



PANKREATİK BETA HÜCRE FONKSİYONU VE DİABETES MELLİTUS'A FİZYOPATOLOJİK YAKLAŞIM

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GİRİŞ

Glikoz, tüm hücreler için önemli bir enerji kaynağıdır. Bu nedenle, yaşam için glikoz seviyelerini normal bir aralıkta tutmak önemlidir. Organizmadaki glikoz homeostazı, kas, karaciğer ve yağ dokusu gibi glikoz metabolik dokularına etki eden bir hormon olan insülin tarafından düzenlenir. İnsülin sekresyonu, pankreas langerhans adacıklarındaki β hücreleri tarafından sentezlenir ve kan glikoz seviyeleri ile düzenlenir. Bu nedenle plazma insülin seviyeleri, β hücrelerinin morfolojik kütlelerine ve β hücrelerinin fonksiyonel durumuna bağlıdır. β hücre kütlesi veya fonksiyonundaki herhangi bir bozukluk yetersiz insülin sekresyonuna yol açarak 'Diabetes Mellitus' ile sonuçlanabilir. Diabetes Mellitus, insülin üretimi ve etkinliğinde oluşan bir bozukluk sebebiyle ortaya çıkan ve hiperglisemi ile karakterize olan metabolik bir hastalıktır. Bununla birlikte, β hücre kütlelerinin ve fonksiyonunun diyabet patogenezi ve altta yatan mekanizmalara olan katkısı halen belirsizdir.

Diabetes Mellitus fizyopatolojisiyle ilgili bu bölümün amacı, insan glikoz homeostazındaki β hücre kütlesi ve fonksiyonu hakkındaki güncel bilgileri özetlemektir. Ayrıca, pankreatik β hücrelerinin tip 1 ve tip 2 diyabet patogenezinin farklı aşamalarına katkısı hakkındaki mevcut bilgileri sunmaktır.

PANKREATİK ENDOKRİN HÜCRELER

Pankreas, hem endokrin (% 2) hem de ekzokrin (%85) fonksiyonu olan ve vücut homeostazında oldukça önemli bir bezdir ⁽¹⁾ Endokrin pankreas, toplam pankreas kütlelerinin % 1-5' ini temsil eder ve farklı hormonlar salgılayan birkaç hücre tipinden oluşan pankreas adacıklarını içerir ⁽²⁾. Ekzokrin pankreas ise sindirim enzimlerini salgılamaktan sorumlu olan asiner dokuya karşılık gelir (2).

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SONUÇ

Plazma insülin seviyeleri ağırlıklı olarak Langerhans adacıklarındaki insülin üreten β hücrelerinin morfolojik kütesinin ve bu β hücrelerinin her birinin fonksiyonel durumunun ürünüdür. Bu nedenle, β hücre kütesi, fonksiyonu veya her ikisindeki eksiklik, yetersiz insülin seviyelerine yol açacağından hiperglisemi ve diyabet ile sonuçlanabilir. Mevcut bilgiler, β hücre kütesi ve fonksiyonunun T1DM ve T2DM gelişimine farklı şekillerde katkıda bulunduğunu düşündürmektedir. T1DM'de prediyabetik faz, β hücre kütesinde hızlı bir düşüş olması nedeniyle uzun süreli, kademeli, fonksiyonel bir bozulma sonucu başlayan hiperglisemi ile karakterize edilir. Klinik sonuçlara bakıldığında kütledeki değişiklikler hastaya göre farklılık göstermektedir ama erken başlangıçlı T1DM'de β hücre kütesinde daha büyük bir azalma vardır. Bununla birlikte β hücrelerindeki fonksiyon kaybı hipergliseminin gelişiminde önemli bir bileşendir. Bu nedenle, T1DM başlangıcında immün sistemi hedef alan müdahaleler, glikoz homeostazının kısmi kontrolünün sağlanmasında başarılı olabilir. Buna karşılık, T2DM gelişimi, insülin direnci sırasında, insülin ihtiyacının artmasına yanıt olarak morfolojik ve fonksiyonel β hücre kompanzasyonunun azalmasının bir sonucudur. Bazı durumlarda, β hücrelerinin fonksiyonel olarak telafisinin yetersiz kalması, hücre iş yükünü artırır ve bu da β hücre ölümüne yol açar. Bu nedenle, T2DM'de β hücre fonksiyonunun korunması ve geri kazanılması tedavi için temel hedef olmalıdır. Bu bulgulara rağmen, β hücre kütesi ve fonksiyonunun diyabet patogenezindeki rolünün daha iyi anlaşılabilmesi için daha fazla çalışmaya ihtiyaç vardır.

