Proyecto Prometeo

Alteraciones de los lípidos en postrasplante renal

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Dossier bibliográfico

Grupo II | Inmunosupresores y Alteraciones de los Lípidos

Portavoz | **Dr. Frederic Cofan**
Hospital Clínic, Barcelona

Con el patrocinio de:

SET
SOCIEDAD ESPAÑOLA DE TRASPLANTE

Sociedad Española de Nefrología

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PROMETEO VI: Lípidos y Trasplante Renal

GRUPO 2- Inmunosupresores y Alteraciones de los Lípidos

Portavoz: Federic Cofan

	Apellidos	Nombre	Hospital	Ciudad	Artículos asignados	Nº Art.
1	Alonso Melgar	Ángel	Hospital Universitario La Paz (TX Pediatricos)	Madrid	**1. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study.** Grenda R, Watson A, Trompeter R, Tönshoff B, Jaray J, Fitzpatrick M, Murer L, Vondrak K, Maxwell H, van Damme-Lombaerts R, Loirat C, Mor E, Cochat P, Milford DV, Brown M, Webb NJ. Am J Transplant 2010;10(4):828-36. **2. Five-year experience using sirolimus-based, calcineurin inhibitor-free immunosuppression in pediatric renal transplantation.** Hymes LC, Warshaw BL. Pediatr Transplant 2011;15(4):437-41.	68 69
2	Cofan Pujol	Frederic	Hospital Clínic	Barcelona	**1. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection.** Marcén R. Drugs. 2009 Nov 12;69(16):2227-43.	52
3	Canal Girol	Cristina	Fundación Puigvert	Barcelona	**1. Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen.** Sampaio EL, Pinheiro-Machado PG, Garcia R, Felipe CR, Park SI, Casarini DE, Moreira S, Franco MF, Tedesco-Silva H Jr, Medina-Pestana JO. Clin Transplant 2008;22(2):141-9. **2. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus.** Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F, Wiecek A, Chadban S, El-Shahawy M, Budde K, Goto N; DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C Monitoring Versus Tacrolimus) Investigators. Am J Transplant 2007;7(6):1506-14. Erratum in: Am J Transplant. 2008 Jan;8(1):1. Am J Transplant. 2008 Apr;8(4):908.	72 73
4	Errasti	Pedro	Clínica Universitaria de Navarra	Pamplona	**1. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies).** Vanrenterghem Y, Bresnahan B, Campistol J, Durrbach A, Grinyó J, Neumayer HH, Lang P, Larsen CP, Mancilla-Urrea E, Pestana JM, Block A, Duan T, Glicklich A, Gujrathi S, Vincenti F. Transplantation. 2011 May 15;91(9):976-83. **2. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study.** Claes K, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Nephrol Dial Transplant. 2012 Feb;27(2):850-7.	48 43
5	Fijo López-Viota	Julia	Hospital Virgen del Rocío (TX Pediátrico)	Sevilla	**1.Unusual pattern of dyslipidemia in children receiving steroid minimization immunosuppression after renal transplantation.** Lau KK, Tancredi DJ, Perez RV, Butani L. 51. Clin J Am Soc Nephrol. 2010 Aug;5(8):1506-12. **2. Hyperlipidaemia in Paediatric Patients The Role of Lipid-Lowering Therapy in Clinical Practice** Drug Saf 2010; 33 (2): 115-125	51 65
6	Gutiérrez Dalmau	Alex	Hospital Miguel Servet	Zaragoza	**1. Everolimus inhibits monocyte/macrophage migration in vitro and their accumulation in carotid lesions of cholesterol-fed rabbits.** Baetta R, Granata A, Canavesi M, Ferri N, Arnaboldi L, Bellosta S, Pfister P, Corsini A. J Pharmacol Exp Ther. 2009 Feb;328(2):419-25. Epub 2008 Nov 20. **2. Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue.** Houde VP, Brûlé S, Festuccia WT, Blanchard PG, Bellmann K, Deshaies Y, Marette A. Diabetes. 2010 Jun;59(6):1338-48. Epub 2010 Mar 18.	26 15
7	Jimeno	Luisa	Hospital Virgen de la Arrixaca	Murcia	**1. Optimizing tacrolimus therapy in the maintenance of renal allografts: 12-month results.** Bolin P Jr, Shihab FS, Mulloy L, Henning AK, Gao J, Bartucci M, Holman J Jr, First MR; OPTIMA Study Group. Transplantation 2008;86:88-95. **2. Conversion from cyclosporine to tacrolimus in patients at risk for chronic renal allograft failure: 60-month results of the CRAF Study.** Shihab FS, Waid TH, Conti DJ, Yang H, Holman MJ, Mulloy LC, Henning AK, Holman J Jr, First MR; CRAF Study Group. Transplantation 2008;85(9):1261-9.	70 71
8	López Oliva	María	Hospital Universitario La Paz	Madrid	**1. Steroid or tacrolimus withdrawal in renal transplant recipients using sirolimus.** de Sandes Freitas TV, Harada KM, Felipe CR, Galante NZ, Sampaio EL, Ikehara E, Alfieri F, Tedesco-Silva Júnior H, Medina-Pestana JO. Int Urol Nephrol 2011;43(4):1221-8. **2. A prospective, randomized, multicenter study evaluating early corticosteroid withdrawal with Thymoglobulin in living-donor kidney transplantation.** Woodle ES, Peddi VR, Tomlanovich S, Mulgaonkar S, Kuo PC; TRIMS Study Investigators. Clin Transplant 2010;24(1):73-83.	66 67
9	Crespo	Marta	Hospital del Mar	Barcelona	**1. Role of cellular cholesterol in pharmacologic preconditioning with cyclosporine in experimental kidney transplantation.** Shihab FS, Bennett WM, Andoh TF. Am J Nephrol. 2010;31(2):134-40. Epub 2009 Nov 17. **2. Cholesterol efflux to apoA-I in ABCA1-expressing cells is regulated by Ca2+-dependent calcineurin signaling.** Karwatsky J, Ma L, Dong F, Zha X. J Lipid Res. 2010 May;51(5):1144-56. Epub 2009 Dec 1.	18 16

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PROMETEO VI: Lípidos y Trasplante Renal

10	Romero Burgos	Rafael	Hospital Clínico Universitario de Santiago	Santiago de Compostela (A Coruña)	**1. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study.** Ekberg H, Grinyó J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, Truman M, Nasmyth-Miller C, Rashford M. Am J Transplant 2007;7(3):560-70. **2. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients.** Kasiske BL, de Mattos A, Flechner SM, Gallon L, Meier-Kriesche HU, Weir MR, Wilkinson A. Am J Transplant. 2008 Jul;8(7):1384-92.	74 61
11	Román Ortiz	Elena	Hospital Universitario La Fe	Valencia	**1. Similar lipid profile but improved long-term outcomes with sirolimus after cyclosporine withdrawal compared to sirolimus with continuous cyclosporine.** Morales JM, Hartmann A, Walker R, Arns W, Senatorski G, Grinyó JM, Shoker A, Wilczek H, Jamieson NV, Lelong M, Brault Y, Burke JT, Scarola JA; Rapamune Maintenance Regimen Study Group. 55. Transplant Proc. 2009 Jul-Aug;41(6):2339-44. **2. Tacrolimus-induced elevation in plasma triglyceride concentrations after administration to renal transplant patients is partially due to a decrease in lipoprotein lipase activity and plasma concentrations.** Tory R, Sachs-Barrable K, Goshko CB, Hill JS, Wasan KM. Transplantation. 2009 Jul 15;88(1):62-8.	55 54
12	Polanco	Natalia	Hospital 12 Octubre	Madrid	**1. Compared effect of immunosuppressive drugs cyclosporine A and rapamycin on cholesterol homeostasis key enzymes CYP27A1 and HMG-CoA reductase.** Gueguen Y, Ferrari L, Souidi M, Batt AM, Lutton C, Siest G, Visvikis S. Basic Clin Pharmacol Toxicol. 2007 Jun;100(6):392-7. **2. Sirolimus modifies cholesterol homeostasis in hepatic cells: a potential molecular mechanism for sirolimus-associated dyslipidemia.** Ma KL, Ruan XZ, Powis SH, Chen Y, Moorhead JF, Varghese Z. Transplantation. 2007 Oct 27;84(8):1029-36.	39 36
13	Melilli	Eduardo	Hospital Bellvitge	Barcelona	**1. Sirolimus inhibits endogenous cholesterol synthesis induced by inflammatory stress in human vascular smooth muscle cells.** Ma KL, Varghese Z, Ku Y, Powis SH, Chen Y, Moorhead JF, Ruan XZ. Am J Physiol Heart Circ Physiol. 2010 Jun;298(6):H1646-51. Epub 2010 Mar 26. **2. Low- but not high-dose FK506 treatment confers atheroprotection due to alternative macrophage activation and unaffected cholesterol levels.** Bai L, Gabriels K, Wijnands E, Rousch M, Daemen MJ, Tervaert JW, Biessen EA, Heeneman S. Thromb Haemost. 2010 Jul;104(1):143-50. Epub 2010 May 10.	14 13
14	Sánchez Hernández	Rosa	Hospital General de Segovia	Segovia	**1. Long-term assessment of plasma lipids in transplant recipients treated with tacrolimus in relation to fatty liver.** Tarantino G, Palmiero G, Polichetti G, Perfetti A, Sabbatini M, Basile V, Kadilli I, Federico S, Capone D. Int J Immunopathol Pharmacol. 2010 Oct-Dec;23(4):1303-8. **2. The mammalian target of rapamycin regulates cholesterol biosynthetic gene expression and exhibits a rapamycin-resistant transcriptional profile.** Wang BT, Ducker GS, Barczak AJ, Barbeau R, Erle DJ, Shokat KM. Proc Natl Acad Sci U S A. 2011 Sep 13;108(37):15201-6. Epub 2011 Aug 29.	75 5

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5. Proc Natl Acad Sci U S A. 2011 Sep 13;108(37):15201-6. Epub 2011 Aug 29.

The mammalian target of rapamycin regulates cholesterol biosynthetic gene expression and exhibits a rapamycin-resistant transcriptional profile.

Wang BT, Ducker GS, Barczak AJ, Barbeau R, Erle DJ, Shokat KM.

Source

Howard Hughes Medical Institute and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94158, USA.

Abstract

The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and proliferation in response to growth factor and nutrient signaling. Consequently, this kinase is implicated in metabolic diseases including cancer and diabetes, so there is great interest in understanding the complete spectrum of mTOR-regulated networks. mTOR exists in two functionally distinct complexes, mTORC1 and mTORC2, and whereas the natural product rapamycin inhibits only a subset of mTORC1 functions, recently developed ATP-competitive mTOR inhibitors have revealed new roles for both complexes. A number of studies have highlighted mTORC1 as a regulator of lipid homeostasis. We show that the ATP-competitive inhibitor PP242, but not rapamycin, significantly down-regulates cholesterol biosynthesis genes in a 4E-BP1-dependent manner in NIH 3T3 cells, whereas S6 kinase 1 is the dominant regulator in hepatocellular carcinoma cells. To identify other rapamycin-resistant transcriptional outputs of mTOR, we compared the expression profiles of NIH 3T3 cells treated with rapamycin versus PP242. PP242 caused 1,666 genes to be differentially expressed whereas rapamycin affected only 88 genes. Our analysis provides a genomewide view of the transcriptional outputs of mTOR signaling that are insensitive to rapamycin.

