NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-3-e010

Editorial

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Volume 3 : Issue 1
Article Ref. #: 1000NPOJ3e010

Article History
Received: October 6th, 2017
Accepted: December 18th, 2017
Published: December 18th, 2017

Citation
Triñanes J. Post-transplant diabetes: New insights beyond calcineurin inhibition. *Nephrol Open J*. 2017; 3(1): e22-e25. doi: 10.17140/NPOJ-3-e010

Post-Transplant Diabetes: New Insights Beyond Calcineurin Inhibition

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Despite impressive improvements in the 1-year graft survival for kidney transplantation, which has risen from 60% to 95% over the last few decades, little progress has been made in long-term graft survival. Half of the grafted and functional kidneys are lost within 10-12 years after transplantation because of premature recipient mortality; cardiovascular disease being a leading cause of both death and graft loss in this population. Many dialysis patients have acquired into end-stage kidney diseases because of diabetes, but among those non-diabetic patients, the majority suffer from a constellation of cardiovascular risk factors, including overweight, hypertension, dyslipidemia, and insulin resistance. After kidney transplantation, recipients often experience about 10-15% of weight gain,[1] owing to increased appetite by steroids, as well as the loss of uremia and dietary restrictions from the dialysis period. Additionally, many recipients experience difficulties with exercise due to comorbid conditions like sarcopenia, amputations, or heart failure. All these circumstances make a perfect breeding ground for the development of diabetes after transplantation, or post-transplant diabetes (PTDM). PTDM develops from the interplay of transplant-specific factors such as immunosuppressive drugs on top of all these traditional risk factors.[2] PTDM is a relatively common complication after kidney transplantation that influences graft and patient survival, and is defined as a type of diabetes that occurs after a transplant procedure in patients who did not present any remarkable feature of diabetes before the transplantation. The timing for diagnosis has not been clearly established but most PTDM happen during the first three months after transplantation,[3] which is the period with the greatest exposure to the immunosuppressive cocktail. Therefore, the disease seems to develop because of the effect of immunosuppressive drugs in both insulin sensitivity (in peripheral tissues) and insulin secretion (by pancreatic beta-cells). However, minimising or withdrawing immune suppression is often unwanted because of the fear of rejection, and it remains difficult to lose weight after transplantation. Since no established therapy exists to prevent or revert PTDM, understanding the mechanisms involved in the effects of the immunosuppressive therapies in pancreatic beta-cells will be essential to improve preventive and therapeutic strategies for transplant recipients.

Calcineurin inhibition is one of the corner stones for current immunosuppressive regimens,[4] it is based on two major drugs: tacrolimus and cyclosporine-A; tacrolimus being the most widely used now-a-days. The traditional paradigm is that calcineurin inhibition acts not only in lymphocytes, but also subsequently the main action of the drug itself induces failures in insulin production/secretion by inhibiting the calcineurin/nuclear factor of activated T-cells (NFAT) pathway in pancreatic beta-cells.[5] However, trial and registry data have demonstrated that the use of tacrolimus increases the risk of PTDM when compared with cyclosporine-A,[6] while both drugs share calcineurin as target. The general thought is that tacrolimus is more diabetogenic because it is a more potent calcineurin inhibitor; but taking into account that the trough levels used in clinical practise for cyclosporine-A are usually 20-times higher than those used for tacrolimus, the inhibition of the phosphatase calcineurin is not different between drugs.[7] Additionally, when those clinical trough levels were used to treat beta-cells in culture, the same grade of calcineurin activity and NFAT activation was observed.[8] So the higher diabetogenicity of tacrolimus must be due to some other factors in addition to the inhibition of calcineurin.