KAYNAKLAR

1. Arsenijevic T, Perret J, Van Laethem JL, et al. Aquaporins Involvement in Pancreas Physiology and in Pancreatic Diseases. *Int J Mol Sci*, 2019;20(20). doi: 10.3390/ijms20205052.
2. Kim SK, Hebrok M. Intercellular signals regulating pancreas development and function. *Genes Dev*, 2001;15(2):111-27. doi: 10.1101/gad.859401.
3. McClenaghan NH. Physiological regulation of the pancreatic {beta}-cell: functional insights for understanding and therapy of diabetes. *Exp Physiol*, 2007;92(3):481-96. doi: 10.1113/expphysiol.2006.034835.
4. Jolles S, Paul Langerhans. *J Clin Pathol*, 2002;55(4):243. doi: 10.1136/jcp.55.4.243.
5. Ionescu-Tirgoviste C, Gagniuc PA, Gubceac E, et al. A 3D map of the islet routes throughout the healthy human pancreas. *Sci Rep*, 2015;5:14634. doi: 10.1038/srep14634.
6. Shahid Z, Singh G, *Physiology, Islets of Langerhans*, in *StatPearls*. 2020: Treasure Island (FL).
7. Da Silva Xavier G. The Cells of the Islets of Langerhans. *J Clin Med*, 2018;7(3). doi: 10.3390/jcm7030054.
8. Mayer J. Glucostatic mechanism of regulation of food intake. *N Engl J Med*, 1953;249(1):13-6. doi: 10.1056/NEJM195307022490104.
9. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 2009;58(4):773-95. doi: 10.2337/db09-9028.

