BÖLÜM 25

DENEY HAYVANLARINDA DİYABET MODELLERİ

Prof. Dr. Çiğdem ÖZER[1]
Araş. Gör. Dr. Hatice Betül MOĞULKOÇ[2]

A. GİRİŞ

Diabetes mellitus (DM), pankreasın insülin sekresyonunun yetersizliği ve/veya dokuların insüline cevabının bozulmasıyla (insülin direnci) oluşan, protein, yağ ve karbonhidrat metabolizmasını etkileyen kronik metabolik endokrin bir hastalıktır. Kan glikozu takibi ve insülin gibi eksojen farmakolojik ajanların uygulanması yoluyla hastalığın yönetimi zahmetli ve maliyetlidir.

Diabetes Mellitus:

A. Primer (idiopatik) DM

» Tip I (İnsüline bağlı) DM
» Tip II (İnsüline bağımlı olmayan) DM

B. Sekonder DM
C. Gestasyonel DM
D. Bozulmuş glikoz toleransı
E. Sınıflanamayan tipler olarak gruplandırılabilir

Tip 1 DM tüm diyabet vakalarının yaklaşık %10'unu oluşturur ve otoimmün bir süreç nedeniyle pankreas beta hücrelerinin yıkımı sonucu meydana gelir [1][2]. Bu tip diyabette pankreasın insülin üretememesine bağlı olarak mutlak

[1] Prof. Dr., Gazi Üniversitesi, Tıp Fakültesi, Temel Tıp Bilimleri Bölümü, Fizyoloji AD. E-posta: cigdemozer@gazi.edu.tr, ORCID iD: 0000-0002-2705-4522
[2] Araş. Gör. Dr., Gazi Üniversitesi Tıp Fakültesi Temel Tıp Bilimleri Bölümü Fizyoloji AD. E-posta: hbmogulkoc@gazi.edu.tr, ORCID iD: 0000-0002-8326-5631

C. SONUÇ

Deney hayvanlarında diyabet modelleri günümüze kadar DM'in patogenezi hakkında paha biçilemez bilgiler sağlamıştır. Bundan dolayı deney hayvanları modellerinin yeri doldurulamaz. Her biri spesifik özelliklere sahip birçok diyabet modeli vardır. Ancak bir araştırma planlanırken bu modellerin insan diyabetini tam olarak taklit edemedikleri göz önünde bulundurulmalıdır. Diyabet ile ilgili bir araştırmaya başlamadan önce kullanılacak model dikkatle seçilmeli, 3R kuralına bağlı kalınarak hayvan sayısı azaltılmaya çalışılmalı ve hayvanlara en az rahatsızlık verecek şekilde planlanmalıdır.