ISSN 2380-0445 http://dx.doi.org/10.17140/NPOJ-3-e010

Porriniet al[9] analysed separately, kidney recipients with normal levels of triglycerides in blood before the transplantation from those with hypertriglyceridemia (hypertriglyceridemia is one of the characteristics of the metabolic syndrome). Their results showed that the use of tacrolimus as main immunosuppressive drug significantly increased the risk of developing PTDM compared with patients on cyclosporine-A, only in the hypertriglyceridemic group. In the absence of hypertriglyceridemia the risk for developing PTDM was the same for both calcineurin inhibitors. Additionally, in a study developed in obese Zucker rats, an animal model of insulin resistance that can compensate the increased demand of insulin not developing diabetes by itself, tacrolimus caused more diabetes than cyclosporin (100% *vs*. 40%), whereas neither tacrolimus nor cyclosporine-A caused diabetes in lean (insulin sensitive) Zucker rats.[10] In these animals, tacrolimus reduced beta-cell proliferation compared with cyclosporine-A, together with a reduction in insulin levels and in islet area, but apoptosis was not identified as a reason for beta-cell failure or islet area reduction in this model. *Consequently, the toxic effect of tacrolimus on pancreatic beta-cells depends on the pre-existence of metabolic alterations induced by increased levels of lipids, increased oxidative stress or an increased demand of insulin due to insulin resistance.* Furthermore, both cessation of tacrolimus and conversion to cyclosporine-A, led to partial recovery of beta-cell function and proliferation. Importantly, this improvement in glucose metabolism after switching from tacrolimus to cyclosporine-A has been also observed in clinical studies,[11] and it indicates that beta-cells are resilient enough to overcome the negative effect of the drug when it is not present anymore. The fact that cyclosporine-A has no such effects on the glucose metabolism indicates that there must be something else beyond calcineurin inhibition. However, the pathways involved in the mechanisms of tacrolimus-induced beta-cell failure are still unknown, but further research has evaluated similarities between beta-cell failure induce by tacrolimus with the "*normal*" beta-cell failure that happens in the progression towards type-2 diabetes.[8]

Now-a-days we know that, during development, when a progenitor cell differentiates into a beta-cell it does not acquire a *locked* state, but the maintenance of that differentiated new state (the functional beta-cell) needs an active and continuous production process of the pieces that form the machinery for glucose sensing, insulin synthesis and secretion. In other words, maintenance of the beta-cell identity requires the continuous activation of beta-cell-specific transcription factors.[12] We have several evidences indicating that the alterations in these mechanisms of maintenance may conduce to a *dedifferentiated* state, a state in which the cell is not producing beta-cell identity markers anymore, and therefore it cannot be identified as beta-cell with the traditional immunological techniques. This may explain the contradictory absence of apoptosis observed together with a reduction in beta-cell mass in some experimental models.[10] Importantly, whether this dedifferentiation in the absence of apoptosis is confirmed, it may bring some hope for the recovery of our patients with PTDM, and it opens a door for future treatments based on the reconstitution of beta-cell mass.

Among the transcription factors that are essential to maintain a functional beta-cell, it is worth to highlight the pancreatic and duodenal homeobox 1 (PDX1), v-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), and neuronal differentiation 1 (NEUROD). The beta-cell transcription factors work together to induce the expression of those genes that give a beta-cell its fingerprint.[13] Interestingly, the loss of some of them has been observed in patients with type-2 diabetes.[14] Triñanes et al has shown how the addition of tacrolimus in metabolically stressed beta-cells induce the loss of some of these factors, while these changes cannot be induced neither by the treatment with cyclosporine-A nor in metabolically non-stressed beta-cells.[8] Accordingly, with the fact that tacrolimus needs some metabolic alterations to induce beta-cell failure, we have examined what could be the molecular link between metabolic stress and tacrolimus-induced beta-cell failure. This synergy, or combined mechanism, does not have a molecular translation yet, but the fork-head box protein O1 (FOXO1) might be a relevant player in the process of PTDM.[15] We have found that the nuclear translocation of FOXO1 in beta-cells is a characteristic that happens when these cells are more susceptible to tacrolimus-induced damage. This important transcription factor mediates proliferation in rodents' beta-cells, being its nuclear exclusion necessary for beta-cell expansion in insulin resistant states.[16] It is also known that FOXO1 plays an early role in beta-cell dysfunction, and normally its nuclear presence precedes the loss of the essential beta-cell transcription factor MAFA,[17] being also related with the loss of other important beta-cell transcription factor like PDX1.[18] Additionally, analyses of pancreata from type-2 diabetic patients have shown that nuclear levels of FOXO1 are higher in diabetic patients than in normal population.[14]

