

Bölüm 18

TRANSPLANTASYON SONRASI DİABETES MELLİTUSA YAKLAŞIM ve YÖNETİM

Çiğdem ÖZDEMİR¹

TANIM VE TARİHÇE

Cerrahi tekniklerdeki gelişme ve immunsupresif ilaçların kullanımı sayesinde solid organ nakli son dönem organ yetmezliği için başarılı bir tedavi haline gelmiştir(1).5 yıllık greft sağkalım oranı böbrek nakli için %80, karaciğer nakli için %70, akciğer nakli için %67 ve kalp nakli için %78'lere ulaşmıştır(2,3).Ancak solid organ nakli alıcılarında kardiyovasküler hastalık ve erken ölüm riski hala en büyük problemdir. Bu hasta grubunda yaşam beklentisi arttıkça metabolik hastalık insidansı (DM, dislipidemi, obezite) artmaktadır (4-7).

Organ nakli sonrası ortaya çıkan diyabet(PTDM) azalmış greft fonksiyonu, greft kaybı ve hasta sağkalımı için önemli bir risk faktörüdür, artmış kardiyovasküler morbidite ve mortalite ile ilişkilidir(8-9).PTDM insidansı farklı çalışmalarda %2-53 arasında bildirilmektedir(10).Literatürde insidans ile ilgili çok değişik rakamlar verilmesinin nedeni önceki yıllarda tanım için fikir birliğinin olmaması ve farklı araştırma grupları tarafından farklı kriterlerin kullanılmasıdır. Ayrıca bazı vakaların geçici olması, izlem süresinin uzunluğu ve tanıya kadar geçen süre de insidansı etkilemektedir.

Uluslararası Kalp ve Akciğer Nakli Topluluğu'nun kayıtlarına göre kalp nakli sonrası 1.yılda DM prevalansı %23 iken 5.yılda %37 'e çıkmaktadır(11). Böbrek nakli sonrası PTDM insidansı zamanla azalmakta iken kalp nakli sonrası PTDM prevalansı 5.yılda 2002 de %32 iken 2016 da %37'e ulaşmıştır(11).Hiperglisemi karaciğer naklinin yaygın bir komplikasyonu olup nakil sonrası dönemdeki hastaların %70' inde görülmektedir.Kuo ve ark. tarafından yapılan bir analizde 15.463 diyabetik olmayan karaciğer nakli alıcılarında PTDM sıklığı %26.5 olarak rapor edilmiştir.Akciğer nakli sonrası PTDM için %25-40 prevalans, 1.yılda %6-43 ve 3-5. yılda %21-60 insidans bildirilmektedir. Uluslararası Kalp ve Akciğer Nak-

1 Uzm.Dr.Çiğdem ÖZDEMİR Antalya Eğitim ve Araştırma Hastanesi cgdemir@gmail.com

LDL-K deęerinin 100mg/dl üzerinde olması nedeniyle statin tedavisi planlanabilir mümkünse atorvastatin dıřı bir řeçenek düşünölmelidir.