KAYNAKLAR

1. D. Mathis, L. Vence, and C. Benoist, "beta-Cell death during progression to diabetes.," *Nature*, vol. 414, no. 6865, pp. 792–798, Dec. 2001.
2. W. T. Cefalu, "Animal Models of Type 2 Diabetes: Clinical Presentation and Pathophysiological Relevance to the Human Condition," *ILAR J.*, vol. 47, no. 3, pp. 186–198, Jan. 2006.
3. A. Al-Awar *et al.*, "Experimental Diabetes Mellitus in Different Animal Models," *J. Diabetes Res.*, vol. 2016, 2016.
4. S. Lenzen and R. Munday, "Thiol-group reactivity, hydrophilicity and stability of alloxan, its reduction products and its N-methyl derivatives and a comparison with ninhydrin," *Biochem. Pharmacol.*, vol. 42, no. 7, pp. 1385–1391, Sep. 1991.
5. S. Lenzen, "The mechanisms of alloxan- and streptozotocin-induced diabetes," *Diabetologia*, vol. 51, no. 2, pp. 216–226, Feb. 2008.
6. M. Radenković, M. Stojanović, and M. Prostran, "Experimental diabetes induced by alloxan and streptozotocin: The current state of the art," *J. Pharmacol. Toxicol. Methods*, vol. 78, pp. 13–31, Mar. 2016.
7. R. Gunnarsson and C. Hellerström, "Acute effects of alloxan on the metabolism and insulin secretion of the pancreatic B-cell.," *Horm. Metab. Res. = Horm. und Stoffwechselforsch. = Horm. Metab.*, vol. 5, no. 6, pp. 404–409, Nov. 1973.
8. S. Lenzen and U. Panten, "Alloxan: history and mechanism of action.," *Diabetologia*, vol. 31, no. 6, pp. 337–342, Jun. 1988.
9. R. Munday, "Dialuric acid autoxidation: Effects of transition metals on the reaction rate and on the generation of 'active oxygen' species," *Biochem. Pharmacol.*, vol. 37, no. 3, pp. 409–413, Feb. 1988.
10. K. Katsumata, M. Miyao, and Y. Katsumata, "Insulin potentiating effect on development of alloxan diabetes and its prevention by the Ca-channel blocker nicardipine.," *Horm. Metab. Res. = Horm. und Stoffwechselforsch. = Horm. Metab.*, vol. 30, no. 9, pp. 557–558, Sep. 1998.
11. H. R. Kim *et al.*, "Role of Ca2+ in alloxan-induced pancreatic beta-cell damage.," *Biochim. Biophys. Acta*, vol. 1227, no. 1–2, pp. 87–91, Oct. 1994.
12. K. Srinivasan and P. Ramarao, "Animal models in type 2 diabetes research: an overview.," *Indian J. Med. Res.*, vol. 125, no. 3, pp. 451–472, Mar. 2007.