PMCID: PMC3174577 Free PMC Article

PMID: 21876130 [PubMed - indexed for MEDLINE]

13. Thromb Haemost. 2010 Jul;104(1):143-50. Epub 2010 May 10.

Low- but not high-dose FK506 treatment confers atheroprotection due to alternative macrophage activation and unaffected cholesterol levels.

Bai L, Gabriels K, Wijnands E, Rousch M, Daemen MJ, Tervaert JW, Biessen EA, Heeneman S.

Source

Maastricht University Medical Center, P. Debyelaan 25, Maastricht, The Netherlands.

Abstract

Previous studies showed both pro- and anti-atherogenic effects of immunosuppressant drug FK506 on atherosclerosis. As these divergent/paradoxical results of FK506 may at least in part be attributable to differences in FK506 dosing, we have, in the current study, assessed dose-dependent effects of FK506 on atherosclerotic lesion formation as well as on inflammatory parameters relevant to atherosclerosis. Unlike low-dose FK506, high-dose FK506 did not protect against atherosclerosis in ApoE-/- mice. The high-dose induced hypercholesterolaemia, whereas the low-dose did not. Both low- and high-dose FK506 treatment significantly reduced systemic CD3+ and CD4+CD25+ T-cell populations, and showed similar suppression of FoxP3 regulatory T-cell populations. Increased IL-4+ CD4+ T-cells and decreased IgG-MDA-LDL antibody titres pointed to a selective, albeit modest Th2 skewing in the high-dose treatment group, despite the advanced stage of atherosclerosis. Low concentrations of FK506, however, skewed bone marrow-derived macrophage polarisation towards a M2 macrophage phenotype, whereas high concentration did not. A low-dose FK506 treatment regime protected against atherosclerosis by suppressing T-cell activation and favouring (M2) macrophage polarisation. Although a high-dose FK506 treatment effected a similar T-cell suppressive effect, with an even more pronounced shift towards Th2 type immune responses, this did not translate in atheroprotection due to the hypercholesterolaemia and absent M2 skewing.

PMID: 20458432 [PubMed - indexed for MEDLINE]

14. Am J Physiol Heart Circ Physiol. 2010 Jun;298(6):H1646-51. Epub 2010 Mar 26.

Sirolimus inhibits endogenous cholesterol synthesis induced by inflammatory stress in human vascular smooth muscle cells.

Ma KL, Varghese Z, Ku Y, Powis SH, Chen Y, Moorhead JF, Ruan XZ.

Source

Centre for Nephrology, Univ. College London Medical School, Royal Free campus, Rowland Hill St., London, NW3 2PF, UK.

Abstract

Inflammatory stress accelerates the progression of atherosclerosis. Sirolimus, a new immunosuppressive agent, has been shown to have pleiotropic antiatherosclerotic effects. In this study we hypothesized that sirolimus inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR)-mediated cholesterol synthesis in human vascular smooth muscle cells (VSMCs) under inflammatory stress. Using radioactive assay, we demonstrated that sirolimus inhibited the increase of interleukin-1beta (IL-1beta)-induced cholesterol synthesis in VSMCs. Further studies showed that sirolimus inhibited both the HMGR gene and protein expression in VSMCs treated with or without IL-1beta. These effects were mediated by inhibiting the gene expression of sterol regulatory element-binding protein-2 (SREBP-2) and SREBP-2 cleavage-activating protein (SCAP) as checked by real-time PCR, Western blot analysis, and confocal microscopy for the observation of decreased protein translocation of the SCAP/SREBP-2 complex from the endoplasmic reticulum (ER) to the Golgi. Insulin-induced gene-1 (Insig-1) is a key ER protein controlling the feedback regulation of HMGR at transcriptional and posttranscriptional levels. We demonstrated that sirolimus increased Insig-1 expression which may bind to the SCAP, preventing the exit of SCAP-SREBP complexes from the ER. The increased Insig-1 also accelerated HMGR protein degradation in VSMCs as shown by pulse-chase analysis. In conclusion, sirolimus inhibits cholesterol synthesis induced by inflammatory stress through the downregulation of HMGR expression and the acceleration of HMGR protein degradation. These findings may improve our understanding of the molecular mechanisms of the antiatherosclerosis properties of sirolimus.

Free Article

PMID: 20348217 [PubMed - indexed for MEDLINE]

15. Diabetes. 2010 Jun;59(6):1338-48. Epub 2010 Mar 18.

Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue.

Houde VP, Brûlé S, Festuccia WT, Blanchard PG, Bellmann K, Deshaies Y, Marette A.

Source

Department of Medicine, Faculty of Medicine, Cardiology Axis of the Quebec Heart and Lung Institute, and the Metabolism, Vascular and Renal Health Axis, Laval University Hospital Research Center, Laval University, Quebec, Canada.

Abstract

OBJECTIVE: The mammalian target of rapamycin (mTOR)/p70 S6 kinase 1 (S6K1) pathway is a critical signaling component in the development of obesity-linked insulin resistance and operates a nutrient-sensing negative feedback loop toward the phosphatidylinositol 3-kinase (PI 3-kinase)/Akt pathway. Whereas acute treatment of insulin target cells with the mTOR complex 1 (mTORC1) inhibitor rapamycin prevents nutrient-induced insulin resistance, the chronic effect of rapamycin on insulin sensitivity and glucose metabolism in vivo remains elusive.

RESEARCH DESIGN AND METHODS:

To assess the metabolic effects of chronic inhibition of the mTORC1/S6K1 pathway, rats were treated with rapamycin (2 mg/kg/day) or vehicle for 15 days before metabolic phenotyping.

RESULTS: Chronic rapamycin treatment reduced adiposity and fat cell number, which was associated with a coordinated downregulation of genes involved in both lipid uptake and output. Rapamycin treatment also promoted insulin resistance, severe glucose intolerance, and increased gluconeogenesis. The latter was associated with elevated expression of hepatic gluconeogenic master genes, PEPCK and G6Pase, and increased expression of the transcriptional coactivator peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha) as well as enhanced nuclear recruitment of FoxO1, CRTC2, and CREB. These changes were observed despite normal activation of the insulin receptor substrate/PI 3-kinase/Akt axis in liver of rapamycin-treated rats, as expected from the blockade of the mTORC1/S6K1 negative feedback loop.

CONCLUSIONS: These findings unravel a novel mechanism by which mTORC1/S6K1 controls gluconeogenesis through modulation of several key transcriptional factors. The robust induction of the gluconeogenic program in liver of rapamycin-treated rats underlies the development of severe glucose intolerance even in the face of preserved hepatic insulin signaling to Akt and despite a modest reduction in adiposity.

PMCID: PMC2874694 Free PMC Article

PMID: 20299475 [PubMed - indexed for MEDLINE]

16. J Lipid Res. 2010 May;51(5):1144-56. Epub 2009 Dec 1.

Cholesterol efflux to apoA-I in ABCA1-expressing cells is regulated by Ca2+-dependent calcineurin signaling.

Karwatsky J, Ma L, Dong F, Zha X.

Source

Ottawa Hospital Research Institute and Department of Biochemistry Microbiology and Immunology, University of Ottawa, Ottawa, ON K1H 8L6, Canada.

Abstract

ATP-binding cassette transporter A1 (ABCA1) is required for the lipidation of apolipoprotein A-I (apoA-I), although molecular mechanisms supporting this process remain poorly defined. In this study, we focused on the role of cytosolic Ca(2+) and its signaling and found that cytosolic Ca(2+) was required for cholesterol efflux to apoA-I. Removing extracellular Ca(2+) or chelating cytosolic Ca(2+) were equally inhibitory for apoA-I lipidation. We provide evidence that apoA-I induced Ca(2+) influx from the medium. We further demonstrate that calcineurin activity, the downstream target of Ca(2+) influx, was essential; inhibition of calcineurin activity by cyclosporine A or FK506 completely abolished apoA-I lipidation. Furthermore, calcineurin inhibition abolished apoA-I binding and diminished JAK2 phosphorylation, an established signaling event for cholesterol efflux to apoA-I. Finally, we demonstrate that neither Ca(2+) manipulation nor calcineurin inhibition influenced ABCA1's capacity to release microparticles or to remodel the plasma membrane. We conclude that this Ca(2+)-dependent calcineurin/JAK2 pathway is specifically responsible for apoA-I lipidation without directly modifying ABCA1 activity.

PMCID: PMC2853441 Free PMC Article

PMID: 19965585 [PubMed - indexed for MEDLINE]

18. Am J Nephrol. 2010;31(2):134-40. Epub 2009 Nov 17.

Role of cellular cholesterol in pharmacologic preconditioning with cyclosporine in experimental kidney transplantation.

Shihab FS, Bennett WM, Andoh TF.

Source

Division of Nephrology, University of Utah School of Medicine, Salt Lake City, UT 84132, USA. Fuad.Shihab@hsc.utah.edu

Abstract

BACKGROUND/AIMS:

Ischemia reperfusion injury in the early posttransplant period affects immediate graft function and late allograft dysfunction. Recently, we showed that pharmacologic preconditioning with a calcineurin inhibitor improved transplant outcomes in rat syngeneic kidney transplantation. There is also evidence that cellular cholesterol content increases after many types of renal injury.

METHODS:

In this study, we looked at the effect of cyclosporine (CsA) on the donor kidney free cholesterol (FC) content in this model. Donor rats were pretreated with one dose of CsA 10 mg/kg administered 24 h or 7 days before being subjected to 2 h cold ischemia and then transplanted.

RESULTS:

Pharmacologic preconditioning with CsA significantly improved renal function and histology and increased donor kidney FC content. On the other hand, fluvastatin co-administration with CsA abrogated that beneficial effect in association with a decrease in donor kidney FC content.

CONCLUSION:

CsA preconditioning leads to better outcomes in kidney transplantation and is associated with up-regulation of renal FC content. The latter may then contribute to acquired cytoresistance, possibly by stabilizing the plasma membrane. Thus, use of statins around the time of transplantation may need to be evaluated until further studies are conducted to determine the clinical relevance of this observation.

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PMID: 19923799 [PubMed - indexed for MEDLINE]

26. J Pharmacol Exp Ther. 2009 Feb;328(2):419-25. Epub 2008 Nov 20.

Everolimus inhibits monocyte/macrophage migration in vitro and their accumulation in carotid lesions of cholesterol-fed rabbits.

Baetta R, Granata A, Canavesi M, Ferri N, Arnaboldi L, Bellosta S, Pfister P, Corsini A.

Source

Department of Pharmacological Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy. roberta.baetta@unimi.it

Abstract

Monocytes/macrophages recruited into the arterial wall during atherogenesis are crucial in the initiation and progression of atherosclerosis and play a fundamental role in the destabilization process that is the main causal event of acute coronary syndromes. In the present study, we investigated the effect of the mammalian target of rapamycin inhibitor everolimus on macrophage accumulation within carotid lesions elicited by perivascular collar placement in cholesterol-fed rabbits. Everolimus (1.5 mg/kg given 1 day before collaring followed by 1 mg/kg/day for 14 days, administered by oral gavage) markedly decreased lesion macrophage content as compared with vehicle control (-65%; $p < 0.01$). This effect was associated with a reduction in intimal thickening and occurred in the absence of changes in plasma cholesterol concentrations. To gain insights on the potential mechanism(s) underlying this effect, we investigated the influence of everolimus on chemoattractant-induced migration of human monocytes in vitro. Pretreatment with therapeutic concentrations of everolimus (10 nM) significantly lowered monocyte chemotaxis in response to various chemotactic factors (i.e., monocyte chemoattractant protein-1/CCL2, fractalkine/CX3CL1, interleukin-8/CXCL8, complement fragment 5a, or N-formyl-Met-Leu-Phe) without inducing monocyte cell death. These results suggest that everolimus may favorably influence the atherosclerotic process by affecting the recruitment of monocytes into early lesions.