KAYNAKLAR

1. Rana A, Gruessner A, Aopian VG. Survival benefit of solid-organ transplant in the United States. *JAMA Surg* 2015;150(3):252-9.
2. Kim W,et al .OPTN/SRTR 2016 annual data report: liver.*Am.J.Transplant* 2018;18 Suppl.1:172-253.
3. Valapour M, et al.OPTN/SRTR 2016 annual data report: lung.*Am.J.Transplant* 2018;18 Suppl.1:363-433.
4. Bloom RD, Crutchlow MF. New-onset diabetes mellitus in the kidney recipient: diagnosis and-management strategies.*Clin J Am Soc Nephrol* 2008 ;3(Suppl.2):S38-48.
5. Kobashigawa JA, KasiskeBL.Hyperlipidemia in solid organ transplantation.*Tranplantation* 1997;63(3):331-8.
6. Friedman AN, Miskulin DC, Rosenberg IH.Demographic trends in over weight and obesity in patients at time of kidney transplantation. *Am J Kidney Dis* 2003;41(2):480-7
7. Laryea M,Watt KD, Molinari M. Metabolic syndrome in liver transplant recipients:prevalence and association with major vascular events. *Liver Transpl* 2007;13(8):1109-14.
8. Kasiske BL,Synder JJ, Gilbertson D,Diabetes mellitus after transplantation in the United States. *Am J Transplant* 2003;3:178.
9. Kasiske BL, Chakkeri HA, RoelJ.Explained and unexplained ischemic heart disease risk after-renal transplantation. *J Am Soc Nephrol* 2000;11:1735.
10. Montori V, Basu A, Erwin PJ. Post transplantation diabetes: asystematic review of the literature. *Diabetes Care* 2002; 5:583.
11. Lund LH, Edwards LB, Dipchand. 'The Registry of the international society for heart and lung-transplantation:thirty-third adult heart transplantation report-2016;focus theme: primary diagnostic indications for transplant' *The Journal of Heartand Lung Transplantation*,vol. 35,no.10,pp 1158-1169,2016.
12. Sharif A, Hecking M, de Vries AP. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014;14(9):1992-2000.
13. Hjelmsaeth J, Hartmann A, Leivestad T. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006;69(3):588-95.
14. Starzl TE, Marchioro TL, Rifkind D. Factors in successful renal transplantation. *Surgery* 1964;56:296-318.
15. Davidson J, Wilkinson A, Dantal J. New-onset diabetes after transplantation:2003 International consensus guidelines. Proceedings of an international expert panel meeting. *Transplantation* 2003;75:SS3-24.
16. Armstrong KA, Prins JB, Beller EM. Should an oral glucose tolerance test be performed routinely in all renal transplant recipients? *Clin J Am Soc Nephrol.* 2006;1:100-108.
17. Sulanc E, Lane JT, Puumala SE.New-onset diabetes after kidney transplantation:an application of 2003 international guidelines. *Transplantation.*2005;80:945-952.
18. Shabir S, Jham S, Harper L. Validity of glycated haemoglobin to diagnose new on set diabetes after transplantation. *Transpl Int.*2013;26:315-321.
19. Cosio FG, Pesavento TE, Osei K.Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int*2001;59:732-7.
20. Association AD(2018) Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41(Supplement 1):s1-s159.