13. G. Y. Sy, A. Cissé, R. B. Nongonierma, M. Sarr, N. A. Mbodj, and B. Faye, "Hypoglycaemic and antidiabetic activity of acetonic extract of Vernonia colorata leaves in normoglycaemic and alloxan-induced diabetic rats.," *J. Ethnopharmacol.*, vol. 98, no. 1–2, pp. 171–175, Apr. 2005.
14. C. Soares de Alencar Mota *et al.*, "Exercise training in the aerobic/anaerobic metabolic transition prevents glucose intolerance in alloxan-treated rats.," *BMC Endocr. Disord.*, vol. 8, p. 11, Oct. 2008.
15. L. Golfman, I. M. Dixon, N. Takeda, A. Lukas, K. Dakshinamurti, and N. S. Dhalla, "Cardiac sarcolemmal Na(+)-Ca2+ exchange and Na(+)-K+ ATPase activities and gene expression in alloxan-induced diabetes in rats.," *Mol. Cell. Biochem.*, vol. 188, no. 1–2, pp. 91–101, Nov. 1998.
16. K. Katsumata, K. J. Katsumata, and Y. Katsumata, "Protective effect of diltiazem hydrochloride on the occurrence of alloxan- or streptozotocin-induced diabetes in rats.," *Horm. Metab. Res. = Horm. und Stoffwechselforsch. = Horm. Metab.*, vol. 24, no. 11, pp. 508–510, Nov. 1992.
17. Z. Kurçer and D. Karaoğlu, "Deneysel Diyabet Modellerinde Alloksan ve Streptozotosin Kullanımı," *Turkish J. Endocrinol. Metab.*, vol. 16, no. 2, pp. 34–40, 2012.
18. S. B. Sharma, A. Nasir, K. M. Prabhu, and P. S. Murthy, "Antihyperglycemic effect of the fruit-pulp of Eugenia jambolana in experimental diabetes mellitus.," *J. Ethnopharmacol.*, vol. 104, no. 3, pp. 367–373, Apr. 2006.
19. A. Kiersztan *et al.*, "Differential effects of vanadium, tungsten and molybdenum on inhibition of glucose formation in renal tubules and hepatocytes of control and diabetic rabbits: beneficial action of melatonin and N-acetylcysteine.," *Mol. Cell. Biochem.*, vol. 261, no. 1–2, pp. 9–21, Jun. 2004.
20. T. Amalraj and S. Ignacimuthu, "Evaluation of the hypoglycaemic effect of Memecylon umbellatum in normal and alloxan diabetic mice.," *J. Ethnopharmacol.*, vol. 62, no. 3, pp. 247–250, Oct. 1998.
21. X. Zhang, W. Liang, Y. Mao, H. Li, Y. Yang, and H. Tan, "Hepatic glucokinase activity is the primary defect in alloxan-induced diabetes of mice.," *Biomed. Pharmacother.*, vol. 63, no. 3, pp. 180–186, Mar. 2009.
22. M. M. Sailaja Devi and U. N. Das, "Effect of prostaglandins against alloxan-induced diabetes mellitus.," *Prostaglandins. Leukot. Essent. Fatty Acids*, vol. 74, no. 1, pp. 39–60, Jan. 2006.
23. N. S. Rajasekaran, M. Nithya, C. Rose, and T. S. Chandra, "The effect of finger millet feeding on the early responses during the process of wound healing in diabetic rats.," *Biochim. Biophys. Acta*, vol. 1689, no. 3, pp. 190–201, Aug. 2004.
24. R. H. J. Bell and R. J. Hye, "Animal models of diabetes mellitus: physiology and pathology.," *J. Surg. Res.*, vol. 35, no. 5, pp. 433–460, Nov. 1983.
25. M. V. Vijayakumar and M. K. Bhat, "Hypoglycemic effect of a novel dialysed fenugreek seeds extract is sustainable and is mediated, in part, by the activation of hepatic enzymes.," *Phytother. Res.*, vol. 22, no. 4, pp. 500–505, Apr. 2008.
26. W. Liu *et al.*, "Effects of berberine on matrix accumulation and NF-kappa B signal pathway in alloxan-induced diabetic mice with renal injury.," *Eur. J. Pharmacol.*, vol. 638, no. 1–3, pp. 150–155, Jul. 2010.
27. F. C. Howarth, Z. Hassan, and M. A. Qureshi, "The chronic effects of neonatal alloxan-induced diabetes mellitus on ventricular myocyte shortening and cytosolic Ca2+.," *Mol. Cell. Biochem.*, vol. 347, no. 1–2, pp. 71–77, Jan. 2011.