The loss of these beta-cell essential factors in our experimental set-up,[8] together with the necessity of this metabolic stress (maybe mediated by FOXO1) for the induction of beta-cell failure by tacrolimus, have pushed us to think that beyond calcineurin inhibition, tacrolimus may induce an accelerated progression towards a beta-cell failure, resembling at a pancreatic level the progression towards type-2 diabetes. It is important to highlight that despite the higher incidence of PTDM in tacrolimus-treated patients, this drug produces better graft function and less nephrotoxicity than other immunosuppressive regimenes,[19] therefore become the standard therapy for kidney transplantation. On the other hand, calcineurin and NFAT, common targets of tacrolimus and cyclosporine-A, may have a relevant role in beta-cell function and integrity,[5] and the inhibition of this pathway may also promote beta-cell dysfunction. However, tacrolimus definitely has additional effects in beta-cells and these effects need to be further studied. Likewise, it is also important to have a better knowledge about the diabetogenic mechanisms induced by other family of immunosuppressive drugs, the inhibitors of the mammalian target of rapamycin (mTOR), being sirolimus the most representative among them. These drugs act inhibiting the mTOR kinase, which is a downstream effector of the insulin signalling pathway that integrates different anabolic signals and enhances protein synthesis. The existence of this pathway in beta-cells indicates that sirolimus might

ISSN 2380-0445 http://dx.doi.org/10.17140/NPOJ-3-e010

affect mechanisms of insulin synthesis and secretion,[20] but further studies are needed to clarify the precise effects. The importance of organ transplantation now-a-days in medicine and the essential use of immunosuppressive drugs to achieve good results makes it crucial to obtain a better knowledge about these mechanisms. This approach will drive us to better immunosuppressive therapies and better long-term graft survival in kidney transplantation.

REFERENCES

1. Aksoy N. Weight gain after kidney transplant. *Exp Clin Transplant*. 2016; 14(Suppl 3): 138-140.

2. Rodrigo E, Fernández-Fresnedo G, Valero R, et al. New-onset diabetes after kidney transplantation: Risk factors. *J Am Soc-Nephrol*. 2006; 17(12 Suppl 3): S291-S295. doi: 10.1681/ASN.2006080929

3. Hornum M, Jorgensen KA, Hansen JM, et al. New-onset diabetes mellitus after kidney transplantation in Denmark. *Clin J Am Soc Nephrol*. 2010; 5(4): 709-716. doi: 10.2215/CJN.05360709

4. Ponticelli C. Calcineurin inhibitors in renal transplantation. Too precious to be abandoned. *Nephrology Dialysis Transplantation*. 2000; 15(9): 1307-1309. doi: 10.1093/ndt/15.9.1307

5. Heit JJ, Apelqvist AA, Gu X, et al. Calcineurin/NFAT signalling regulates pancreatic beta-cell growth and function. *Nature*. 2006; 443(7109): 345-349. doi: 10.1038/nature05097

6. O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A; UK and Republic of Ireland Liver Transplant Study Group. Tacrolimus versus micro emulsified ciclosporin in liver transplantation: The TMC randomised controlled trial. *Lancet*. 2002; 360(9340): 1119-1125. doi: 10.1016/S0140-6736(02)11196-2

7. Fruman DA, Klee CB, Bierer BE, Burakoff SJ. Calcineurin phosphatase activity in T lymphocytes is inhibited by FK 506 and cyclosporin A. *Proc Natl Acad Sci U S A*. 1992; 89(9): 3686-3690.