Free Article

PMID: 19023042 [PubMed - indexed for MEDLINE]

36. Transplantation. 2007 Oct 27;84(8):1029-36.

Sirolimus modifies cholesterol homeostasis in hepatic cells: a potential molecular mechanism for sirolimus-associated dyslipidemia.

Ma KL, Ruan XZ, Powis SH, Chen Y, Moorhead JF, Varghese Z.

Source

Centre for Nephrology, Royal Free and University College Medical School, Royal Free Campus, London, United Kingdom.

Abstract

BACKGROUND: Sirolimus is a potent immunosuppressive agent, which is associated with dyslipidemia in clinical transplantation. The present study was undertaken to investigate the potential hepatocyte mechanisms by which sirolimus causes dyslipidemia.

METHODS: Using both a quantitative assay of intracellular cholesterol and an [3H]-labeled cholesterol efflux assay, we studied the effect of sirolimus on cholesterol accumulation and cholesterol efflux in HepG2 cells in the absence or presence of inflammatory stress induced by interleukin-1beta. The gene and protein expression of molecules involved in cholesterol homeostasis were examined by real-time reverse-transcription polymerase chain reaction and Western blotting.

RESULTS: Sirolimus inhibited low-density lipoprotein (LDL) receptor (LDLr)-mediated cholesterol ester accumulation induced by interleukin-1beta in HepG2 cells. This inhibitory effect was mediated by down-regulation of sterol regulatory element-binding proteins (SREBP) cleavage activating protein (SCAP) and SREBP-2 mRNA expression. Using confocal microscopy, we demonstrated that sirolimus reduced translocation of SCAP-SREBP2 complex from endoplasmic reticulum to Golgi for activation, thereby inhibiting LDLr gene transcription. Reduction of LDLr in the liver may result in a delay of LDL-cholesterol clearance from circulation causing an increase of plasma cholesterol concentration. Furthermore, sirolimus increased cholesterol efflux mediated by adenosine triphosphate-binding cassette transporter A1 gene expression by increasing peroxisome proliferator-activated receptor-alpha and liver X receptor-alpha gene and protein expression. Increased cholesterol efflux from HepG2 cells may increase high-density lipoprotein cholesterol level and also contribute to apolipoprotein B lipoprotein formation by enhancing transfer of high-density lipoprotein cholesterol to apolipoprotein B lipoproteins.

CONCLUSIONS: This study demonstrates that the increase of LDL cholesterol by sirolimus is partly due to the reduction of LDLr on hepatocytes.

PMID: 17989609 [PubMed - indexed for MEDLINE]

39. Basic Clin Pharmacol Toxicol. 2007 Jun;100(6):392-7.

Compared effect of immunosuppressive drugs cyclosporine A and rapamycin on cholesterol homeostasis key enzymes CYP27A1 and HMG-CoA reductase.

Gueguen Y, Ferrari L, Souidi M, Batt AM, Lutton C, Siest G, Visvikis S.

Source

Faculty of Pharmacy 1, Nancy Universities, Institut National de la Santé et de la Recherche Médicale, INSERM U525, 30 Rue Lionnois, Nancy, France. yann.gueguen@irsn.fr

Abstract

Hyperlipidaemia, i.e. increase in total cholesterol and triglycerides, is a common side-effect of the immunosuppressive drugs rapamycin (RAPA) and cyclosporine A (CsA), and is probably related to inhibition of the 27-hydroxylation of cholesterol (acid pathway of bile acid biosynthesis). This might be one of the causes for the increase in plasma cholesterol, as 27-hydroxycholesterol is a potent suppressor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR), a key enzyme of cholesterol synthesis. As the sterol 27-hydroxylase (CYP27A1) inhibition by CsA is well known, we evaluated the effect of another immunosuppressive drug, RAPA, on this enzyme in HepG2 mitochondria, which confirmed the dose-dependent inhibition of mitochondrial CYP27A1 by cyclosporine (10-20 microM), while the inhibition by RAPA required a higher dose (50-100 microM). Corresponding K(i) was 10 microM for CsA (non-competitive inhibition) and 110 microM for RAPA (competitive inhibition). Cotreatment with both immunosuppressive drugs showed an additive inhibitory effect on CYP27A1 activity. Later, we analysed the effect of these immunosuppressants on HMGR expression in HepG2 cells, and a dose-dependent up-regulation of HMGR gene expression was observed. The results suggest that RAPA and CsA are both inhibitors of CYP27A1 activity with slightly different mechanisms and that they may accordingly increase HMGR expression.

PMID: 17516993 [PubMed - indexed for MEDLINE]

43. Nephrol Dial Transplant. 2012 Feb;27(2):850-7.

Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study.

Claes K, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H.

Department of Nephrology and Renal Transplantation, University Hospital Gasthuisberg, Leuven, Belgium.

BACKGROUND: The metabolic syndrome (MS) is an important risk factor for graft dysfunction and patient death after renal transplantation. The aim of this sub-analysis of the Symphony study was to assess the progression of the laboratory parameters associated with MS in the first year after transplantation.
METHODS: Data collected from the Symphony study were used; 1645 patients were randomized to receive standard-dose cyclosporine (Stand-CsA), low-dose cyclosporine (Low-CsA), tacrolimus (Low-Tac) or sirolimus (Low-SRL), in addition to mycophenolate mofetil (MMF) and corticosteroids. Data were collected for levels and progression over the first year post-transplantation of systolic and diastolic blood pressure, uric acid, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and fasting glucose
levels by treatment arm.
RESULTS: The low-SRL group had significantly higher levels of triglycerides and LDL. The two CsA arms were associated with the highest uric acid levels at each time point. There were no significant differences in overall levels or changes in glucose or HDL. Patients in the standard-CsA arm had significantly higher diastolic blood pressure than those in the Low-SRL and Low-Tac arms. Systolic blood pressure was higher in the Low-CsA arm than in the Low-Tac arm. The use of antihypertensive and antidiabetic agents was similar between the treatment arms. In the Low-SRL arm, more patients were treated with lipid-lowering therapy. Mean daily steroid doses were the highest in the Low-SRL arm.
CONCLUSIONS: This sub-analysis demonstrates that there is a difference in metabolic parameters between immunosuppressive groups. CsA therapy was associated with the highest values of uric acid and systolic and diastolic blood pressure. Patients on SRL therapy had the worst lipaemic control. A possible effect of Tac on new-onset diabetes could not be excluded.

PMID: 21617197 [PubMed - in process]

48. Transplantation. 2011 May 15;91(9):976-83.

Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies).

Vanrenterghem Y, Bresnahan B, Campistol J, Durrbach A, Grinyó J, Neumayer HH, Lang P, Larsen CP, Mancilla-Urrea E, Pestana JM, Block A, Duan T, Glicklich A, Gujrathi S, Vincenti F.

Nephrology Department, University Hospital Leuven, Leuven, Belgium.
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BACKGROUND: Cardiovascular disease, the most common cause of death with a functioning graft among kidney transplant recipients, can be exacerbated by immunosuppressive drugs, particularly the calcineurin inhibitors. Belatacept, a selective co-stimulation blocker, may provide a better cardiovascular/metabolic risk profile than current immunosuppressants.
METHODS: Cardiovascular and metabolic endpoints from two Phase III studies (BENEFIT and BENEFIT-EXT) of belatacept-based regimens in kidney transplant recipients were assessed at month 12. Each study assessed belatacept in more intensive (MI) and less intensive (LI) regimens versus cyclosporine A (CsA). These secondary endpoints included changes in blood pressure, changes in serum lipids, and the incidence of new-onset diabetes after transplant (NODAT).
RESULTS: A total of 1209 patients were randomized and transplanted across the two studies. Mean systolic blood pressure was 6 to 9 mm Hg lower and mean diastolic blood pressure was 3 to 4 mm Hg lower in the MI and LI groups versus CsA ($P \leq 0.002$) across both studies at month 12. Non-HDL cholesterol was lower in the belatacept groups versus CsA ($P<0.01$ MI or LI vs. CsA in each study). Serum triglycerides were lower in the belatacept groups versus CsA ($P<0.02$ MI or LI vs. CsA in each study). NODAT occurred less often in the belatacept groups versus CsA in a prespecified pooled analysis ($P<0.05$ MI or LI vs. CsA).
CONCLUSIONS: At month 12, belatacept regimens were associated with better cardiovascular and metabolic risk profiles, with lower blood pressure and serum lipids and less NODAT versus CsA. The overall profile of belatacept will continue to be assessed over the 3-year trials.

PMID: 21372756 [PubMed - indexed for MEDLINE]

51. Clin J Am Soc Nephrol. 2010 Aug;5(8):1506-12.

Unusual pattern of dyslipidemia in children receiving steroid minimization immunosuppression after renal transplantation.

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BACKGROUND AND OBJECTIVES: Corticosteroids are an important contributor to posttransplant hyperlipidemia. Since 2004, we have used a steroid minimization immunosuppression protocol. This study investigated the effect of steroid minimization on dyslipidemia in pediatric renal allograft recipients.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: Children (<18 years) who underwent renal transplants at our center from January 2001 to January 2008 were studied. Data analyzed included age, gender, race, body mass index, cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and steroid dose. Data between the cohorts receiving maintenance steroids and steroid-minimization were compared using multivariable analyses. The primary outcome measures were the prevalence of, and the effect of steroid use, on dyslipidemia.
RESULTS: Twenty-nine patients were studied. Sixteen were receiving maintenance steroids, and 13 were on a steroid minimization regimen. Mixed effects analysis of covariance models demonstrated that at 1 month, children receiving maintenance steroids had higher cholesterol compared with the steroid minimization group. Statistically significant differences in total cholesterol were not seen at other time points. Similar findings were noted for the LDL cholesterol, LDL/HDL, and cholesterol/HDL ratios. At 1 month, the serum HDL cholesterol was substantially lower in the steroid minimization group. Differences in the HDL cholesterol levels remained significant throughout the first year.
CONCLUSIONS: Steroid use is a significant independent risk factor for hypercholesterolemia during the first post-transplant month. The significance of lower HDL cholesterol among patients receiving steroid minimization needs further study and may be cause for concern.

PMCID: PMC2924403
PMID: 20507961 [PubMed - indexed for MEDLINE]

52. Drugs. 2009 Nov 12;69(16):2227-43.

Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection.