28. T. Szkudelski, K. Kandulska, and M. Okulicz, "Alloxan in vivo does not only exert deleterious effects on pancreatic B cells.," *Physiol. Res.*, vol. 47, no. 5, pp. 343–346, 1998.
29. N. RAKIETEN, M. L. RAKIETEN, and M. R. NADKARNI, "Studies on the diabetogenic action of streptozotocin (NSC-37917).," *Cancer Chemother. reports*, vol. 29, pp. 91–98, May 1963.
30. H. Tjälve, E. Wilander, and E. B. Johansson, "Distribution of labelled streptozotocin in mice: uptake and retention in pancreatic islets.," *J. Endocrinol.*, vol. 69, no. 3, pp. 455–456, Jun. 1976.
31. M. Murata, A. Takahashi, I. Saito, and S. Kawanishi, "Site-specific DNA methylation and apoptosis: induction by diabetogenic streptozotocin.," *Biochem. Pharmacol.*, vol. 57, no. 8, pp. 881–887, Apr. 1999.
32. S. Sandler and I. Swenne, "Streptozotocin, but not alloxan, induces DNA repair synthesis in mouse pancreatic islets in vitro.," *Diabetologia*, vol. 25, no. 5, pp. 444–447, Nov. 1983.
33. J. Turk, J. A. Corbett, S. Ramanadham, A. Bohrer, and M. L. McDaniel, "Biochemical evidence for nitric oxide formation from streptozotocin in isolated pancreatic islets.," *Biochem. Biophys. Res. Commun.*, vol. 197, no. 3, pp. 1458–1464, Dec. 1993.
34. M. Nukatsuka, Y. Yoshimura, M. Nishida, and J. Kawada, "Allopurinol protects pancreatic beta cells from the cytotoxic effect of streptozotocin: in vitro study.," *J. Pharmacobiodyn.*, vol. 13, no. 4, pp. 259–262, Apr. 1990.
35. H. Cheon *et al.*, "Role of JNK activation in pancreatic beta-cell death by streptozotocin.," *Mol. Cell. Endocrinol.*, vol. 321, no. 2, pp. 131–137, Jun. 2010.
36. A. Gülinnaz and S. V. İRER, "Deneysel Diyabet Modelleri," *Türk Klin. Biyokim. Derg*, vol. 2, no. 3, pp. 127–136, 2004.
37. M. J. Reed *et al.*, "A new rat model of type 2 diabetes: the fat-fed, streptozotocin-treated rat.," *Metabolism.*, vol. 49, no. 11, pp. 1390–1394, Nov. 2000.
38. M. Zhang, X.-Y. Lv, J. Li, Z.-G. Xu, and L. Chen, "The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model.," *Exp. Diabetes Res.*, vol. 2008, p. 704045, 2008.
39. P. Kumar Bhateja and R. Singh, "Antidiabetic activity of Acacia tortilis (Forsk.) Hayne ssp. raddiana polysaccharide on streptozotocin-nicotinamide induced diabetic rats.," *Biomed Res. Int.*, vol. 2014, p. 572013, 2014.
40. T. Szkudelski, "The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas.," *Physiol. Res.*, vol. 50, no. 6, pp. 537–546, 2001.
41. D. De, K. Chatterjee, K. M. Ali, T. K. Bera, and D. Ghosh, "Antidiabetic Potentiality of the Aqueous-Methanolic Extract of Seed of Swietenia mahagoni (L.) Jacq. in Streptozotocin-Induced Diabetic Male Albino Rat: A Correlative and Evidence-Based Approach with Antioxidative and Antihyperlipidemic Activities.," *Evid. Based. Complement. Alternat. Med.*, vol. 2011, p. 892807, 2011.
42. X.-S. Shu, J.-H. Lv, J. Tao, G.-M. Li, H.-D. Li, and N. Ma, "Antihyperglycemic effects of total flavonoids from Polygonatum odoratum in STZ and alloxan-induced diabetic rats.," *J. Ethnopharmacol.*, vol. 124, no. 3, pp. 539–543, Jul. 2009.
43. E. Shen *et al.*, "Rac1 is required for cardiomyocyte apoptosis during hyperglycemia.," *Diabetes*, vol. 58, no. 10, pp. 2386–2395, Oct. 2009.