21. Valderhaug TG, Jenssen T, Hartmann A. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. *Transplantation* 2009;88(3):429-434.
22. Nam JH, Mun JI, Kim SI. Beta cell dysfunction rather than insulin resistance is the main contributing factor for the development of post renal transplantation diabetes mellitus. *Transplantation* 2001;71:1417.
23. Hornum M, Jorgensen KA, Hansen JM. New-onset diabetes mellitus after kidney transplantation in Denmark. *Clin J Am Soc Nephrol*. 2010;5:709-16.
24. Hagen M, Hjelmestaeth J, Jenssen T. A 6-year prospective study on new onset diabetes mellitus, insulin release and insulin sensitivity in renal transplant recipients. *Nephrol Dial Transplant*. 2003;18(10):2154-9
25. Gallagher EJ, LeRoith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. *J Diabetes* 2009;1:9.
26. Winkelmayr WC, Chandraker A. Posttransplantation anemia: management and rationale. *Clin J Am Soc Nephrol* 2008;3(Suppl 2):S49.
27. Pimentel AL, Cavagnoli G, Camargo JL. Diagnostic accuracy of glycosylated hemoglobin for post-transplantation diabetes mellitus after kidney transplantation: systematic review and meta-analysis. *Nephrol Dial Transplant* 2017;32(3):565-572
28. Sabanayagam C, Liew G, Tai ES. Relationship between glycosylated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? *Diabetologia* 2009;52:1279.
29. Sharif A, Baboolal K. Complications associated with new-onset diabetes after kidney transplantation. *Nat Rev Nephrol* 2012; 8-34.
30. Schweer T, Gwinner W, Scheffner I. High impact of rejection therapy on the incidence of post-transplant diabetes mellitus after kidney transplantation. *Clin Transplant*. 2014;28:512-519.
31. Siraj ES, Abacan C, Chinnappa P. Risk factors and outcomes associated with post transplant diabetes mellitus in kidney transplant recipients. *Transplant Proc*. 2010;42:1685-1689.
32. Koo DD, Welsh KI, McLaren AJ. Cadaver versus living donor kidneys: impact of donor factors on antigen induction before transplantation. *Kidney Int*. 1999;56:1551-1559.
33. Naesens M, Li L, Ying L. Expression of complement components differs between kidney allografts from living and deceased donors. *J Am Soc Nephrol*. 2009;20:1839-1851.
34. Gourishankar S, Jhangri GS, Tonelli M. Development of diabetes mellitus following kidney transplantation: a Canadian experience. *Am J Transplant*. 2004;4:1876-1882.
35. Rodrigo E, Fernandez-Fresnedo G, Valero R. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 2006;17:S291.
36. Boudreaux JP, Mchugh L, Canafax DM. The impact of cyclosporine and combination immunosuppression on the incidence of posttransplant diabetes in renal-allograft recipients. *Transplantation* 1987;44(3):376-381.
37. Sumrani NB, Delaney V, Ding ZK. Diabetes mellitus after renal transplantation in the cyclosporine era - an analysis of risk factors. *Transplantation* 1991;51:343-7.
38. Yang J, Hutchinson II, Shah T. Genetic and clinical risk factors of new-onset diabetes after transplantation in Hispanic kidney transplant recipients. *Transplantation*. 2011;91:1114-1119.
39. Ghisdal L, Baron C, Le Meur Y. TCF7L2 polymorphism associates with new-onset diabetes after transplantation. *J Am Soc Nephrol*. 2009;20:2459-2467.
40. Tavira B, Coto E, Torres A. Association between a common KCNJ11 polymorphism (rs5219) and new-onset posttransplant diabetes in patients treated with tacrolimus. *Mol Genet Metab*. 2012;105:525-527.
41. Tavira B, Coto E, Diaz-Corte C. KCNQ1 gene variants and risk of new-onset diabetes in tacrolimus-treated renal-transplanted patients. *Clin Transplant*. 2011;25:E284-E291.
42. Kim YG, Ihm CG, Lee TW. Association of genetic polymorphisms of interleukins with new-onset diabetes after transplantation in renal transplantation. *Transplantation*. 2012;93:900-907.