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Renal transplant recipients have increased mortality rates when compared with the general population. The new immunosuppressive drugs have improved short-term patient survival up to 95% at 1-2 years, but these data have to be confirmed in long-term follow-up. Furthermore, no particular regimen has proved to be superior over others with regard to patient survival. Cardiovascular diseases are the most common cause of mortality in renal transplant recipients and while no immunosuppressive drug has been directly associated with cardiovascular events, immunosuppressive drugs have different impacts on traditional risk factors. Corticosteroids and ciclosporin are the agents with the most negative impact on weight gain, blood pressure and lipids. Tacrolimus increases the risk of new-onset diabetes mellitus. Sirolimus and everolimus have the most impact on risk factors for post-transplant hyperlipidaemia. Modifications in immunosuppression could improve the cardiovascular profile but there is little evidence regarding the beneficial effects of these changes on patient outcomes. Malignancies are also an increasing cause of mortality, overtaking cardiovascular disease in some series. Induction therapy, azathioprine and calcineurin inhibitors (CNIs) are probably the immunosuppressive agents most linked with post-transplant malignancies. Mycophenolate mofetil (MMF) has no negative impact on the incidence of malignancies. Target of rapamycin (mTOR) inhibitors have antioncogenic properties and they are associated with a lower incidence of malignancies. In addition, these agents have been recommended for use to decrease the dose or withdrawal of CNIs in patients with malignancies. Infections are still an important cause of morbidity and mortality in renal transplant recipients. Some immunosuppressive agents such as MMF increase the incidence of cytomegalovirus infection and the need for prophylactic measures in risk recipients. The use of potent immunosuppressive therapy has resulted in the appearance of BK virus nephropathy, which progresses to graft failure in a high percentage of patients. Although first associated with tacrolimus and MMF immunosuppression, recent data suggest that BK nephropathy appears with any kind of triple therapy. In conclusion, reducing risk factors for patient death should be a major target to improve outcomes after renal transplantation. Effort should be made to control cardiovascular diseases, malignancies and infections with improved use of immunosuppressive drugs. Preliminary results with belatacept suggest its safety and efficacy, and open new perspectives in the immunosuppression of de novo renal transplant recipients.

PMID: 19852526 [PubMed - indexed for MEDLINE]

54. Transplantation. 2009 Jul 15;88(1):62-8.

Tacrolimus-induced elevation in plasma triglyceride concentrations after administration to renal transplant patients is partially due to a decrease in lipoprotein lipase activity and plasma concentrations.

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BACKGROUND: Hyperlipidemia is a frequent and persistent complication in solid organ transplant recipients, leading to the high occurrence of cardiovascular disease in this patient population. Lipid abnormalities including increased total cholesterol, triglycerides (TG), and low-density lipoprotein-cholesterol have been reported frequently in transplantation patients and a variety of immunosuppressive therapies seem to be one of the main factors that influence posttransplant lipidemic profiles. For many years, tacrolimus (TAC) has been used as an immunosuppressive drug in transplantation. The aim of our investigation was to determine the effect of TAC administration on the plasma lipid profile and some key regulatory proteins of plasma lipid metabolism including cholesterol ester transfer protein, hepatic lipase and lipoprotein lipase (LPL) within renal transplant patients.
METHODS: Twenty-five renal transplant patients were recruited and received TAC therapy, of which nine of these patients were treated with statin therapy for dyslipidemia. The effects of TAC on plasma total cholesterol, TG, HDL-C, low-density lipoprotein-cholesterol, cholesterol ester transfer protein, hepatic lipase and LPL concentration and activity were determined from patients plasma samples collected before the transplant surgery (baseline), and weekly for four consecutive weeks after surgery and TAC administration.
RESULTS: We observed that TAC significantly increases plasma TG concentrations and reduces LPL plasma concentration and activity in renal transplant patients, independent of any lipid lowering drug treatment patients received.
CONCLUSIONS: Taken together, these findings suggest that the reduction in LPL activity, partly due to the decrease of plasma LPL concentration after TAC administration may be an explanation for hypertriglyceridemia observed in patients administered TAC.

PMID: 19584682 [PubMed - indexed for MEDLINE]

55. Transplant Proc. 2009 Jul-Aug;41(6):2339-44.

Similar lipid profile but improved long-term outcomes with sirolimus after cyclosporine withdrawal compared to sirolimus with continuous cyclosporine.

Morales JM, Hartmann A, Walker R, Arns W, Senatorski G, Grinyó JM, Shoker A, Wilczek H, Jamieson NV, Lelong M, Brault Y, Burke JT, Scarola JA; Rapamune Maintenance Regimen Study Group.

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Renal transplant recipients show an increased risk of cardiovascular disease compared with a nontransplant population. Herein we have shown an analysis of a randomized controlled trial wherein 525 patients receiving a first or second (9.7%) renal allograft from a deceased (89.1%), a living-related (7.8%), or a living-unrelated donor (3.1%) received sirolimus (SRL), cyclosporine (CsA), and steroids (ST) at the time of transplantation with randomization at 3 months after transplantation of 430 eligible patients to continue on SRL-CsA-ST or to have CsA withdrawn with increased SRL trough targets (SRL-ST group). Graft survival, patient survival, and renal function at 5 years were analyzed by average fasting total cholesterol (<or=200 or >200 mg/dL) and triglyceride (<or=240 or >240 mg/dL) subgroups. At 5 years, total, high-density lipoprotein (HDL), and low-density lipoprotein [LDL] cholesterol and triglyceride values were similar between the groups. Statins (approximately 80% of patients of both groups) were most effective to lower cholesterol (approximately 50 mg/dL; P < .001; both groups), and fibrates (approximately 25% of patients of both groups) were most effective to decrease triglycerides (approximately 100 mg/dL; P < .001; both groups). Renal function and blood pressure were significantly better with SRL-ST. Hypercholesterolemia and hypertriglyceridemia were associated with reduced graft survival, patient survival, and calculated GFR, but the only significant difference was lower graft survival among SRL-CsA-ST patients with hypertriglyceridemia. Cardiovascular-related deaths were reported in 3.7% and 2.8% of patients in the SRL-CsA-ST and SRL-ST groups, respectively. In conclusion, when compared with continuous SRL-CsA-ST, CsA withdrawal at 3 months followed by SRL-ST significantly improved glomerular filtration rate (GFR) and blood pressure without a further increase in lipid parameters or an incidence of untoward effects from hyperlipidemia, despite a 2-fold higher SRL exposure.

PMID: 19715914 [PubMed - indexed for MEDLINE]

61. Am J Transplant. 2008 Jul;8(7):1384-92.

Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients.

Kasiske BL, de Mattos A, Flechner SM, Gallon L, Meier-Kriesche HU, Weir MR, Wilkinson A.

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The incidence, pathogenesis, consequences and treatment of mammalian target of rapamycin (mTOR) inhibitor dyslipidemia are not well described. We conducted a systematic review of randomized controlled trials reporting cholesterol and triglycerides in mTOR versus non-mTOR inhibitor immunosuppressive treatment regimens in kidney transplant recipients. All but one of 17 trials reported higher levels of cholesterol and triglycerides, or an increased prevalence of treatment with lipid-lowering agents. Approximately 60% of mTOR inhibitor-treated patients received lipid-lowering agents (2-fold higher than controls). There appeared to be little difference between dyslipidemias caused by sirolimus (14 trials) versus everolimus (3 trials). It was difficult to determine the extent to which declines in lipids over time posttransplant were due to lipid-lowering therapy, changes in doses and/or discontinuations of mTOR inhibitors. From the four trials that measured lipoproteins, it appeared that at least some of the increase in total cholesterol with mTOR inhibitors was due to increased low-density lipoprotein cholesterol. What direct or indirect effects mTOR inhibitors have on atherosclerotic cardiovascular disease in kidney transplant patients are unknown. However, in the absence of the necessary clinical trials, dyslipidemia should be managed, as it would be in nontransplant patients at high risk for cardiovascular disease.

PMID: 18510633 [PubMed - indexed for MEDLINE]

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Proyecto **Prometeo**

Grupo I | Tratamiento de la Hiperlipemia Postrasplante

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Percentages of Water, Muscle, and Bone Decrease and Lipid increases in Early Period After Successful Kidney Transplantation: A Body Composition Analysis.

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BACKGROUND: Successful kidney transplantation (KT) can theoretically reconstitute body composition of a patient with chronic kidney disease (CKD). However, the practical changes have not been well documented. We evaluated changes in body composition among candidates before and 1 year after KT.
METHODS: We enrolled 37 male and 18 female kidney recipients eligible for comparison of their body mass index (BMI), body composition, and lipid metabolism before and 1 year after KT. Twenty-one patients had been induced with a calcineurin inhibitor, mycophenolate mofetil, steroid, and basiliximab, and 34 others underwent steroid withdrawal on postoperative day 3. The body composition was analyzed using bioelectrical impedance. We also analyzed changes in BMI and lipid profiles.
RESULTS: There was no significant change in BMI (21.4 ± 3.1 vs 21.7 ± 3.5 kg/m(2)). Regarding body composition, the water level decreased significantly (61.2 ± 4.9% vs 58.3 ± 5.3%; $P < .05$). In contrast, fat significantly increased (16.4 ± 6.7% vs 20.3 ± 7.1%; $P < .05$). More interestingly, successful KT significantly decreased the muscle and bone mass at 1 year after KT (37.3 ± 5.1% vs 34.8 ± 4.7%; 16.3 ± 2.1% vs 15.2 ± 2.1%; respectively; $P < .05$). Serum lipid profiles of total cholesterol, low-density lipoprotein cholesterol, and triglyceride worsened after KT. Comparing the 2 protocols, there was no difference in any item.
CONCLUSIONS: Care must be taken even after successful KT to avoid dyslipidemia, which is a risk factor for cardiovascular disease. Well programmed dietary and/or exercise protocols to prevent muscle atrophy and fat gain should be considered even after successful KT.

PMID: 22483465 [PubMed - in process]

3. J Ren Nutr. 2012 Mar 22. [Epub ahead of print]

Metabolic Disorders Following Kidney Transplantation.

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Kidney transplantation in patients suffering from end-stage renal disease, although beneficial, may result in potential complications increasing cardiovascular risk of mortality. Common metabolic problems after surgery are weight gain, hypertension, hyperlipidemia, and insulin resistance. Immunosuppressant therapy can enhance comorbidity progression. Early identification and treatment of these abnormalities can promote transplant function. Lifestyle modifications have shown to be promising in the reduction of the metabolic syndrome symptoms, but there remain limited trials focusing on this area. This article reflects a comprehensive review of the available research of each of the potential metabolic complications within the renal transplant population. Immunosuppressant medication effects, biochemical values, and medical nutrition therapy intervention are also included with regard to their influence with these metabolic disorders. Methods for review completion included a MEDLINE search for peer-reviewed research, using the following keywords: transplant, chronic kidney disease, nutrition, metabolic syndrome, and diet after transplantation.

PMID: 22445053 [PubMed - as supplied by publisher]

4. Ann Transplant. 2011 Sep 30;16(3):132-4.

Ezetimibe in sirolimus-associated hyperlipidemia: to add or not to add to statins?

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BACKGROUND: Hyperlipidemia is a universal adverse effect of proliferation signal inhibitors (PSI). We report our experience with ezetimibe/statin combined therapy in a case of a kidney transplant recipient receiving sirolimus (SRL)-based immunosuppression. We also present our doubts concerning the need for ezetimibe in kidney transplant recipients on PSI-based immunosuppression. CASE REPORT: Results. In the reported patient, ezetimibe/statin combination therapy successfully decreased cholesterol level. CONCLUSIONS: Combined therapy with ezetimibe and statin seems to be effective and safe in transplant recipients with SRL-associated hyperlipidemia. However, well-designed clinical trials should be performed to evaluate if there is an impact of such treatment on the frequency of cardiovascular events and patient survival.

PMID: 21959521 [PubMed - indexed for MEDLINE]

5. Exp Clin Transplant. 2011 Aug;9(4):230-5.

Lipid disturbances before and after renal transplant.