44. P. Masiello *et al.*, "Experimental NIDDM: development of a new model in adult rats administered streptozotocin and nicotinamide.," *Diabetes*, vol. 47, no. 2, pp. 224–229, Feb. 1998.
45. I. G. Makom Ndifossap *et al.*, "Sclerocarya birrea (Anacardiaceae) stem-bark extract corrects glycaemia in diabetic rats and acts on beta-cells by enhancing glucose-stimulated insulin secretion.," *J. Endocrinol.*, vol. 205, no. 1, pp. 79–86, Apr. 2010.
46. K. Srinivasan, B. Viswanad, L. Asrat, C. L. Kaul, and P. Ramarao, "Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening.," *Pharmacol. Res.*, vol. 52, no. 4, pp. 313–320, Oct. 2005.
47. J. Y. T. Leung, E. W. Y. Kwok, G. Y. Liu, and C. C. Y. Pang, "Attenuated alpha-adrenoceptor-mediated arterial and venous constrictions in rat models of diabetes.," *Eur. J. Pharmacol.*, vol. 642, no. 1–3, pp. 128–133, Sep. 2010.
48. T. Kobayashi, K. Taguchi, T. Yasuhiro, T. Matsumoto, and K. Kamata, "Impairment of PI3-K/Akt pathway underlies attenuated endothelial function in aorta of type 2 diabetic mouse model.," *Hypertens. (Dallas, Tex. 1979)*, vol. 44, no. 6, pp. 956–962, Dec. 2004.
49. B.-S. Teng *et al.*, "A protein tyrosine phosphatase 1B activity inhibitor from the fruiting bodies of Ganoderma lucidum (Fr.) Karst and its hypoglycemic potency on streptozotocin-induced type 2 diabetic mice.," *J. Agric. Food Chem.*, vol. 59, no. 12, pp. 6492–6500, Jun. 2011.
50. J. Mu *et al.*, "Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic beta-cell mass and function in a rodent model of type 2 diabetes.," *Diabetes*, vol. 55, no. 6, pp. 1695–1704, Jun. 2006.
51. I. F. Federiuk, H. M. Casey, M. J. Quinn, M. D. Wood, and W. K. Ward, "Induction of type-1 diabetes mellitus in laboratory rats by use of alloxan: route of administration, pitfalls, and insulin treatment.," *Comp. Med.*, vol. 54, no. 3, pp. 252–257, Jun. 2004.
52. N. A. Shah and M. R. Khan, "Antidiabetic effect of Sida cordata in alloxan induced diabetic rats.," *Biomed Res. Int.*, vol. 2014, p. 671294, 2014.
53. J. Raju, D. Gupta, A. R. Rao, P. K. Yadava, and N. Z. Baquer, "Trigonellafoenum graecum (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes.," *Mol. Cell. Biochem.*, vol. 224, no. 1–2, pp. 45–51, Aug. 2001.
54. C. Daniel, K. Schaub, K. Amann, J. Lawler, and C. Hugo, "Thrombospondin-1 is an endogenous activator of TGF-beta in experimental diabetic nephropathy in vivo.," *Diabetes*, vol. 56, no. 12, pp. 2982–2989, Dec. 2007.
55. J. B. 3rd Watkins and S. E. Sherman, "Long-term diabetes alters the hepatobiliary clearance of acetaminophen, bilirubin and digoxin.," *J. Pharmacol. Exp. Ther.*, vol. 260, no. 3, pp. 1337–1343, Mar. 1992.
56. M. M. Swindle, A. Makin, A. J. Herron, F. J. J. Clubb, and K. S. Frazier, "Swine as models in biomedical research and toxicology testing.," *Vet. Pathol.*, vol. 49, no. 2, pp. 344–356, Mar. 2012.
57. Y. Brito-Casillas, C. Melián, and A. M. Wägner, "Study of the pathogenesis and treatment of diabetes mellitus through animal models," *Endocrinol. Nutr.*, vol. 63, no. 7, pp. 345–353, Aug. 2016.
58. D. A. Rees and J. C. Alcolado, "Animal models of diabetes mellitus," *Diabet. Med.*, vol. 22, no. 4, pp. 359–370, Apr. 2005.