43. Chen Y,Sampaio MS,Yang JW. Genetic polymorphisms of the transcription factor NFATc4 and development of new-onset diabetes after transplantation in Hispanic kidney transplant recipients. *Transplantation*.2012;93:325-330.
44. Nicoletto BB, Souza GC,Fonseca NK. Association between 276 G/T adiponectin gene polymorphisms and new-onset diabetes after kidney transplantation. *Transplantation*. 2013; 96: 1059-1064.
45. Cron DC,Noon KA,Cote DR.Using analytic morphomics to describe body composition associated with post-kidney transplantation diabetes mellitus. *Clin Transplant*.2017.
46. Sharif A,Cohney S.Post-transplantation diabetes-state of the art. *Lancet Diabetes Endocrinol* 2016; 4(4):337-349.
47. Le Fur A,Fournier MC,Gillaizeau F. Vitamin D deficiency is an independent risk factor for PTDM after kidney transplantation. *Transpl Int* 2016;29(2):207-215
48. Shah T,Kasravi A,Huang E.Risk factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation* 2006;82:1673-6.
49. Armstrong KA, Campbell SB,Hawley CM. Obesity is associated with worsening cardiovascular risk factor profiles and proteinuria progression in renal transplant recipients. *Am J Transplant* 2005;5:2710-8.
50. Cosio FG, Pesavento TE, Kin S.Patient survival after renal transplantation: IV.Impact of post-transplant diabetes. *Kidney Int* 2002;62:1440.
51. Marrero D,HernandezD,TamajonLP.Pre-transplant weight but not weight gain is associated with new-onset diabetes after transplantation: a multi-centre cohort Spanish study. *NDT Plus* 2010;3:ii15-20.
52. Mehta SH,Brancati FL,Sulkowski MS.Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000;133:592-9.
53. Bloom RD, Rao V, Weng F.Association of hepatitis C with post-transplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002;13:1374-80.
54. Fabrizi E,Martin P,Dixit V. Post-transplant diabetes mellitus and HCV seropositivity after renal transplantation: meta-analysis of clinical studies. *Am J Transplant* 2005;5:2433-40.
55. Kamar N, Toupan O,Buchler M. Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation *J Am Soc Nephrol* 2003;14:2092-8.
56. Hjelmestaeth J,Muller F,Jenssen T.Is there a link between cytomegalo virus infection and new-onset post-transplantation diabetes mellitus? Potential mechanisms of virus-induced beta-cell damage. *Nephrol Dial Transplant* 2005;20:2311-5.
57. Kimmel PL,Venet J-P, Meylan P.Cytomegalo virus infection and new-onset post-transplant diabetes mellitus. *Clin Transplant* 2008;22:245-9.
58. Vannini SD, Mazzola BL,Rodoni L.Permanently reduced plasma ionized magnesium among renal transplant recipients on cyclosporine. *Transpl Int* 1999;12:244-9.
59. Nadler JL,Buchanan T,Natarajan R. Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* 1993;21:1024-9.
60. Van Laecke S, Van Biesen W, Verbeke F. Post transplantation hypomagnesemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. *Am J Transplant* 2009;9:2140-9.
61. Hirsch IB, Paauw DS. Diabetes management in special situations. *Endocrinol Metab Clin North Am* 1997;26:631-45.
62. Van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009 39(2):81-93.
63. Dong M, Parsa AK, Eberhardt NL. Cellular and physiological mechanisms of new-onset diabetes mellitus after solid organ transplantation. *Diabet Med* 2012 29(7):e1-12.
64. Penforis A, Kuryl-Paulin S. Immunosuppressive drug-induced diabetes. *Diabetes Metab* 2006;32:539-546.