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OBJECTIVES: Hyperlipidemia is a significant metabolic disorder that is commonly encountered in renal transplant recipients. This study was conducted to investigate lipid disturbances and define its pattern in kidney recipients.
MATERIALS AND METHODS: The records of 103 patients who had undergone a renal transplant between the years of 2004 and 2005 were retrospectively investigated. The lipid profile of these patients including total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglyceride levels before and within 2 years' follow-up after transplant was evaluated. The demographics of the patients, cause of the end-stage renal failure, along with their immunosuppressive regimens were also considered.
RESULTS: The study group included 43 women (41.8%) and 60 men (58.2%) (mean age, 39.25 ± 13.9 y). After transplant, laboratory analyses yielded significantly increased levels of total cholesterol, low-density lipoproteins, triglyceride levels, and high-density lipoproteins despite statin therapy, and the most important predictor for developing hypercholesterolemia and hypertriglyceridemia-pre-existing dyslipidemia. The effects of the various drugs on lipid metabolism were not different. These effects seen on the lipid profiles also were independent of the patients' age, sex, and cause of end-stage renal failure.
CONCLUSIONS: Despite statin treatment, renal transplants in our subjects were associated with a characteristic pattern of lipid disturbance with raised total cholesterol, low-density lipoproteins, high-density lipoproteins, and a concomitant increase in triglycerides. A more-aggressive approach to managing posttransplant hypercholesterolemia is warranted, especially in patients with pre-existing dyslipidemia.

PMID: 21819366 [PubMed - indexed for MEDLINE]

6. Clin J Am Soc Nephrol. 2011 Mar;6(3):664-78.

The efficacy and safety of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors in chronic kidney disease, dialysis, and transplant patients.

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Coronary heart disease (CHD) is the leading cause of death in Western civilizations, in particular in chronic kidney disease (CKD) patients. Serum total cholesterol and LDL have been linked to the development of atherosclerosis and progression to CHD in the general population. However, the reductions of total and LDL cholesterol in the dialysis population have not demonstrated the ability to reduce the morbidity, mortality, and cost burden associated with CHD. The patients at greatest risk include those with pre-existing CHD, a CHD-risk equivalent, or multiple risk factors. However, data in the dialysis population are much less impressive, and the relationship between plasma cholesterol, cholesterol reduction, use of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and reduction in incidence of CHD or effect on progression of renal disease have not been proven. Adverse event information from published trials indicates that agents within this class share similar tolerability and adverse event profiles. Hepatic transaminase elevations may occur in 1 to 2% of patients and is dose related. Myalgia, myopathy, and rhabdomyolysis occur infrequently and are more common in kidney transplant patients and patients with CKD. This effect appears to be dose related and may be precipitated by administration with agents that inhibit cytochrome P-450 isoenzymes. Caution should be exercised when coadministering any statin with drugs that metabolize through cytochrome P-450 IIIA-4 in particular fibrates, cyclosporine, and azole antifungals. Elderly patients with CKD are at greater risk of adverse drug reactions, and therefore the lowest possible dose of statins should be used for the treatment of hyperlipidemia.

PMID: 21393488 [PubMed - indexed for MEDLINE]

7. Clin Nephrol. 2011 Feb;75(2):107-12.

Ezetimibe is effective in the treatment of persistent hyperlipidemia of renal allograft recipients.

Savvidaki E, Koukoulaki M, Benou A, Roumeliotou M, Fourtounas C, Kalliakmani P, Papachristou E, Vlachojannis JG, Goumenos D.

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INTRODUCTION: Ezetimibe is a hypolipidemic agent acting via inhibition of cholesterol absorption from the small intestine. The effectiveness and safety of long-term administration of ezetimibe was evaluated in renal allograft recipients with persistent hyperlipidemia.
PATIENTS AND METHODS: 67 renal allograft recipients with post-transplantation hyperlipidemia resistant to statins were included in the study; 11 were treated with ezetimibe (10 mg/day) alone and 56 with ezetimibe and statin. The effectiveness of ezetimibe was assessed by determination of total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides (TR). Its safety was determined by liver enzymes (ALT, AST), LDH, CPK, serum creatinine and blood levels of immunosuppressive drugs (cyclosporine, tacrolimus, everolimus, sirolimus) over the follow-up period of 18±6 months.
RESULTS: A significant reduction of TC and LDL-C blood levels by 25% and 34% respectively, was observed during the first month of treatment with ezetimibe ($p<0.001$). This reduction was maintained for the whole period of ezetimibe administration. Renal function remained stable over the follow-up period, while no changes of the blood levels of immunosuppressive drugs were observed. Liver enzymes, LDH and CPK remained normal in all patients except for one diabetic patient who developed rhabdomyolysis. Apart from gastrointestinal symptoms in 2 patients, no other side effects were observed.
CONCLUSION: Combination of ezetimibe with statins represents an effective and safe regimen for treatment of persistent hyperlipidemia in renal allograft recipients.

PMID: 21255539 [PubMed - indexed for MEDLINE]

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Dyslipidemia treatment and cardiovascular disease in the renal patient.

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Cardiovascular disease is the most prevalent cause of death in patients with chronic kidney disease (CKD), even at an early stage of the disease and is considered a coronary heart disease risk equivalent. Therefore, therapeutic efforts to control modifiable additional cardiovascular risk factors such as dyslipidemia in this population seems reasonable. Indeed, abnormalities of lipid metabolism are often encountered in patients with CKD, end stage renal disease or after kidney transplantation. In this review we will summarize the currently available data on etiology, epidemiology, and impact on cardiovascular morbidity in patients with CKD, renal pathologies like the nephrotic syndrome and after kidney transplantation and give a brief overview of the existing guidelines on treating dyslipidemia.

PMID: 21418028 [PubMed - indexed for MEDLINE]

10. Saudi J Kidney Dis Transpl. 2010 Nov;21(6):1021-9.

Ezetimibe as a potential treatment for dyslipidemia associated with chronic renal failure and renal transplant.

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Individuals with chronic renal disease (CKD) are prone to have accelerated process of atherosclerosis. Importantly, cardiovascular disease is the main cause of morbidity and mortality in kidney transplant recipients. Recent studies suggest a potential benefit of the lipid lowering medica-tions in preventing cardiovascular events in the CKD and the transplant populations. In particular, statin was shown to be effective in reducing low density lipoprotein (LDL)-cholesterol. However, refractory dyslipidemia and difficulty in lowering LDL to target were reported with the CKD and the kidney transplant patients. The second United Kingdom Heart and Renal protection study (UK-HARP-II) showed that the addition of ezetimibe to simvastatin was safe and effective in treating dyslipidemia in CKD. Furthermore, the combination of ezetimibe and statin was also effective and safe in treating dyslipidemia in kidney transplant recipients. The Study of Heart and Renal Pro-tection (SHARP) trial will evaluate the effects of lowering LDL-C with ezetimibe 10 mg and simvastatin 20 mg daily versus placebo in 9,000 patients with chronic kidney disease. The current evidence suggests that the addition of ezetimibe to satin is effective and safe in treating dyslipidemia in the CKD and the kidney transplant patients. Future clinical trials are needed to determine whether ezetimibe will reduce cardiovascular risk in the CKD patients.

PMID: 21060168 [PubMed - indexed for MEDLINE]

12. Clin Transplant. 2009 Nov-Dec;23(6):914-20.

Metabolic syndrome and cardiovascular risk in renal transplant recipients: effects of statin treatment.

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BACKGROUND: Renal transplant recipients (RTR) have high risk for cardiovascular disease (CVD). They also have high prevalence of insulin resistance and metabolic syndrome (MS). Statin treatment reduces CVD risk in RTR. The aim was to study MS as CVD risk factor in RTR, and to investigate the effect of statin treatment in RTR with MS.
METHODS: In total, 1706 non-diabetic RTR from the Assessment of Lescol in Renal Transplantation trial were followed for 7-8 yr. The captured endpoints included major adverse cardiac events [MACE, defined as cardiac death (CD), non-fatal myocardial infarction or coronary revascularization procedure], and CD. MS was defined at baseline according to Adult Treatment Panel III definition with waist girth replaced by body mass index > or =30 kg/m2.
RESULTS: MS was diagnosed in 32% of the patients. During the follow-up, MACE incidence was 16% in those with MS and 11% in those without MS ($p < 0.001$). Statin treatment reduced MACE risk by 53% in the group with MS. CD risk was 74% higher in RTR with MS ($p = 0.012$), and statin treatment reduced CD risk in those with MS ($p = 0.03$).
CONCLUSIONS: RTR with MS have increased risk for CVD. RTR with MS are an easily identifiable group of patients who benefit from statin treatment.

PMID: 19594771 [PubMed - indexed for MEDLINE]

13. J Nephrol. 2009 Sep-Oct;22(5):598-609.

Statin treatment for dyslipidemia in chronic kidney disease and renal transplantation: a review of the evidence.

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Patients with chronic kidney disease (CKD) have significantly increased risks of cardiovascular (CV) morbidity and mortality. Dyslipidemia is a common disorder in CKD patients. CKD patients have a different lipid profile with increased atherogenic lipid fractions, and serum low-density lipoprotein cholesterol (LDL-C) levels may underestimate the atherogenic effect of LDL-C in these patients. Dyslipidemia may contribute to the increased CV morbidity and mortality, and to the progression of kidney disease in CKD patients. Currently, statins are the pharmacologic intervention of first choice, if lifestyle changes fail adequately to lower LDL-C levels in the setting of normal or moderately elevated triglycerides. Statins have been extensively studied in a large variety of patient populations and have proven efficacy in the treatment of dyslipidemia, and in reducing CV mortality. Although much evidence supports the CV benefits of statins in patients with normal renal function, there are contradictory results for the beneficial effect of statin therapy on CV morbidity and mortality in CKD patients. While post hoc subgroup analyses of multiple randomized trials support statin use in early CKD patients, the only randomized trial conducted in diabetic dialysis patients found no evidence of benefit in overall mortality. Post transplant there is some definite CV benefit, albeit in a patient cohort selected to be at reduced CV risk by virtue of being eligible for organ transplant. The results from the AURORA and SHARP studies are awaited anxiously.

PMID: 19809992 [PubMed - indexed for MEDLINE]

14. Korean J Intern Med. 2009 Sep;24(3):233-7. Epub 2009 Aug 26.

The efficacy and safety of ezetimibe and low-dose simvastatin as a primary treatment for dyslipidemia in renal transplant recipients.

Yoon HE, Song JC, Hyoung BJ, Hwang HS, Lee SY, Jeon YJ, Choi BS, Kim YS, Yang CW.

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BACKGROUND/AIMS: The efficacy and safety of a combination of ezetimibe and low-dose statin as primary treatment for dyslipidemia in renal transplant patients were evaluated prospectively.
METHODS: The study enrolled 77 renal transplant recipients with dyslipidemia. They were given ezetimibe (10 mg) and simvastatin (10 mg) for 6 months as the initial treatment for dyslipidemia. Efficacy and safety were evaluated using lipid profiles, trough calcineurin inhibitor levels, allograft function, and adverse effects. The effects on proteinuria and high sensitivity C-reactive protein (hsCRP) levels were also evaluated.
RESULTS: Ezetimibe and low-dose simvastatin significantly decreased the levels of total cholesterol (34.6%), triglyceride (16.0%), and low-density lipoprotein cholesterol (LDL-C) (47.6%), and 82.5% of the patients reached the target LDL-C level of <100 mg/dL. No significant change in the trough calcineurin inhibitor levels or allograft function occurred, and no serious adverse effects were observed. Fourteen patients (18.2%) discontinued treatment; eight patients (11.7%) developed muscle pain or weakness without an increase in creatinine kinase levels, and two patients (2.6%) developed elevated liver transaminase levels. The proteinuria and hsCRP levels did not change significantly.
CONCLUSIONS: Ezetimibe and low-dose statin treatment is safe and effective as a primary treatment for dyslipidemia in renal transplant patients.