10. Mari A, Tura A, Natali A, et al. Impaired beta cell glucose sensitivity rather than inadequate compensation for insulin resistance is the dominant defect in glucose intolerance. *Diabetologia*, 2010;53(4):749-56. doi: 10.1007/s00125-009-1647-6.
11. Vergari E, Knudsen JG, Ramracheya R, et al. Insulin inhibits glucagon release by SGLT2-induced stimulation of somatostatin secretion. *Nat Commun*, 2019;10(1):139. doi: 10.1038/s41467-018-08193-8.
12. Stagner JI, Samols E, Weir GC. Sustained oscillations of insulin, glucagon, and somatostatin from the isolated canine pancreas during exposure to a constant glucose concentration. *J Clin Invest*, 1980;65(4):939-42. doi: 10.1172/JCI109750.
13. Curry DL, Bennett LL, Grodsky GM. Dynamics of insulin secretion by the perfused rat pancreas. *Endocrinology*, 1968;83(3):572-84. doi: 10.1210/endo-83-3-572.
14. Henquin JC. Regulation of insulin secretion: a matter of phase control and amplitude modulation. *Diabetologia*, 2009;52(5):739-51. doi: 10.1007/s00125-009-1314-y.
15. Aguilar-Bryan L, Clement JPt, Gonzalez G, et al. Toward understanding the assembly and structure of KATP channels. *Physiol Rev*, 1998;78(1):227-45. doi: 10.1152/physrev.1998.78.1.227.
16. Hiriart M, Aguilar-Bryan L. Channel regulation of glucose sensing in the pancreatic beta-cell. *Am J Physiol Endocrinol Metab*, 2008;295(6):E1298-306. doi: 10.1152/ajpendo.90493.2008.
17. Rorsman P, Renstrom E. Insulin granule dynamics in pancreatic beta cells. *Diabetologia*, 2003;46(8):1029-45. doi: 10.1007/s00125-003-1153-1.
18. Renstrom E, Ding WG, Bokvist K, et al. Neurotransmitter-induced inhibition of exocytosis in insulin-secreting beta cells by activation of calcineurin. *Neuron*, 1996;17(3):513-22. doi: 10.1016/s0896-6273(00)80183-x.
19. Alfa RW, Park S, Skelly KR, et al. Suppression of insulin production and secretion by a incretin hormone. *Cell Metab*, 2015;21(2):323-334. doi: 10.1016/j.cmet.2015.01.006.
20. Klec C, Ziomek G, Pichler M, et al. Calcium Signaling in ss-cell Physiology and Pathology: A Revisit. *Int J Mol Sci*, 2019;20(24). doi: 10.3390/ijms20246110.
21. Henquin JC, Nenquin M, Ravier MA, et al. Shortcomings of current models of glucose-induced insulin secretion. *Diabetes Obes Metab*, 2009;11 Suppl 4:168-79. doi: 10.1111/j.1463-1326.2009.01109.x.
22. Alam MR, Groschner LN, Parichatikanond W, et al. Mitochondrial Ca²⁺ uptake 1 (MICU1) and mitochondrial ca²⁺ uniporter (MCU) contribute to metabolism-secretion coupling in clonal pancreatic beta-cells. *J Biol Chem*, 2012;287(41):34445-54. doi: 10.1074/jbc.M112.392084.
23. Rutter GA, Tsuboi T, Ravier MA. Ca²⁺ microdomains and the control of insulin secretion. *Cell Calcium*, 2006;40(5-6):539-51. doi: 10.1016/j.ceca.2006.08.015.
24. Strehler EE, Treiman M. Calcium pumps of plasma membrane and cell interior. *Curr Mol Med*, 2004;4(3):323-35. doi: 10.2174/1566524043360735.
25. Prasad V, Okunade GW, Miller ML, et al. Phenotypes of SERCA and PMCA knockout mice. *Biochem Biophys Res Commun*, 2004;322(4):1192-203. doi: 10.1016/j.bbrc.2004.07.156.
26. Noble D, Herchuelz A. Role of Na/Ca exchange and the plasma membrane Ca²⁺-ATPase in cell function. Conference on Na/Ca exchange. *EMBO Rep*, 2007;8(3):228-32. doi: 10.1038/sj.embor.7400914.
27. Bagur R, Hajnoczky G. Intracellular Ca(2+) Sensing: Its Role in Calcium Homeostasis and Signaling. *Mol Cell*, 2017;66(6):780-788. doi: 10.1016/j.molcel.2017.05.028.
28. Ravier MA, Daro D, Roma LP, et al. Mechanisms of control of the free Ca²⁺ concentration in the endoplasmic reticulum of mouse pancreatic beta-cells: interplay with cell metabolism and (Ca²⁺)_c and role of SERCA2b and SERCA3. *Diabetes*, 2011;60(10):2533-45. doi: 10.2337/db10-1543.
29. Philipson KD, Nicoll DA. Sodium-calcium exchange: a molecular perspective. *Annu Rev Physiol*, 2000;62:111-33. doi: 10.1146/annurev.physiol.62.1.111.