65. Ulrich S, Berchtold S, Ranta F. Serum and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. *Diabetes* 2005;54(4):1090-9.
66. Hjelmesaeth J, Hartmann A, Kofstad J. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 1997;64:979-83.
67. Heisel O, Heisel R, Balshaw R. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004;4:583-95.
68. Midvedt K, Hjelmesaeth J, Hartmann A. Insulin resistance after renal transplantation: the effect of steroid dose reduction and with draw al. *J Am Soc Nephrol* 2004;15:3233-9.
69. Woodle ES, First MR, Pirsch JA. Prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low dose corticosteroid therapy. *Ann Surg* 2008;248:564-77.
70. Vincenti F, Schena FP, Paraskevas S. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transplant* 2008;8:307-16.
71. Rostaing L, Cantarovich D, Mourad G. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation* 2005;79:807-14.
72. Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. *Transplant Proc.* 2004;36(Suppl 2):25S-32S.
73. Clipstone NA, Crabtree GR. Identification of calcineurin as a key signalling enzyme in T-lymphocyte activation. *Nature.* 1992;357:695-7.
74. Jain J, McCaffrey PG, Miner Z. The T-cell transcription factor NFATp is a substrate for calcineurin and interacts with Fos and Jun. *Nature.* 1993;365:352-5.
75. Soleimanpour SA, Crutchlow MF, Ferrari AM. Calcineurin signaling regulates human islet (beta)-cell survival. *J Biol Chem.* 2010;285:40050-9.
76. Kung L, Batiuk TD, Palomo-Pinon S. Tissue distribution of calcineurin and its sensitivity to inhibition by cyclosporine. *Am J Transplant.* 2001;1:325-33.
77. Heit JJ, Apelqvist AA, Gu X. Calcineurin/NFAT signalling regulates pancreatic beta-cell growth and function. *Nature.* 2006;443:345-9.
78. Ho IC, Kim JH, Rooney JW. A potential role for the nuclear factor of activated T cells family of transcriptional regulatory proteins in adipogenesis. *Proc Natl Acad Sci USA.* 1998;95:15537-41.
79. Delling U, Tureckova J, Lim HW. A calcineurin -NFATc3-dependent pathway regulates skeletal muscle differentiation and slow myosin heavy-chain expression. *Mol Cell Biol.* 2000;20:6600-11.
80. Hahn HJ, Dunger A, Laube F. Reversibility of the acute toxic effect of cyclosporin A on pancreatic B cells of Wistar rats. *Diabetologia.* 1986;29:489-94.
81. Hahn HJ, Laube F, Lucke S. Toxic effects of cyclosporine on the endocrine pancreas of Wistar rats. *Transplantation.* 1986;41:44-7.
82. Yagisawa T, Takahashi K, Teraoka S. Effects of cyclosporine on glucose metabolism in kidney transplant recipients and rats. *Transplant Proc.* 1987;19:1801-3.
83. Rostambeigi N, Lanza I, Dzeja P. Unique cellular and mitochondrial defects mediate FK506-induced islet beta-cell dysfunction. *Transplantation.* 2011;91:615-23.
84. Fuhrer DK, Kobayashi M, Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporine A are through regulation of the ATP-sensitive potassium channel. *Diabetes Obes Metab.* 2001;3:393-402.
85. Garvin PJ, Niehoff M, Staggborg J. Cyclosporine's effect on canine pancreatic endocrine function. *Transplantation.* 1988;45:1027-31.
86. Nielsen JH, Mandrup-Poulsen T, Nerup J. Direct effects of cyclosporine A on human pancreatic beta-cells. *Diabetes.* 1986;35:1049-52.
87. Tamura K, Fujimura T, Tsutsumi T. Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. *Transplantation.* 1995;59:1606-1613.
88. Yale JF, Chamelian M, Courchesne S. Peripheral insulin resistance and decreased insulin secretion after cyclosporine A treatment. *Transplant Proc.* 1988;20:985-8.