PMCID: PMC2732783
PMID: 19721860 [PubMed - indexed for MEDLINE]

15. Curr Diab Rep. 2009 Aug;9(4):305-11.

Dyslipidemia following kidney transplantation: diagnosis and treatment.

Badiou S, Cristol JP, Mourad G.

Lipid abnormalities are a common complication of kidney transplantation, occurring in up to 60% of patients. In fact, impairment of lipid metabolism is often present before renal transplantation due to the uremic state. After transplantation and recovery of renal function, lipid disturbances usually persist but show a different profile due to the various effects of immunosuppressive drugs on lipid metabolism. Actually, steroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors usually lead to quantitative and qualitative abnormalities of very low-density, low-density, and high-density lipoproteins. As cardiovascular diseases remain the leading cause of death in renal transplant recipients, management of dyslipidemia and other traditional risk factors, such as smoking, arterial hypertension, diabetes mellitus, and obesity, is of great importance to prevent cardiovascular complications and chronic allograft dysfunction. This review addresses the causes of dyslipidemia, the role of immunosuppressive drugs, and current recommendations to manage lipid disorders in renal transplant recipients.

PMID: 19640344 [PubMed - indexed for MEDLINE]

17. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005019.

HMG CoA reductase inhibitors (statins) for kidney transplant recipients.

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BACKGROUND: Cardiovascular deaths account for the majority of deaths in kidney transplant recipients and dyslipidaemia contributes significantly to their cardiovascular disease. Statins are widely used in kidney transplant patients given their established benefits in the general population, however evidence favouring their use is lacking.
OBJECTIVES: To assess the benefits and harms of statin therapy on mortality and renal outcomes in kidney transplant recipients.
SEARCH STRATEGY: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and hand searched reference lists of articles and scientific proceedings.
SELECTION CRITERIA: Randomised controlled trials (RCTs) and quasi-RCTs comparing statins with placebo, no treatment or other statins in kidney transplant recipients.
DATA COLLECTION AND ANALYSIS: Two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random effects model after testing for heterogeneity. Results were expressed as mean difference (MD) for continuous outcomes (lipid parameters) and risk ratio (RR) for dichotomous outcomes (mortality, allograft rejection, liver enzymes, occurrence of rhabdomyolysis and study withdrawal) with 95% confidence intervals (CI).
MAIN RESULTS: Sixteen studies (3229 patients) comparing statins versus placebo (15) or another statin (1) were included. Compared to placebo, statins did not decrease all-cause mortality (14 studies: RR 1.30, 95% CI 0.54 to 3.12). Point estimates favoured statins in terms of cardiovascular mortality (13 studies: RR 0.68, 95% CI 0.46 to 1.03) and non-fatal cardiovascular events (1 study: RR 0.70, 95% CI 0.48 to 1.01), however the results were not statistically significant. Compared to placebo, the use of statins was associated with a significantly lower end of treatment average total cholesterol (10 studies: MD -42.33 mg/dL (1.26 mmol/L), 95% CI -53.02 to -31.64), LDL cholesterol (10 studies: MD -46.15 mg/dL (1.19 mmol/L), 95% CI -55.97 to -36.33) and triglycerides (10 studies: MD -25.46 mg/dL (0.26 mmol/L), 95% CI -33.95 to 16.9). There was no significant difference in the risk of acute rejection (5 studies: RR 0.61; 95% C.I.0.32 to 1.16.) No data on chronic rejection was available and no major toxicity was noted.
AUTHORS' CONCLUSIONS: Statins significantly reduced hyperlipidaemia and tended to reduce cardiovascular events in kidney transplant recipients, but no effect has yet been demonstrated for mortality outcomes. Most of the data was derived from one large long-term study. Considering the significant impact of statins on all-cause and cardiovascular mortality in the general and predialysis populations, more studies are needed in kidney transplant patients.

PMID: 19370615 [PubMed - indexed for MEDLINE]

19. J Ren Care. 2009 Mar;35(1):42-7.

Can a functional food exert a cholesterol lowering effect in renal transplant patients?

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This study examined whether stanols can exert their cholesterol lowering effect in renal transplant recipients who develop hypercholesterolaemia. The rise in cholesterol is related to the use of cyclosporine. The study was a randomized parallel-group intervention study. The Intervention group (I) was given three months supply of stanol containing food products. Fasting serum lipids were measured monthly. Parameters that might influence serum cholesterol were measured on all subjects at the start of the study period and at three months. These included body weight, blood pressure and drug therapy, dietary intake, exercise, smoking and alcohol intake. 84 patients completed the study. Cholesterol was reduced in both groups. The difference between control (C) and I group reached significance at p = 0.0196. Reduction in cholesterol in subjects also using statins was greater in the I group. Functional foods appear to be effective in reducing cholesterol in this group of patients. Data collection with respect to other factors that influence CV risk suggests that an overall assessment of diet and lifestyle as well as cholesterol lowering should be undertaken.

PMID: 19200277 [PubMed - indexed for MEDLINE]

20. Transplant Proc. 2009 Mar;41(2):751-5.

A prudent algorithm for hyperlipoproteinemia in renal transplant recipients.

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BACKGROUND: Hyperlipidemia and particularly low-density lipoprotein cholesterol (LDL-C) have been proposed as independent risk factors predisposing to chronic allograft nephropathy.
OBJECTIVE: The primary objective of this prospective randomized study was to evaluate the efficacy of the modified National Cholesterol Education Program (NCEP) Step I Diet to prevent posttransplantation hyperlipidemia. The secondary objective was to assess the impact of fluvastatin on the lipid profile of patients unresponsive to dietary measures.
METHODS: The study population consisted of 143 consecutive patients who underwent transplantation between October 1998 and January 2005. Patients who failed to demonstrate total and LDL-C levels below the optimal values of 200 mg/dL and 130 mg/dL respectively, were recruited for fluvastatin treatment. The remaining patients who achieved and maintained the target lipid levels continued on the same dietary regimen.
RESULTS: Baseline demographic characteristics were not different among the fluvastatin and modified Step I Diet groups. Mean total cholesterol (231.2 vs 187.3 mg/dL; P < .000), LDL-C (134.5 vs 99.2 mg/dL; P < .000), high-density lipoprotein cholesterol (HDL-C; 62.9 vs 55.7 mg/dL; P = .012), and triglyceride (170.3 vs 138.7 mg/dL; P = .011) levels following the dietary run-in period were significantly different between the patients assigned to fluvastatin treatment and those left on the diet, respectively. Fluvastatin achieved reductions ranging from 12% to 14% in the concentrations of total cholesterol (231.2 +/- 4.29 mg/dL to 202.7 +/- 3.89 mg/dL; P < .000) and LDL-C (134.5 +/- 3.53 mg/dL to 115.6 +/- 3.18 mg/dL; P < .000) among 91% of patients after 1 year of treatment. A substantial decrease in all lipoprotein concentrations occurred in 53 patients in the modified Step I Diet group with significant reductions in total cholesterol (187.3 +/- 4.98 mg/dL to 172.7 +/- 3.8 mg/dL; P < .000) and LDL-C (99.2 +/- 4.0 mg/dL to 96.2 +/- 3.44 mg/dL; P < .000).
CONCLUSION: Initiation and education of the Step I Diet should be provided during hospitalization. The 3-month dietary run-in period was deemed sufficient to determine the effect of diet on lipid abnormalities. Reduction of lipoprotein levels by a 40-mg daily fluvastatin dose was sufficient, safe, and tolerable.

PMID: 19328972 [PubMed - indexed for MEDLINE]

21. J Investig Med. 2009 Feb;57(2):456-9.

Effects of diet and gemfibrozil on posttransplant hyperlipidemia in renal transplant recipients.

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BACKGROUND: Posttransplant hyperlipidemia increases cardiovascular morbidity and mortality rate in renal transplant recipients. It also leads to graft loss due to atherosclerosis and glomerular damage. It is essential to control hyperlipidemia in renal transplant recipients to prevent these events.
METHODS: In our study, we determined lipid profiles in 59 renal transplant recipients. Twenty of the recipients had hyperlipidemia; 9 had type IV, and 11 had type II hyperlipoproteinemia. Randomly selected 14 of 20 hyperlipidemic patients consisted of the diet group and were treated with American phase 3 diet for 1 month. Randomly selected 6 of the 20 hyperlipidemic patients received their regular diet as the control group. Five diet-resistant patients in the American phase 3 diet group were given diet plus placebo for another 1 month and then they were given diet plus Gemfibrozil (600 mg twice a day) for 2 months.
RESULTS: Lipid profile was normalized in 9 of the 14 patients on American phase 3 diet. The lipid profile of 5 patients in the American phase 3 diet group did not change significantly after 1-month diet. These 5 diet-resistant patients were given diet plus placebo for another 1 month, and their lipid levels again did not change significantly. Afterward, they were treated with Gemfibrozil (600 mg twice a day) plus American phase 3 diet for 2 months. At the end of this therapy period, their cholesterol level and triglyceride level decreased significantly. No change was observed in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels.
CONCLUSIONS: We conclude that American phase 3 diet and/or Gemfibrozil are effective in controlling posttransplant hyperlipidemia in renal transplant recipients.

PMID: 19174703 [PubMed - indexed for MEDLINE]

22. Transplant Proc. 2008 Dec;40(10):3492-5.

Ezetimibe in the treatment of uncontrolled hyperlipidemia in kidney transplant patients.

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Dyslipidemia is an important complication affecting kidney transplant recipients. Statins, the first-line therapy, are often insufficient. Ezetimibe may be effective in combination with statin therapy. We performed a retrospective study to determine the safety and efficacy of ezetimibe treatment in addition to statin therapy among 27 stable renal transplant patients with uncontrolled hypercholesterolemia. We obtained fasting lipid profiles at 3 and 6 months before ezetimibe therapy, while the patients were receiving statins at maximum tolerated doses. Statin doses were stable during the study. All patients received ezetimibe (10 mg) once daily. Fasting lipid profile, kidney function, liver enzymes, creatine kinase, and immunosuppressive drug levels were obtained at baseline as well as at 3 and 6 months post-ezetimibe initiation. Combination therapy resulted in median reductions in total cholesterol of 29% (interquartile range [IQR] 12-39; P = .0001) and 28% (IQR 9-38; P = .0001); in low-density lipoprotein cholesterol of 34% (IQR 16-61; P = .0001) and 44% (IQR 24-56; P = .0001); and in triglycerides of 14% (IQR 4-31; P = .01) and 19% (IQR 1-37; P = .006) at 3 and 6 months post-ezetimibe therapy, respectively. There were no significant differences in high-density lipoprotein cholesterol, renal function, proteinuria, creatine kinase, amylase, liver function, body mass index, or drug levels. There were no adverse drug reactions that mandated treatment withdrawal. When combined with statin therapy ezetimibe seemed to be a safe and effective treatment for uncontrolled dyslipidemia among renal transplant patients.

PMID: 19100421 [PubMed - indexed for MEDLINE]

24. Transplant Proc. 2008 Nov;40(9):2925-6.

Treatment with ezetimibe in kidney transplant recipients with uncontrolled dyslipidemia.