30. Varadi A, Lebel L, Hashim Y, et al. Sequence variants of the sarco(endo)plasmic reticulum Ca(2+)-transport ATPase 3 gene (SERCA3) in Caucasian type II diabetic patients (UK Prospective Diabetes Study 48). *Diabetologia*, 1999;42(10):1240-3. doi: 10.1007/s001250051298.
31. Wiederkehr A, Park KS, Dupont O, et al. Matrix alkalization: a novel mitochondrial signal for sustained pancreatic beta-cell activation. *EMBO J*, 2009;28(4):417-28. doi: 10.1038/emboj.2008.302.
32. Denton RM, McCormack JG. On the role of the calcium transport cycle in heart and other mammalian mitochondria. *FEBS Lett*, 1980;119(1):1-8. doi: 10.1016/0014-5793(80)80986-0.
33. Denton RM, McCormack JG. Ca²⁺ transport by mammalian mitochondria and its role in hormone action. *Am J Physiol*, 1985;249(6 Pt 1):E543-54. doi: 10.1152/ajpendo.1985.249.6.E543.
34. Wiederkehr A, Wollheim CB. Impact of mitochondrial calcium on the coupling of metabolism to insulin secretion in the pancreatic beta-cell. *Cell Calcium*, 2008;44(1):64-76. doi: 10.1016/j.ceca.2007.11.004.
35. Aizawa T, Sato Y, Komatsu M. Importance of nonionic signals for glucose-induced biphasic insulin secretion. *Diabetes*, 2002;51 Suppl 1:S96-8. doi: 10.2337/diabetes.51.2007.s96.
36. Aizawa T, Komatsu M. Rab27a: a new face in beta cell metabolism-secretion coupling. *J Clin Invest*, 2005;115(2):227-30. doi: 10.1172/JCI24269.
37. Kamal MM, Kassem DH. Therapeutic Potential of Wharton's Jelly Mesenchymal Stem Cells for Diabetes: Achievements and Challenges. *Front Cell Dev Biol*, 2020;8:16. doi: 10.3389/fcell.2020.00016.
38. Aguirre F, Brown A, Cho NH, et al. IDF diabetes atlas. 2013.
39. Sapra A, Vaqar S, Bhandari P, *Diabetes Mellitus*, in *StatPearls*. 2020: Treasure Island (FL).
40. Chen C, Cohrs CM, Stertmann J, et al. Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis. *Mol Metab*, 2017;6(9):943-957. doi: 10.1016/j.molmet.2017.06.019.
41. Brozzi F, Nardelli TR, Lopes M, et al. Cytokines induce endoplasmic reticulum stress in human, rat and mouse beta cells via different mechanisms. *Diabetologia*, 2015;58(10):2307-2316. doi: 10.1007/s00125-015-3669-6.
42. Herold KC, Usmani-Brown S, Ghazi T, et al. beta cell death and dysfunction during type 1 diabetes development in at-risk individuals. *J Clin Invest*, 2015;125(3):1163-73. doi: 10.1172/JCI78142.
43. Koskinen MK, Helminen O, Matomaki J, et al. Reduced beta-cell function in early preclinical type 1 diabetes. *Eur J Endocrinol*, 2016;174(3):251-9. doi: 10.1530/EJE-15-0674.
44. Sosenko JM, Skyler JS, Beam CA, et al. Acceleration of the loss of the first-phase insulin response during the progression to type 1 diabetes in diabetes prevention trial-type 1 participants. *Diabetes*, 2013;62(12):4179-83. doi: 10.2337/db13-0656.
45. Campbell-Thompson M, Fu A, Kaddis JS, et al. Insulinitis and beta-Cell Mass in the Natural History of Type 1 Diabetes. *Diabetes*, 2016;65(3):719-31. doi: 10.2337/db15-0779.
46. Butler AE, Galasso R, Meier JJ, et al. Modestly increased beta cell apoptosis but no increased beta cell replication in recent-onset type 1 diabetic patients who died of diabetic ketoacidosis. *Diabetologia*, 2007;50(11):2323-2331. doi: 10.1007/s00125-007-0794-x.
47. Tersey SA, Nishiki Y, Templin AT, et al. Islet beta-cell endoplasmic reticulum stress precedes the onset of type 1 diabetes in the nonobese diabetic mouse model. *Diabetes*, 2012;61(4):818-27. doi: 10.2337/db11-1293.
48. Butler AE, Galasso R, Meier JJ, et al. Modestly increased beta cell apoptosis but no increased beta cell replication in recent-onset type 1 diabetic patients who died of diabetic ketoacidosis. *Diabetologia*, 2007;50(11):2323-31. doi: 10.1007/s00125-007-0794-x.
49. Levitt HE, Cyphert TJ, Pascoe JL, et al. Glucose stimulates human beta cell replication in vivo in islets transplanted into NOD-severe combined immunodeficiency (SCID) mice. *Diabetologia*, 2011;54(3):572-82. doi: 10.1007/s00125-010-1919-1.

