruction of pancreatic tissue.

SUMMARY

Diabetes is a fascinating disease complex. Although much progress has been made in the last three decades to unravel the mysteries behind its multifaceted expressions, much work lies ahead. In dogs diabetes is not identified until late in the disease process. Future research might be directed at identifying early markers of the disease as an aid to improving current modes of treatment.

References

1. Atkinson MA, Maclaren NK: Islet cell autoantigens in insulin-dependent diabetes. J Clin Invest 92:1608–1616, 1993
2. Baekkeskov S, Landin M, Kristenesen JK, et al: Antibodies to a 64,000 M human islet cell antigen precede the clinical onset of insulin-dependent diabetes. J Clin Invest 79:926–934, 1987
3. Beck-Nielsen H, Hother-Nielsen O, Vaag A, et al: Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: The role of skeletal muscle glucose uptake and hepatic glucose production in the development of hyperglycemia. A critical comment. Diabetologia 37:217–221, 1994
4. Bingley PJ, Bonifacio E, Gale EAM: Can we really predict IDDM? Diabetes 42:213–220, 1993
5. Bonner-Weir S, Orci L: New perspectives on the microvasculature of the islets of Langerhans in the rat. Diabetes 31:883–889, 1982
6. Bottcher G, Sjoberg J, Ekman R, et al: Peptide YY in the mammalian pancreas: Immunocytochemical localization and immunochemical characterization. Regul Pept 43:115–130, 1993
7. Chiu KC, Tanizawa Y, Permutt MA: Glucokinase gene variants in the common form of NIDDM. Diabetes 42:579–582, 1993
8. Consoli A: Role of liver in pathophysiology of NIDDM. Diabetes Care 15:430–441, 1992
9. Cook AK, Breitschwerdt EB, Levine JF, et al: Risk factors associated with acute pancreatitis in dogs: 101 cases (1985–1990). J Am Vet Med Assoc 203:673–679, 1993
10. DeFronzo RA: The triumvirate: β-cell, muscle, and liver: A collusion responsible for NIDDM. Diabetes 37:667–687, 1988
11. DeFronzo RA: Pathogenesis of type II (non-insulin dependent) diabetes mellitus: A balanced overview. Diabetologia 35:389–397, 1992
12. Dyrberg T, Poussier P, Nakhooda F, et al: Islet cell surface and lymphocyte antibodies often precede the spontaneous diabetes in the BB rat. Diabetologia 26:159–165, 1984
13. Eigenmann JE, Eigenmann RY, Rijnberk A, et al: Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly. Acta Endocrinologia 104:167–178, 1983
14. Eisenbarth GS: Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med 314:1360–1368, 1986
15. Eisenbarth GS, Verge CV, Allen H, Reweres MJ: The design of trials for prevention of IDDM. Diabetes 42:941–947, 1993
16. Eizirik DL, Sandler S, Palmer JP: Repair of pancreatic β-cells. Diabetes 42:1383–1391, 1993
17. Elie M, Hoenig M: Canine immune-mediated diabetes mellitus. A case report. Journal of the American Animal Hospital Association, in press
18. Fernandez-Alvarez J, Conget I, Rasschaert J, et al: Enzymatic, metabolic and secretory patterns in human islets of type 2 (non-insulin-dependent) diabetic patients. Diabetologia 37:177–181, 1994
19. Gepts W, Toussaint D: Spontaneous diabetes in dogs and cats. A pathological study. Diabetologia 3:249–265, 1967
20. Haines DM, Penhale WJ: Autoantibodies to pancreatic islet cells in canine diabetes mellitus. Vet Immunol Immunopathol 8:149–156, 1985
21. Halban PA: Proinsulin processing in the regulated and the constitutive secretory pathway. Diabetologia 37(suppl 2):S65–72, 1994
22. Hales CN: The pathogenesis of NIDDM. Diabetologia 37 (suppl 2):S162–168, 1994
23. Hales CN, Barker DJP: Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Diabetologia 35:595–601, 1992
24. Hanenberg H, Kolb-bachofen V, Kantwerk-Funke G, Kolb H: Macrophage infiltration precedes and is prerequisite for lymphocytic insulitis in pancreatic islets of prediabetic BB rats. Diabetologia 32:126–134, 1989
25. Hawkins KL, Summers BA, Kuhajda FP, Smith CA: Immunohistochemistry of normal pancreatic islets and spontaneous islet cell tumors in dogs. Vet Pathol 24:170–179, 1987