89. Ost L, Tyden G, Fehrman I. Impaired glucose tolerance in cyclosporine-prednisolone-treated renal graft recipients. *Transplantation*. 1988;46:370-2.
90. Pereira M J, Palming J, Rizell M. Cyclosporine A and tacrolimus reduce the amount of GLUT4 at the cell surface in human adipocytes: increased endocytosis as a potential mechanism for the diabetogenic effects of immunosuppressive agents. *J Clin Endocrinol Metab*. 2014;99:E1885-E1894.
91. Chin ER, Olson EN, Richardson JA. A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. *Genes Dev*. 1998;12:2499-509.
92. Van Hooff JP, Christiaans MH, van Duijnhoven EM. Tacrolimus and posttransplant diabetes mellitus in renal transplantation. *Transplantation*. 2005;79:1465-9.
93. Vincenti F, Friman S, Scheuermann E. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 2007;7:1506-14.
94. Ghisda L, Bouchta NB, Broeders N. Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature. *Transpl Int*. 2008;21:146-151.
95. Pham PC, Pham PM, Pham SV. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2007;2:366-373.
96. Waldner M, Fantus D, Solari M. New perspectives on mTOR inhibitors (rapamycin, rapalogs and TOR Kinibs) in transplantation. *Br J Clin Pharmacol*. 2016 ;82:1158-70.
97. Bussiere CT, Lakey JR, Shapiro AM. The impact of the mTOR inhibitor sirolimus on the proliferation and function of pancreatic islets and ductal cells. *Diabetologia*. 2006;49:2341-9.
98. Johnston O, Rose CL, Webster AC. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol*. 2008;19:1411.
99. Santos AH Jr, Chen C, Casey MJ. New-onset diabetes after kidney transplantation: can the risk be modified by choosing immunosuppression regimen based on pre transplant viral serology? *Nephrol Dial Transplant*. 2018;33(1):177-184.
100. Murakami N, Riella V, Funakoshi T. Risk of metabolic complications in kidney transplantation after conversion to mTOR inhibitor: A systematic review and meta-analysis. *American Journal of Transplantation*. 2014; vol 14, no. 10:2317-2327.
101. Aasebo W, Midtvedt K, Valderhaug TG. Impaired glucose homeostasis in renal transplant recipients receiving basiliximab. *Nephrol Dial Transplant*. 2011;25:1289-93.
102. Setoguchi R, Hori S, Takahashi T. Homeostatic maintenance of natural Foxp3+ CD25(+)CD4(+) regulatory T cells by interleukin (IL)2 and induction of autoimmune disease by IL-2 neutralization. *J Exp Med*. 2005;201:723-35.
103. Choe EY, Wang HJ, Kwon O. HMG CoA reductase inhibitor treatment induces dysglycemia in renal allograft recipients. *Transplantation*. 2014;97:419-425.
104. Cho Y, Lee MJ, Choe EY. Statin therapy is associated with the development of new-onset diabetes after transplantation in liver recipients with high fasting plasma glucose levels. *Liver Transpl*. 2014;20:557-563.
105. Kuo HT, Sampaio MS, Ye X. Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. *Transplantation*. 2010;89:1134-1140.
106. Moran A, Brunzell C, Cohen RC. Clinical care guide lines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33:2697-708.
107. Fazekas-Lavu M, Reyes M, Malouf M. High prevalence of diabetes before and after lung transplantation: target for improving outcome? *Internal Medicine Journal*. 2018;48:916-924.
108. Belle-van Meerkerk G, Van de Graaf E.A, Kwakkel-van Erp J.M. Short report: Epidemiology Diabetes before and after lung transplantation in patients with cystic fibrosis and other lung diseases. *Diabetic Medicine*. 2012; 1464-5491.