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INTRODUCTION: Cardiovascular disease is the leading cause of death in kidney transplant recipients. Hyperlipidemia is a cardiovascular risk factor present in over 70% of recipients. Ezetimibe has proved effective for the treatment of dyslipidemia in these patients.
AIM: To evaluate the efficacy and safety of treatment with ezetimibe in kidney transplant recipients with uncontrolled hyperlipidemia.
MATERIALS AND METHODS: We undertook a prospective study of 25 kidney transplant recipients with dyslipidemia who started treatment with 10 mg of ezetimibe. Statins were being taken by 96% of these patients. Monotherapy was used in one case. Measurements were made at baseline and after 3, 6, and 12 months of the lipid and hepatic profiles, CPK, lactose dehydrogenase, renal function and levels of immunosuppressive agents.
RESULTS: A significant reduction was noted in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. No patient had changes in the hepatic profile, increased CPK and lactose dehydrogenase levels, or important adverse effects. Renal function remained stable, with no significant variations in plasma levels of the different immunosuppressive agents.
CONCLUSIONS: The use of ezetimibe associated with statins is an efficient and safe therapeutic alternative for the treatment of poorly controlled dyslipidemia in recipients of a kidney graft.

PMID: 19010149 [PubMed - indexed for MEDLINE]

25. Transplantation. 2008 May 15;85(9):1270-6.

Dyslipidemia can be controlled in diabetic as well as nondiabetic recipients after kidney transplant.

Shivaswamy V, Stevens RB, Zephier R, Zephier M, Sun J, Groggel G, Erickson J, Larsen J.

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BACKGROUND: Patients with diabetes have been reported to have greater dyslipidemia after kidney transplant (KTX). Because postKTX management of diabetes has changed markedly since those reports, we hypothesized that lipids can be controlled as well in diabetic as in nondiabetic recipients.
METHODS: We compared lipid levels up to 2 years after KTX (n=192) between diabetic and nondiabetic recipients. The cohort was subdivided into nondiabetic (nonDM-K; n=123), type 2 (DM2-K; n=33), or type 1 diabetes after KTX (DM1-K; n=14), or type 1 after kidney-pancreas transplant (DM1-KP; n=22).
RESULTS: Mean age and body mass index of DM2-K were greater than the others (P<0.01), and diabetes groups had a higher pretransplant A1C than nonDM-K (P<0.001). After KTX, lipid levels were not higher in diabetic than in nondiabetic recipients, and did not increase in any group. Total and low-density lipoprotein cholesterol levels decreased in DM1-K (P<0.001), high-density lipoprotein levels decreased in DM1-KP (P=0.02), and triglyceride levels were unchanged after KTX for all groups. A1C improved in DM1-K and DM1-KP (P<0.0001). There was less improvement in lipid levels with tacrolimus-sirolimus immunosuppression than with other steroid-containing regimens (P<0.05).
CONCLUSIONS: Multiple mechanisms may contribute to better lipid levels in both groups as well as the lack of difference between diabetic and nondiabetic recipients compared with what has been reported previously: greater use of and more effective lipid-lowering agents, no significant weight gain, no difference in renal function between groups, and better control of glucose in the diabetic group. Thus, overall, lipids can be controlled as well in diabetic as in nondiabetic KTX recipients.

PMCID: PMC2762699
PMID: 18475182 [PubMed - indexed for MEDLINE]

26. Nephrol Dial Transplant. 2008 Jan;23(1):369-73.

Ezetimibe treatment in hypercholesterolemic kidney transplant patients is safe and effective and reduces the decline of renal allograft function: a pilot study.

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BACKGROUND: Ezetimibe has shown efficacy in the therapy of hypercholesterolemia in renal transplant patients. This is the first study investigating the effect of ezetimibe on renal function in kidney transplant recipients.
METHODS: Fifty-six patients with statin-resistant hypercholesterolemia (total cholesterol >200 mg/dl) after renal transplantation received additional ezetimibe therapy (10 mg/day) for 12 months. A group receiving statin therapy (n=28) served as controls in this prospective study.
RESULTS: Total cholesterol and LDL cholesterol concentrations decreased significantly in the ezetimibe-treated patients but remained stable in the control group (delta total cholesterol: -24+/-49 mg/dl vs 19+/-49 mg/dl, P<0.01; delta LDL: -30+/-39 mg/dl vs -3+/-31 mg/dl, P<0.01). Mean creatinine clearance remained stable in ezetimibe-treated patients but decreased significantly in control group (delta Cockcroft-Gault: 0.9+/-7.3 ml/min vs - 4.8+/-12.8 ml/min, P=0.025; delta Modification of Diet in Renal Disease: -0.4+/-6.2 ml/min/1.73 m(2) vs 4.7+/-8.8 ml/min/1.73 m(2), P=0.033).
CONCLUSIONS: The data of our prospective case-control study suggest that ezetimibe appears to ameliorate the decline of renal function after renal transplantation.

PMID: 17956887 [PubMed - indexed for MEDLINE]

27. Transplant Proc. 2007 Dec;39(10):3086-92.

Statins benefit outcomes of renal transplant recipients on a sirolimus-cyclosporine regimen.

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BACKGROUND: Statins offer a strategy to address dyslipidemia commonly experienced by immunosuppressed transplant recipients.
METHODS: This single-center, retrospective study of 325 recipients (mean posttransplant follow-up of over 6 years; 75.0+/-26.0 months) correlated four adverse outcomes-biopsy-confirmed acute rejection episodes, biopsy-confirmed chronic rejection/allograft nephropathy, graft loss, or death-with demographic and posttreatment variables. Patients were treated with a combination of sirolimus (SRL), cyclosporine (CsA), and various durations of steroids. Statins were prescribed for 259/325 (79%) recipients whose serum cholesterol exceeded 240 mg/dL and discontinued when the creatine phosphokinase increased fivefold (3.4%) or the liver function, threefold (3.0%) above normal.
RESULTS: Upon univariate (hazard ratio [HR] 0.16; P<.001) and multivariate analysis (HR 0.38; P=.02), statins were markedly protective against acute rejection episodes. They reduced occurrence of chronic nephropathy/chronic rejection (HR 0.60; P=.03 and HR 0.52; P=.01, respectively). Incidences of graft loss were diminished (HR 0.26; P<.001 and HR 0.49; P=.01, respectively). Finally, the mortality rate was decreased (HR 0.21, P=.001 and HR 0.26, P=.01, respectively). Upon multivariate analysis, a reduced incidence of acute rejection was correlated with greater exposure to SRL (HR 0.78, P=.016) and CsA (HR 0.39; P=.006).
CONCLUSIONS: This study demonstrated compelling effects of statins against all adverse outcomes among patients treated with SRL-based, CsA-containing regimens. The profoundly dyslipidemic properties of SRL may explain these unique findings compared with previous studies on patients treated with CsA-based regimens.

PMID: 18089328 [PubMed - indexed for MEDLINE]

28. Am J Ther. 2007 Sep-Oct;14(5):438-41.

Ezetimibe reduces low-density lipoprotein cholesterol (LDL-C) in renal transplant patients resistant to HMG-CoA reductase inhibitors.

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Hyperlipidemia is common after renal transplantation. On the basis of current lipid guidelines, the majority of renal transplant recipients should have plasma low-density lipoprotein cholesterol (LDL-C) levels <100 mg/dL. Even with statin (HMG-CoA [3-hydroxy-3-methylglutaryl CoA] reductase inhibitor) therapy, a significant number of renal transplant recipients have LDL-C levels >100 mg/dL. We report that ezetimibe, a novel inhibitor of intestinal cholesterol absorption, was well tolerated and effectively reduced the LDL-C level to <100 mg/dL in our cohort of renal transplant recipients with persistently elevated LDL-C levels during treatment with maximally tolerated statin medications.

PMID: 17890931 [PubMed - indexed for MEDLINE]

29. Ren Fail. 2007;29(6):705-12.

Disturbed lipids, lipoproteins and triglyceride-rich lipoproteins as well as fasting and nonfasting non-high-density lipoprotein cholesterol in post-renal transplant patients.

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Serum levels of lipids and lipoproteins were determined in 98 post-renal transplant fasting patients, and lipids and non-high density lipoprotein-cholesterol (non-HDL-C) and lipid ratios in the same post-renal transplant non-fasting patients were compared. The reference group was 87 healthy subjects. All patients were divided into two groups: patients with dyslipidemia (n = 69) and patients with normolipidemic (n = 29). The post-renal transplant patients (TX) with dyslipidemia had a significantly increased concentration of triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), non-HDL-C, apoB, and TRL and lipid ratios, and decreased HDL-C level and lipoprotein ratios. The lipids, lipoproteins, and lipoprotein ratios were significantly beneficial in TX patients with normolipidemic than in those with dyslipidemia. However, TRL concentration and lipid ratios were significantly increased and apoAI/apoCIII significantly decreased as compared to the reference group. The TX patients with dyslipidemia showed a significant correlation between TG and apoB:CIII ($r = 0.562$, $p < 0.001$) and apoCIII ($r = 0.380$, $p < 0.004$), but those with normolipidemic showed a significant correlation only between TG and apoCIII ($r = 0.564$, $p < 0.008$). Regression and Bland-Altman analyses showed excellent correlation between fasting and nonfasting non-HDL-C levels ($r = 0.987$, $R(2) + 0.987$) in TX patients both with dyslipidemia and normolipidemic. We think the finding that nonfasting labs that are reliable for non-HDL-C as well as total cholesterol is important, as fasting labs are not always available. Disturbances of lipids, lipoproteins, and TRLs depend not only on the kind of treatment, but due to multiple factors can accelerate cardiovascular complications in post-renal transplant patients with dyslipidemia and also with normolipidemic. Further studies concerning this problem should be completed.

PMID: 17763166 [PubMed - indexed for MEDLINE]

30. Am J Transplant. 2005 Dec;5(12):2929-36.

Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study.

Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Grönhagen-Riska C, Neumayer HH, Maes B, Ambühl P, Hartmann A, Staffler B, Jardine AG; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators.

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Renal transplant recipients (RTR) have an increased risk of premature cardiovascular disease. The ALERT study is the first trial to evaluate the effect of statin therapy on cardiac outcomes following renal transplantation. Patients initially randomized to fluvastatin or placebo in the 5-6 year ALERT study were offered open-label fluvastatin XL 80 mg/day in a 2-year extension to the original study. The primary endpoint was time to first major adverse cardiac event (MACE). Of 1787 patients who completed ALERT, 1652 (92%) were followed in the extension. Mean total follow-up was 6.7 years. Mean LDL-cholesterol was 98 mg/dL (2.5 mmol/L) at last follow-up compared to a pre-study level of 159 mg/dL (4.1 mmol/L). Patients randomized to fluvastatin had a reduced risk of MACE (hazards ratio [HR] 0.79, 95% CI 0.63-0.99, p = 0.036), and a 29% reduction in cardiac death or definite non-fatal MI (HR 0.71, 95% CI 0.55-0.93, p = 0.014). Total mortality and graft loss did not differ significantly between groups. Fluvastatin produces a safe and effective reduction in LDL-cholesterol associated with reduced risk of MACE in RTR. The lipid-lowering and cardiovascular benefits of fluvastatin are comparable to those of statins in other patient groups, and support use of fluvastatin in RTR.

PMID: 16303007 [PubMed - indexed for MEDLINE]

31. Lancet. 2003 Jun 14;361(9374):2024-31.

Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial.

Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators.