8. Triñanes J, Rodriguez-Rodriguez AE, Brito-Casillas Y, et al. Deciphering tacrolimus-induced toxicity in pancreatic β cells. *Am J Transplant*. 2017. doi: 10.1111/ajt.14323

9. Porrini E, Delgado P, Alvarez A, et al. The bcombined effect of pre-transplant triglyceride levels and the type of calcineurin inhibitor in predicting the risk of new onset diabetes after renal transplantation. *Nephrol Dial Transplant*. 2008; 23(4): 1436-1441. doi: 10.1093/ndt/gfm762

10. Rodriguez-Rodriguez AE, Triñanes J, Velazquez-Garcia S, et al. The higher diabetogenic risk of tacrolimus depends on pre-existing insulin resistance. A study in obese and lean Zucker rats. *Am J Transplant*. 2013; 13(7): 1665-1675. doi: 10.1111/ajt.12236

11. Rathi M, Rajkumar V, Rao N, et al. Conversion from tacrolimus to cyclosporine in patients with new-onset diabetes after renal transplant: An open-label randomized prospective pilot study. *Transplant Proc*. 2015; 47(4): 1158-1161. doi: 10.1016/j.transproceed.2014.12.050

12. Szabat M, Lynn FC, Hoffman BG, Kieffer TJ, Allan DW, Johnson JD. Maintenance of β-cell maturity and plasticity in the adult pancreas: developmental biology concepts in adult physiology. *Diabetes*. 2012; 61(6): 1365-1371. doi: 10.2337/db11-1361

13. Xu H, Tsang KS, Chan JC, Yuan P, Fan R, Kaneto H, Xu G. The combined expression of Pdx1 and MafA with either Ngn3 or NeuroD improves the differentiation efficiency of mouse embryonic stem cells into insulin-producing cells. *Cell Transplant*. 2013; 22(1): 147-158. doi: 10.3727/096368912X653057

14. Spijker HS, Song H, Ellenbroek JH, et al. Loss of β-cell identity occurs in type 2 diabetes and is associated with islet amyloid deposits. *Diabetes*. 2015; 64(8): 2928-2938. doi: 10.2337/db14-1752

15. Kitamura T. The role of FOXO1 in β-cell failure and type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2013; 9(10): 615-623. doi: 10.1038/nrendo.2013.157

16. Okamoto H, Hribal ML, Lin HV, Bennett WR, Ward A, Accili D. Role of the forkhead protein FoxO1 in beta cell compensation

ISSN 2380-0445 http://dx.doi.org/10.17140/NPOJ-3-e010

to insulin resistance. *J Clin Invest*. 2006; 116(3): 775-782. doi: 10.1172/JCI24967

17. Guo S, Dai C, Guo M, et al. Inactivation of specific β cell transcription factors in type 2 diabetes. *J Clin Invest*. 2013; 123(8): 3305-3316. doi: 10.1172/JCI65390

18. Kitamura T, Nakae J, Kitamura Y, et al. The forkhead transcription factor Foxo1 links insulin signaling to Pdx1 regulation of pancreatic beta cell growth. *J Clin Invest*. 2002; 110(12): 1839-1847. doi: 10.1172/JCI16857

19. Martins L, Ventura A, Branco A, et al. Cyclosporine versus tacrolimus in kidney transplantation: Are there differences in nephrotoxicity? *Transplant Proc*. 2004; 36(4): 877-879. doi: 10.1016/j.transproceed.2004.03.083

20. Bussiere CT, Lakey JR, Shapiro AM, Korbutt GS. The impact of the mTOR inhibitor sirolimus on the proliferation and function of pancreatic islets and ductal cells. *Diabetologia*. 2006; 49(10): 2341-2349. doi: 10.1007/s00125-006-0374-5