109. Bradbury RA, Shirkhedkar D, Glanville AR. Prior diabetes mellitus is associated with increased-morbidity in cystic fibrosis patients under going bilateral lung transplantation: an 'orphan' area? A retrospective case-control study. *Intern Med J.* 2009;39:384-8.
110. Revanur VK, Jardine AG, Kingsmore DB. Influence of diabetes mellitus on patient and graft survival in recipients of kidney transplantation. *Clin Transplant.* 2001;15:89-94.
111. Cosio FG, Kudva Y, van der Velde M. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int.* 2005;67:2415-2421.
112. Burroughs TE, Swindle J, Takemoto S. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. *Transplantation.* 2007;83:1027-1034.
113. Moro JA, Martinez-Dolz L, Almenar L. Impact of diabetes mellitus on heart transplant recipients (in Spanish) *Rev Esp Cardiol.* 2006;59:1033-1037.
114. Mogollon Jimenez MV, Sobrino Marquez JM, Arizon Munoz JM. Incidence and importance of de-novo diabetes mellitus after heart transplantation. *Transplant Proc.* 2008;40:3053-3055.
115. Cho MS, Choi HI, Kim IO. The clinical course and outcomes of post-transplantation diabetes mellitus after heart transplantation. *J Korean Med Sci.* 2012;27:1460-1467.
116. Lv C, Zhang Y, Chen X. New-onset diabetes after liver transplantation and its impact on complications and patient survival. *J Diabetes.* 2015;7:881-890.
117. Veldt BJ, Poturucha JJ, Watt KD. Insulin resistance, serum adipokines and risk of fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant.* 2009;9:1406-1413.
118. Xu X, Ling Q, He ZL. Post-transplant diabetes mellitus in liver transplantation: Hangzhou experience. *Hepatobiliary Pancreat Dis Int.* 2008;7:465-470.
119. Hackman KL, Bailey MJ, Snell GI. Diabetes is a major risk factor for mortality after lung transplantation. *Am J Transplant.* 2014;14:438-445.
120. Hackman KL, Snell GI, Bach LA. Prevalence and predictors of diabetes after lung transplantation: a prospective, longitudinal study. *Diabetes Care.* 2014;37:2919-2925.
121. Hermayer KL, Egidi MF, Finch NJ. A randomized controlled trial to evaluate the effect of glycemic control on renal transplantation outcomes. *J Clin Endocrinol Metab.* 2012;97:4399-4406.
122. American Diabetes Association. 13. Diabetes care in the hospital, nursing home, and skilled nursing facility. *Diabetes Care.* 2015;38(suppl):S80-S85.
123. Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9(Suppl 3):S1-S155.
124. Diabetes Prevention Program Research Group. Reduction in the incidence of Type 2 Diabetes with Life style Intervention or Metformin. *N Engl J Med.* 2002;346:393-403.
125. Zhou G, Myers R, Li Y. Role of AMP-activated protein kinase in mechanism of metformin action' *The Journal of Clinical Investigation,* 2001; vol. 108 no.8:1167-1174.
126. Shivaswamy V, Bennett RG, Clure CC. Metformin improves immunosuppressant induced hyper-glycemia and exocrine apoptosis in rats. *Transplantation.* 2013;95:280-284.
127. Zhang X, Harmsen WS, Mettler TA. Continuation of metformin use after diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology.* 2014;60:2008-16.
128. McCormack J, Johns K, Tildesley H. Metformin's contra indications should be contraindicated. *CMAJ.* 2005;173:502-4.
129. American Diabetes Association 'Standards of medical care in diabetes -2017' *Journal of Diabetes.* 2017;vol.40 no.7:s1-s135
130. Vanhove T, Remijsen Q, Kuypers D. Drug-drug interactions between immunosuppressant and antidiabetic drugs in the treatment of post transplant diabetes mellitus. *Transplant Rev (Orlando).* 2017;31:69-77.
131. Scheen AJ. Pharmacokinetic considerations for the treatment of diabetes in patients with chronic kidney disease. *Exp Opin Drug Metab Toxicol.* 2013;9(5):529-550.
132. Sagedal S, Asberg A, Hartmann A. Glipizide treatment of post-transplant diabetes does not interfere with cyclosporine pharmacokinetics in renal allograft recipients. *Clin Transplant.* 1998;12:553-6.