26. Hoenig M, Dawe DL: A qualitative assay for beta cell antibodies. Preliminary results in dogs with diabetes mellitus. Vet Immunol Immunopathol 32:195–203, 1992
27. Kaneko JJ: New perspectives on canine diabetes mellitus. Calif Vet 33:24–25, 1979
28. Kaneko JJ, Mattheeuws D, Rottiers RP, Vermeulen A: Glucose tolerance and insulin response in diabetes mellitus of dogs. Journal of Small Animal Practice 18:85–94, 1977
29. Khan A, Chandramouli V, Östenson C-G: Evidence for the presence of glucose cycling in pancreatic islets of the ob/ob mouse. J Biol Chem 264:9732–9733, 1989
30. Kahn SE, Horber FF, Prigeon RL, et al: Effect of glucocorticoids and growth hormone treatment on proinsulin levels in humans. Diabetes 42:1082–1085, 1993
31. Kramer JW, Klaassen JK, Baskin DG, et al: Inheritance of diabetes mellitus in Keeshond dogs. Am J Vet Res 49:428–431, 1988
32. Lernmark A: Molecular biology of type 1(insulin-dependent) diabetes mellitus. Diabetologia 28:195–203, 1985
33. Maake C, Reinecke M: Immunohistochemical localization of insulin-like growth factor 1 and 2 in the endocrine pancreas of rat, dog, and man, and their coexistence with classical islet hormones. Cell Tissue Res 273:249–259, 1993
34. Malaisse WJ: The beta cell in NIDDM: Giving light to the blind. Diabetologia 37 (suppl 2):S36–S42, 1994
35. Malaisse WJ, Marynissen G, Sener A: Possible role of glycogen accumulation in B-cell toxicity. Metabolism 41:814–819, 1992
36. Mandrup-Poulsen T, Helqvist S, Molvig J, et al: Cytokines as immune effector molecules in autoimmune endocrine diseases with special reference to insulin-dependent diabetes mellitus. Autoimmunity 4:191–218, 1989
37. Manns JG, Martin CL: Plasma insulin, glucagon, and nonesterified fatty acids in dogs with diabetes mellitus. Am J Vet Res 33:981–985, 1972
38. Marmor M, Willeberg P, Glickman LT, et al: Epizootiologic patterns of diabetes mellitus in dogs. Am J Vet Res 43:465–470, 1982
39. Mattheuws D, Rottiers R, Baeyens D, Vermeulen A: Glucose tolerance and insulin response in obese dogs. J Am Anim Hosp Assoc 20:287–293, 1984
40. McGarry JD: What if Minkowski had been ageusic? An alternative angle on diabetes. Science 258:766–770, 1992
41. Mehta V, Hao W, Brooks-Worrell BM, Palmer JP: The functional state of the beta cell modulates IL-1 and TNF-induced cytotoxicity. Lymphokine Cytokine Res 12:255–259, 1993
42. Minkus G, Reusch C, Hänichen T, et al: Pathologische Veränderungen des endokrinen Pankreas bei Hund und Katze im Vergleich mit klinischen Daten. Tierärztl Prax 19:282–289, 1991
43. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039–1057, 1979
44. Nelson LW, Kelly WA: Progesterone-related gross and microscopic changes in female beagles. Vet Pathol 13:143–156, 1976
45. Nerup J: On the pathogenesis of IDDM. Diabetologia 37 (suppl 2):S82–S89, 1994
46. O'Brien TD, Butler PC, Westermark P, Johnson KH: Islet amyloid polypeptide: A review of its biology and potential roles in the pathogenesis of diabetes mellitus. Vet Pathol 30:317–332, 1993
47. O'Reilly LA, Hutchings PR, Crocker PR: Characterization of pancreatic islet cell infiltrates in NOD mice: effect of cell transfer and transgene expression. Eur J Immunol 21:1171–1180, 1991
48. Palmer JP, Lernmark A: Pathophysiology of type I (insulin-dependent) diabetes. *In* Ellenberg M, Rifkin H (eds): Diabetes Mellitus, ed 4. Elsevier Science Publ, Amsterdam, The Netherlands, 1990, pp 414–435
49. Peterson ME: Decreased insulin sensitivity and glucose tolerance in spontaneous canine hyperadrenocorticism. Res Vet Sci 36:177–182, 1984
50. Peterson ME, Nesbitt GH, Schaer M: Diagnosis and management of concurrent diabetes mellitus and hyperadrenocorticism in thirty dogs. J Am Vet Med Assoc 178:66–69, 1981
51. Porte D Jr: β-cells in type II diabetes mellitus. Diabetes 40:166–180, 1991
52. Redecker P, Jorns A, Jahn R, Grube D: Synaptophysin immunoreactivity in the mammalian endocrine pancreas. Cell Tissue Res 264:461–467, 1991

53. Sobey WJ, Beer SF, Carrington CA: Sensitive and specific two-site immunoradiometric assay for human insulin, proinsulin 65-66 split and 32-33 split proinsulins. Biochem J 260:535–541, 1989
54. Temple RC, Clark PMS, Nagi DK, et al: Radioimmunoassay may overestimate insulin in non-insulin dependent diabetics. Clin Endocrinol 32:689–693, 1989
55. Unger RH: Diabetic hyperglycemia: Link to impaired glucose transport in pancreatic β-cells. Science 251:1200–1205, 1991
56. Ward WK, Bolgiano DC, McKnight B, et al: Diminished β-cell secretory capacity in patients with non-insulin dependent diabetes mellitus. J Clin Invest 74:1318–1328, 1984
57. Warram JH, Martin BC, Krolewski LS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 113:909–915, 1990
58. WHO Study Group: Diabetes mellitus. Geneva, WHO Technical Reports, Series 727, 1985, pp 1–113

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