50. Meier JJ, Lin JC, Butler AE, et al. Direct evidence of attempted beta cell regeneration in an 89-year-old patient with recent-onset type 1 diabetes. *Diabetologia*, 2006;49(8):1838-44. doi: 10.1007/s00125-006-0308-2.
51. Poudel A, Savari O, Striegel DA, et al. Beta-cell destruction and preservation in childhood and adult onset type 1 diabetes. *Endocrine*, 2015;49(3):693-702. doi: 10.1007/s12020-015-0534-9.
52. Keenan HA, Sun JK, Levine J, et al. Residual insulin production and pancreatic β -cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes*, 2010;59(11):2846-53. doi: 10.2337/db10-0676.
53. Coppieters KT, Wiberg A, Amirian N, et al. Persistent glucose transporter expression on pancreatic beta cells from longstanding type 1 diabetic individuals. *Diabetes Metab Res Rev*, 2011;27(8):746-54. doi: 10.1002/dmrr.1246.
54. Tsai EB, Sherry NA, Palmer JP, et al. The rise and fall of insulin secretion in type 1 diabetes mellitus. *Diabetologia*, 2006;49(2):261-70. doi: 10.1007/s00125-005-0100-8.
55. Sherr JL, Ghazi T, Wurtz A, et al. Characterization of residual beta cell function in long-standing type 1 diabetes. *Diabetes Metab Res Rev*, 2014;30(2):154-62. doi: 10.1002/dmrr.2478.
56. Yang Y, Kim JW, Park HS, et al. Pancreatic stellate cells in the islets as a novel target to preserve the pancreatic beta-cell mass and function. *J Diabetes Investig*, 2019. doi: 10.1111/jdi.13202.
57. Butler AE, Janson J, Bonner-Weir S, et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes*, 2003;52(1):102-10. doi: 10.2337/diabetes.52.1.102.
58. Levy J, Atkinson AB, Bell PM, et al. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. *Diabet Med*, 1998;15(4):290-6. doi: 10.1002/(sici)1096-9136(199804)15:4<290::Aid-dia570>3.0.Co;2-m.
59. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, 2006;444(7121):840-6. doi: 10.1038/nature05482.
60. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*, 2006;91(8):2906-12. doi: 10.1210/jc.2006-0594.
61. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*, 1993;42(11):1663-72. doi: 10.2337/diab.42.11.1663.
62. Saisho Y, Butler AE, Manesso E, et al. beta-cell mass and turnover in humans: effects of obesity and aging. *Diabetes Care*, 2013;36(1):111-7. doi: 10.2337/dc12-0421.
63. Mezza T, Muscogiuri G, Sorice GP, et al. Insulin resistance alters islet morphology in nondiabetic humans. *Diabetes*, 2014;63(3):994-1007. doi: 10.2337/db13-1013.
64. Camastra S, Manco M, Mari A, et al. beta-cell function in morbidly obese subjects during free living: long-term effects of weight loss. *Diabetes*, 2005;54(8):2382-9. doi: 10.2337/diabetes.54.8.2382.
65. Mezghenna K, Pomies P, Chalancon A, et al. Increased neuronal nitric oxide synthase dimerisation is involved in rat and human pancreatic beta cell hyperactivity in obesity. *Diabetologia*, 2011;54(11):2856-66. doi: 10.1007/s00125-011-2264-8.
66. Hanley SC, Austin E, Assouline-Thomas B, et al. beta-Cell mass dynamics and islet cell plasticity in human type 2 diabetes. *Endocrinology*, 2010;151(4):1462-72. doi: 10.1210/en.2009-1277.
67. Rahier J, Guiot Y, Goebbels RM, et al. Pancreatic beta-cell mass in European subjects with type 2 diabetes. *Diabetes Obes Metab*, 2008;10 Suppl 4:32-42. doi: 10.1111/j.1463-1326.2008.00969.x.
68. Inaishi J, Saisho Y, Sato S, et al. Effects of Obesity and Diabetes on alpha- and beta-Cell Mass in Surgically Resected Human Pancreas. *J Clin Endocrinol Metab*, 2016;101(7):2874-82. doi: 10.1210/jc.2016-1374.