59. S. Makino, K. Kunimoto, Y. Muraoka, Y. Mizushima, K. Katagiri, and Y. Tochino, "Breeding of a non-obese, diabetic strain of mice.," *Jikken Dobutsu.*, vol. 29, no. 1, pp. 1–13, Jan. 1980.
60. M. A. Atkinson and E. H. Leiter, "The NOD mouse model of type 1 diabetes: as good as it gets?," *Nat. Med.*, vol. 5, no. 6, pp. 601–604, Jun. 1999.
61. K. T. Coppieters and M. G. von Herrath, "Histopathology of type 1 diabetes: old paradigms and new insights.," *Rev. Diabet. Stud.*, vol. 6, no. 2, pp. 85–96, 2009.
62. M. von Herrath and G. T. Nepom, "Animal models of human type 1 diabetes.," *Nat. Immunol.*, vol. 10, no. 2, pp. 129–132, Feb. 2009.
63. S. Acharjee, B. Ghosh, B. E. Al-Dhubiab, and A. B. Nair, "Understanding type 1 diabetes: etiology and models.," Can. J. diabetes, vol. 37, no. 4, pp. 269–276, Aug. 2013.
64. L. Crisá, J. P. Mordes, and A. A. Rossini, "Autoimmune diabetes mellitus in the BB rat.," *Diabetes. Metab. Rev.*, vol. 8, no. 1, pp. 4–37, Apr. 1992.
65. A. Chatzigeorgiou, A. Halapas, K. Kalafatakis, and E. Kamper, "The use of animal models in the study of diabetes mellitus.," *In Vivo*, vol. 23, no. 2, pp. 245–258, 2009.
66. K. Buschard, "What causes type 1 diabetes? Lessons from animal models.," *APMIS. Suppl.*, no. 132, pp. 1–19, Jul. 2011.
67. B. Wang, P. C. Chandrasekera, and J. J. Pippin, "Leptin- and leptin receptor-deficient rodent models: relevance for human type 2 diabetes.," *Curr. Diabetes Rev.*, vol. 10, no. 2, pp. 131–145, Mar. 2014.
68. M. P. Cohen, R. S. Clements, E. Hud, J. A. Cohen, and F. N. Ziyadeh, "Evolution of renal function abnormalities in the db/db mouse that parallels the development of human diabetic nephropathy.," Exp. Nephrol., vol. 4, no. 3, pp. 166–171, 1996.
69. T. J. Allen, M. E. Cooper, and H. Y. Lan, "Use of genetic mouse models in the study of diabetic nephropathy.," *Curr. Atheroscler. Rep.*, vol. 6, no. 3, pp. 197–202, May 2004.
70. X. J. Cai *et al.*, "Down-regulation of orexin gene expression by severe obesity in the rats: studies in Zucker fatty and zucker diabetic fatty rats and effects of rosiglitazone.," *Brain Res. Mol. Brain Res.*, vol. 77, no. 1, pp. 131–137, Apr. 2000.
71. Y. Goto, M. Kakizaki, and N. Masaki, "Production of spontaneous diabetic rats by repetition of selective breeding.," *Tohoku J. Exp. Med.*, vol. 119, no. 1, pp. 85–90, May 1976.
72. U. Janssen, A. O. Phillips, and J. Floege, "Rodent models of nephropathy associated with type II diabetes.," *J. Nephrol.*, vol. 12, no. 3, pp. 159–172, 1999.
73. Y. Murakawa *et al.*, "Impaired glucose tolerance and insulinopenia in the GK-rat causes peripheral neuropathy.," *Diabetes. Metab. Res. Rev.*, vol. 18, no. 6, pp. 473–483, 2002.
74. H. Sone *et al.*, "Ocular vascular endothelial growth factor levels in diabetic rats are elevated before observable retinal proliferative changes.," *Diabetologia*, vol. 40, no. 6, pp. 726–730, Jun. 1997.
75. M. Nakamura and K. Yamada, "Studies on a diabetic (KK) strain of the mouse.," *Diabetologia*, vol. 3, no. 2, pp. 212–221, Apr. 1967.
76. H. Ueda *et al.*, "The NSY mouse: a new animal model of spontaneous NIDDM with moderate obesity.," *Diabetologia*, vol. 38, no. 5, pp. 503–508, May 1995.
77. E. Ziv, E. Shafrir, R. Kalman, S. Galer, and H. Bar-On, "Changing pattern of prevalence of insulin resistance in Psammomys obesus, a model of nutritionally induced type 2 diabetes.," *Metabolism.*, vol. 48, no. 12, pp. 1549–1554, Dec. 1999.