133. Türk T, Pietruck F, Dolff S. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant.* 2006;6:842-6.
134. Charpentier G, Riveline JP, Varroud-Via IM. Management of drugs affecting blood glucose in diabetic patients with renal failure. *Diabetes Metab.* 2000;26(Suppl.4):73-85.
135. Luther P, Baldwin Jr D. Pioglitazone in the management of diabetes mellitus after transplantation. *Am J Transplant.* 2004;4:2135-8.
136. Grey AB. Skeletal toxicity of thiazolidinediones. *Ann Intern Med.* 2008;148:563.
137. Boerner BP, Miles CD, Shivaswamy V. Efficacy and safety of sitagliptin for the treatment of new-onset diabetes after renal transplantation. *International Journal of Endocrinology.* 2014.
138. Gueler I, Mueller S, Helmschrott M. Effects of vildagliptin (Galvus) therapy in patients with type 2 diabetes mellitus after heart transplantation. *Drug Design, Development and Therapy.* 2013;vol 7:pp.297-303
139. Amin M, Suksomboon. Pharmacotherapy of type 2 diabetes mellitus: An update on drug-drug interactions. *Drug Safety.* 2014;vol 37, no 11:903-919.
140. Ravassa S, Zudaire A, Diez J. GLP-1 and cardioprotection: From bench to bedside. *Cardiovascular Research.* 2012;vol 94 no 2:316-323.
141. Scirica BM, Bhatt DL, Braunwald E. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *The New England Journal of Medicine.* 2013;vol 369 no 14: 1317-1326.
142. White WB, Cannon CP, Heller SR. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *The New England Journal of Medicine.* 2013;vol 369 no 14 :1327-1335.
143. Green JB, Bethel MA, Armstrong PW. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *The New England Journal of Medicine.* 2015;vol 373 no 3:232-242.
144. Pinelli NR, Patel A, Salinitri FD. Coadministration of liraglutide with tacrolimus in kidney transplant recipients: a case series. *Diabetes Care.* 2013;36:e171-e172.
145. Ekberg H, Tedesco-Silva H, Demirbaş A. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med.* 2007;357:2562-75.
146. Zinman B, Wanner C, Lachin JM. EMPA-REG outcome investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:21127-28.
147. Neal B, Perkovic V, Mahaffey KW. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644-57.
148. Wanner C, Inzucchi SE, Lachin JM. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375:323-34.
149. Jin J, Jin L, Luo K. Effect of empagliflozin on tacrolimus-induced pancreas islet dysfunction and renal injury. *Am J Transplant.* 2017;17:2601-16.
150. Muir CA, Greenfield JR, Mac Donald PS. Empagliflozin in the management of diabetes mellitus after cardiac transplantation. *J Heart Lung Transplant.* 2011;36:914-6.
151. Rajasekaran H, Kim SJ, Cardella CJ. Use of canagliflozin in kidney transplant recipients for the treatment of type 2 diabetes: a case series. *Diabetes Care.* 2017;40:e75-6.
152. Pei D, Chen TW, Kuo YL. The effect of surgical stress on insulin sensitivity, glucose effectiveness and acute insulin response to glucose load. *J Endocrinol Invest.* 2003;26:397-402.
153. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. *Diabetologia.* 1984;27:351-357.
154. Garcia C, Wallia A, Gupta S. Intensive glycemic control after heart transplantation is safe and effective for diabetic and non-diabetic patients. *Clin. Transplant.* 2013;27:444-454.
155. Keegan MT, Vrchota JM, Haala PM. Safety and effectiveness of intensive insulin protocol use in postoperative liver transplant recipients. *Transplant Proc.* 2010;42:2617-2624.
156. Boerner B, Shivaswamy V, Goldner W. Management of the hospitalized transplant patient. *Curr Diab Rep.* 2015;15:585.
157. Pelaez-Jaramillo JM, Cardenas-Mojica AA, Gaete PV. Post-Liver Transplantation Diabetes Mellitus: A Review of Relevance and Approach to Treatment. *Diabetes Ther.* 2018;9:521-543.
158. Rochl KA, Lach K, Coltman AE. Predictors of insulin requirement among hospitalized adults receiving parenteral nutrition. *J Parenter Enteral Nutr.* 2013;37:755-762.

159. Taler SJ, Agarwa IR, Bakris GL. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. *Am J Kidney Dis.* 2013;62:201-213.
160. Bia M, Adey DB, Bloom RD. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Kidney Dis.* 2010;56:189-218.
161. Kasiske B, Cosio FG, Beto J. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: are part from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant.* 2004;4(suppl 7):13-53.
162. Brattström C, Wilczek H, Tyden G. Hyperlipidemia in renal transplant recipients treated with sirolimus (rapamycin). *Transplantation.* 1998;65:1272-1274.
163. Gruessner RW, Sutherland DE, Parr E. A prospective, randomized, open-label study of steroid withdrawal in pancreas transplantation - a preliminary report with 6-month follow-up. *Transplant Proc.* 2001;33:1663-1664.
164. Shivaswamy V, Boerner B, Larsen J. Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. *Endocrine Reviews.* February 2016;37(1):37-61.
165. Mack-Shipman LR, Ratanasuwan T, Leone JP. Reproductive hormones after pancreas transplantation. *Transplantation.* 2000;70:1180-1183.
166. Shivaswamy V, Ochsner L, Maroni D. Tacrolimus and sirolimus induce productive abnormalities in female rats. *Transplantation.* 2011;91:1333-1339.
167. Deutsch MA, Kczmarek L, Huber S. Sirolimus-associated infertility: case report and literature review of possible mechanisms. *Am J Transplant.* 2007;7:2414-2421.