69. Sakuraba H, Mizukami H, Yagihashi N, et al. Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. *Diabetologia*, 2002;45(1):85-96. doi: 10.1007/s125-002-8248-z.
70. Marchetti P, Bugliani M, Lupi R, et al. The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients. *Diabetologia*, 2007;50(12):2486-94. doi: 10.1007/s00125-007-0816-8.
71. Ferrannini E, Gastaldelli A, Miyazaki Y, et al. beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab*, 2005;90(1):493-500. doi: 10.1210/jc.2004-1133.
72. Gastaldelli A, Ferrannini E, Miyazaki Y, et al. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*, 2004;47(1):31-9. doi: 10.1007/s00125-003-1263-9.
73. Kendall DM, Sutherland DE, Najarian JS, et al. Effects of hemipancreatectomy on insulin secretion and glucose tolerance in healthy humans. *N Engl J Med*, 1990;322(13):898-903. doi: 10.1056/nejm199003293221305.
74. Robertson RP, Lanz KJ, Sutherland DE, et al. Relationship between diabetes and obesity 9 to 18 years after hemipancreatectomy and transplantation in donors and recipients. *Transplantation*, 2002;73(5):736-41. doi: 10.1097/00007890-200203150-00013.
75. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *N Engl J Med*, 1988;318(19):1231-9. doi: 10.1056/nejm198805123181903.
76. Talchai C, Xuan S, Lin HV, et al. Pancreatic beta cell dedifferentiation as a mechanism of diabetic beta cell failure. *Cell*, 2012;150(6):1223-34. doi: 10.1016/j.cell.2012.07.029.
77. Accili D, Talchai SC, Kim-Muller JY, et al. When beta-cells fail: lessons from dedifferentiation. *Diabetes Obes Metab*, 2016;18 Suppl 1:117-22. doi: 10.1111/dom.12723.
78. Wang Z, York NW, Nichols CG, et al. Pancreatic beta cell dedifferentiation in diabetes and redifferentiation following insulin therapy. *Cell Metab*, 2014;19(5):872-82. doi: 10.1016/j.cmet.2014.03.010.
79. Butler AE, Dhawan S, Hoang J, et al. beta-Cell Deficit in Obese Type 2 Diabetes, a Minor Role of beta-Cell Dedifferentiation and Degranulation. *J Clin Endocrinol Metab*, 2016;101(2):523-32. doi: 10.1210/jc.2015-3566.
80. Cinti F, Bouchi R, Kim-Muller JY, et al. Evidence of beta-Cell Dedifferentiation in Human Type 2 Diabetes. *J Clin Endocrinol Metab*, 2016;101(3):1044-54. doi: 10.1210/jc.2015-2860.
81. Meier JJ, Menge BA, Breuer TG, et al. Functional assessment of pancreatic beta-cell area in humans. *Diabetes*, 2009;58(7):1595-603. doi: 10.2337/db08-1611.
82. Weyer C, Bogardus C, Mott DM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest*, 1999;104(6):787-94. doi: 10.1172/jci7231.
83. Matveyenko AV, Liuwantara D, Gurlo T, et al. Pulsatile portal vein insulin delivery enhances hepatic insulin action and signaling. *Diabetes*, 2012;61(9):2269-79. doi: 10.2337/db11-1462.
84. Leahy JL, Hirsch IB, Peterson KA, et al. Targeting beta-cell function early in the course of therapy for type 2 diabetes mellitus. *J Clin Endocrinol Metab*, 2010;95(9):4206-16. doi: 10.1210/jc.2010-0668.
85. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*, 2007;316(5829):1336-41. doi: 10.1126/science.1142364.
86. Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*, 2007;316(5829):1331-6. doi: 10.1126/science.1142358.