78. E. Cerasi, N. Kaiser, and D. J. Gross, "From sand rats to diabetic patients: is non-insulin-dependent diabetes mellitus a disease of the beta cell?," *Diabetes Metab.*, vol. 23 Suppl 2, pp. 47–51, Mar. 1997.
79. K. Kawano, T. Hirashima, S. Mori, Y. Saitoh, M. Kurosumi, and T. Natori, "Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka Long-Evans Tokushima Fatty (OLETF) strain.," *Diabetes*, vol. 41, no. 11, pp. 1422–1428, Nov. 1992.
80. R. L. Joshi *et al.*, "Targeted disruption of the insulin receptor gene in the mouse results in neonatal lethality.," *EMBO J.*, vol. 15, no. 7, pp. 1542–1547, Apr. 1996.
81. P. Y. Chang, H. Benecke, Y. Le Marchand-Brustel, J. Lawitts, and D. E. Moller, "Expression of a dominant-negative mutant human insulin receptor in the muscle of transgenic mice.," *J. Biol. Chem.*, vol. 269, no. 23, pp. 16034–16040, Jun. 1994.
82. H. Tamemoto *et al.*, "Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1.," *Nature*, vol. 372, no. 6502, pp. 182–186, Nov. 1994.
83. D. J. Withers *et al.*, "Disruption of IRS-2 causes type 2 diabetes in mice.," *Nature*, vol. 391, no. 6670, pp. 900–904, Feb. 1998.
84. N. Kubota *et al.*, "Disruption of insulin receptor substrate 2 causes type 2 diabetes because of liver insulin resistance and lack of compensatory beta-cell hyperplasia.," *Diabetes*, vol. 49, no. 11, pp. 1880–1889, Nov. 2000.
85. A. Grupe, B. Hultgren, A. Ryan, Y. H. Ma, M. Bauer, and T. A. Stewart, "Transgenic knockouts reveal a critical requirement for pancreatic beta cell glucokinase in maintaining glucose homeostasis.," *Cell*, vol. 83, no. 1, pp. 69–78, Oct. 1995.
86. M. L. Liu *et al.*, "Transgenic mice expressing the human GLUT4/muscle-fat facilitative glucose transporter protein exhibit efficient glycemic control.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 90, no. 23, pp. 11346–11350, Dec. 1993.
87. R. N. Kulkarni, J. C. Brüning, J. N. Winnay, C. Postic, M. A. Magnuson, and C. R. Kahn, "Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes.," *Cell*, vol. 96, no. 3, pp. 329–339, Feb. 1999.
88. H. Okamoto and D. Accili, "In vivo mutagenesis of the insulin receptor.," *J. Biol. Chem.*, vol. 278, no. 31, pp. 28359–28362, Aug. 2003.
89. E. D. Rosen *et al.*, "Targeted elimination of peroxisome proliferator-activated receptor gamma in beta cells leads to abnormalities in islet mass without compromising glucose homeostasis.," *Mol. Cell. Biol.*, vol. 23, no. 20, pp. 7222–7229, Oct. 2003.
90. Y. Minokoshi, C. R. Kahn, and B. B. Kahn, "Tissue-specific ablation of the GLUT4 glucose transporter or the insulin receptor challenges assumptions about insulin action and glucose homeostasis.," *J. Biol. Chem.*, vol. 278, no. 36, pp. 33609–33612, Sep. 2003.
91. M. I. Hawa, H. Beyan, L. R. Buckley, and R. D. G. Leslie, "Impact of genetic and non-genetic factors in type 1 diabetes.," *Am. J. Med. Genet.*, vol. 115, no. 1, pp. 8–17, May 2002.
92. A. J. F. King, "The use of animal models in diabetes research.," *Br. J. Pharmacol.*, vol. 166, no. 3, pp. 877–894, Jun. 2012.
93. S. Acharjee, B. Ghosh, B. E. Al-Dhubiab, and A. B. Nair, "Understanding type 1 diabetes: etiology and models.," *Can. J. diabetes*, vol. 37, no. 4, pp. 269–276, Aug. 2013.