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BACKGROUND: Renal transplant recipients are at increased risk of premature cardiovascular disease. Although statins reduce cardiovascular risk in the general population, their efficacy and safety in renal transplant recipients have not been established. We investigated the effects of fluvastatin on cardiac and renal endpoints in this population.
METHODS: We did a multicentre, randomised, double-blind, placebo-controlled trial in 2102 renal transplant recipients with total cholesterol 4.0-9.0 mmol/L. We randomly assigned patients fluvastatin (n=1050) or placebo (n=1052) and follow up was for 5-6 years. The primary endpoint was the occurrence of a major adverse cardiac event, defined as cardiac death, non-fatal myocardial infarction (MI), or coronary intervention procedure. Secondary endpoints were individual cardiac events, combined cardiac death or non-fatal MI, cerebrovascular events, non-cardiovascular death, all-cause mortality, and graft loss or doubling of serum creatinine. Analysis was by intention to treat.
FINDINGS: After a mean follow-up of 5.1 years, fluvastatin lowered LDL cholesterol concentrations by 32%. Risk reduction with fluvastatin for the primary endpoint (risk ratio 0.83 [95% CI 0.64-1.06], p=0.139) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs 104, 0.65 [0.48-0.88] p=0.005) in the fluvastatin group than in the placebo group. Coronary intervention procedures and other secondary endpoints did not differ significantly between groups.
INTERPRETATION: Although cardiac deaths and non-fatal MI seemed to be reduced, fluvastatin did not generally reduce rates of coronary intervention procedures or mortality. Overall effects of fluvastatin were similar to those of statins in other populations.

PMID: 12814712 [PubMed - indexed for MEDLINE]

32. Nephron. 1994;67(3):317-21.

Hyperlipidemia after renal transplantation: treatment with gemfibrozil.

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33. American Journal of Transplantation. 2012;12:1975–1982

Dyslipidemia and Its Therapeutic Challenges in Renal Transplantation

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Proyecto Prometeo

Grupo III | Lípidos y Riesgo Cardiovascular Postrasplante Renal

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Risk factors associated with coronary artery calcification should be examined before kidney transplantation.

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Source

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Abstract

The best treatment for end stage renal disease (ESRD) patients is kidney transplantation, but the renal transplant recipients still have a higher incidence of cardiovascular events compared with general population. Cardiovascular risk factors were imposed long before ESRD, as the majority of patients starting dialysis or kidney transplantation already have signs of advanced atherosclerosis. Artery calcification is an organized, regulated process similar to bone formation. Coronary artery calcification (CAC) is found frequently in advanced atherosclerotic lesions and could be a useful marker of them. We evaluated the prevalence of CAC in 49 stable renal transplant recipients and in 48 age- and gender-matched patients with chronic kidney disease (CKD) in stages 2-5 not requiring dialysis to assess risk factors associated with CAC. Computed tomography was used for CAC detection and quantification (CAC score). The prevalence of CAC was 43.8% in transplant recipients and 16.7% in CKD patients ($p < 0.001$). Transplant recipients with CAC were significantly older and had longer duration of CKD and/or dialysis than recipients without CAC. In contrast, the serum levels of fetuin A (an inhibitor of vascular calcification) and albumin were significantly lower in CKD patients with CAC than those without CAC. During the observation period (30 months), 30 patients, including 23 CKD patients, began dialysis, and 4 transplant recipients and 2 CKD patients died. Independent predictors of mortality were age, serum amyloid A and the CAC score. In conclusion, the examination and prevention of risk factors associated with atherosclerosis should be started at the beginning of renal failure.

Free Article

PMID: 22293651 [PubMed - in process]

15. Am J Pathol. 2011 Jan;178(1):55-60. Epub 2010 Dec 23.

Endothelial nitric oxide synthase overexpression restores the efficiency of bone marrow mononuclear cell-based therapy.

Mees B, Récalde A, Loinard C, Tempel D, Godinho M, Vilar J, van Haperen R, Lévy B, de Crom R, Silvestre JS.

Source

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Abstract

Bone marrow-derived mononuclear cells (BMMNCs) enhance postischemic neovascularization, and their therapeutic use is currently under clinical investigation. However, cardiovascular risk factors, including diabetes mellitus and hypercholesterolemia, lead to the abrogation of BMMNCs proangiogenic potential. NO has been shown to be critical for the proangiogenic function of BMMNCs, and increased endothelial NO synthase (eNOS) activity promotes vessel growth in ischemic conditions. We therefore hypothesized that eNOS overexpression could restore both the impaired neovascularization response and decreased proangiogenic function of BMMNCs in clinically relevant models of diabetes and hypercholesterolemia. Transgenic eNOS overexpression in diabetic, atherosclerotic, and wild-type mice induced a 1.5- to 2.3-fold increase in postischemic neovascularization compared with control. eNOS overexpression in diabetic or atherosclerotic BMMNCs restored their reduced proangiogenic potential in ischemic hind limb. This effect was associated with an increase in BMMNC ability to differentiate into cells with endothelial phenotype in vitro and in vivo and an increase in BMMNCs paracrine function, including vascular endothelial growth factor A release and NO-dependent vasodilation. Moreover, although wild-type BMMNCs treatment resulted in significant progression of atherosclerotic plaque in ischemic mice, eNOS transgenic atherosclerotic BMMNCs treatment even had antiatherogenic effects. Cell-based eNOS gene therapy has both proangiogenic and antiatherogenic effects and should be further investigated for the development of efficient therapeutic neovascularization designed to treat ischemic cardiovascular disease.

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PMID: 21224043 [PubMed - indexed for MEDLINE]

21. Transplant Proc. 2010 Nov;42(9):3450-4.

Presence of cardiovascular disease in patients on a waiting list for renal transplantation and in patients after kidney transplantation in a single center.

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Source

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Abstract

BACKGROUND:

Cardiovascular risk in hemodialysis patients is enhanced, resulting in a higher mortality rate compared with the general population, yet the average wait time for renal transplantation in Germany is 5-7 years. The age of wait-listed patients has risen progressively. The aim of this study was to evaluate the prevalence of cardiovascular disease in patients on the waiting list in our center before and after renal transplantation as well as the extent to which invasive treatment was required in these patients.

METHODS:

The study investigated 2 groups: 350 patients on the renal transplantation waiting list at our center in 2008 and 324 patients who underwent renal transplantation at the same center in the years 2003-2007.

RESULTS:

In 2008, 141 women and 209 men with a mean age of 48.6 years (range 13-71 years) were on the waiting list. In the years 2003-2007, 98 women and 226 men with a mean age of 54.3 years (range 16-78 years) received renal transplants. One hundred six patients on the waiting list for renal transplantation had to undergo coronary angiography. There is no upper age limit for donors or recipients in our program. Mean age at admission on the waiting list was 48.6 years (range 13-71 years). Mean age at transplantation was 54.3 years (range 16-78 years) in our center. Most of these patients were asymptomatic but presented a risk profile that included diabetes mellitus, severe general atherosclerosis, a pathologic ergometric test, or abnormal myocardial scintigraphy. Only in 1 case could coronary heart disease be excluded. Seventy patients (20%) suffered from mild to moderate coronary heart disease without the need for intervention. In 5 patients (1.4%) coronary bypass surgery was necessary due to severe 3-vessel coronary heart disease. In 2 cases (0.6%) replacement of the aortic valve was performed because of aortic valvular stenosis. Coronary angioplasty without implantation of stents was done in 2 patients (0.6%). Twenty-two patients (6.8%) were treated with implantation of bare metal stents and 6 patients (1.7%) with drug-eluting stents. After renal transplantation, 22 patients (6.8%) suffered from peripheral arterial occlusive disease. In 58 patients, coronary heart disease was documented by angiography. 16 patients (4.9%) had 1-vessel disease, 23 patients (7%) 2-vessel disease, and 19 patients (5.8%) 3-vessel disease. Myocardial infarction was documented in 18 patients (5.5%) before and in 5 patients (1.5%) after renal transplantation. Bare metal stent implantation was performed in 6 patients (1.8%) after

transplantation. One patient received a drug-eluting stent after renal transplantation. In the years 2003-2007, 22 patients underwent coronary bypass surgery before kidney transplantation.

CONCLUSION:

The prevalence of coronary heart disease is high in patients on the waiting list and after renal transplantation. The majority of these patients are clinically asymptomatic. One-third of the patients with coronary heart disease had to be treated invasively. Nevertheless, many diabetic patients are very sick from multiple complications after the waiting time, making theme unsuitable for transplantation.

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PMID: 21094795 [PubMed - indexed for MEDLINE]

23. Cardiovasc Hematol Disord Drug Targets. 2010 Sep 1;10(3):161-6.

Challenges in vascular repair by endothelial progenitor cells in diabetic patients.

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Source

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Abstract

Endothelial progenitor cells (EPCs) are a special type of stem cells, derived from bone marrow that can be mobilized to the peripheral circulation in response to many stimuli. EPCs play a crucial role in the vascular repair, as well as in neovascularization processes. Recent studies have shown that EPCs are impaired, both in number and function, in diabetic patients independently of other cardiovascular risk factors. Accelerated atherosclerosis is probably the most devastating among diabetes complications and endothelial dysfunction might be the beginning of the atherosclerosis. The impairment of EPCs seems to significantly contribute to atherogenesis and atherosclerotic disease progression in diabetes. Autologous EPCs therapy represents a novel treatment option for vascular complications requiring therapeutic revascularization and vascular repair. Diabetic patients represent a population that may benefit from cell-based therapy; however the dysfunction of their endogenous cells may limit the feasibility of this approach. In fact, EPCs isolated from these patients for autologous cell transplantation may retain their dysfunctional characteristics in vivo and as a consequence display a reduced capacity to improve therapeutic neovascularization. In the present review, we summarize the most relevant mechanisms of EPC dysfunction in diabetes.

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72. Transplant Proc. 2012 Apr;44(3):672-5.

Percentages of Water, Muscle, and Bone Decrease and Lipid increases in Early Period After Successful Kidney Transplantation: A Body Composition Analysis.

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BACKGROUND: Successful kidney transplantation (KT) can theoretically reconstitute body composition of a patient with chronic kidney disease (CKD). However, the practical changes have not been well documented. We evaluated changes in body composition among candidates before and 1 year after KT.
METHODS: We enrolled 37 male and 18 female kidney recipients eligible for comparison of their body mass index (BMI), body composition, and lipid metabolism before and 1 year after KT. Twenty-one patients had been induced with a calcineurin inhibitor, mycophenolate mofetil, steroid, and basiliximab, and 34 others underwent steroid withdrawal on postoperative day 3. The body composition was analyzed using bioelectrical impedance. We also analyzed changes in BMI and lipid profiles.
RESULTS: There was no significant change in BMI (21.4 ± 3.1 vs 21.7 ± 3.5 kg/m(2)). Regarding body composition, the water level decreased significantly (61.2 ± 4.9% vs 58.3 ± 5.3%; $P < .05$). In contrast, fat significantly increased (16.4 ± 6.7% vs 20.3 ± 7.1%; $P < .05$). More interestingly, successful KT significantly decreased the muscle and bone mass at 1 year after KT (37.3 ± 5.1% vs 34.8 ± 4.7%; 16.3 ± 2.1% vs 15.2 ± 2.1%; respectively; $P < .05$). Serum lipid profiles of total cholesterol, low-density lipoprotein cholesterol, and triglyceride worsened after KT. Comparing the 2 protocols, there was no difference in any item.
CONCLUSIONS: Care must be taken even after successful KT to avoid dyslipidemia, which is a risk factor for cardiovascular disease. Well programmed dietary and/or exercise protocols to prevent muscle atrophy and fat gain should be considered even after successful KT.

PMID: 22483465 [PubMed - in process]

74. Lancet. 2011 Jun 25;377(9784):2181-92.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial.

Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK.

BACKGROUND: Lowering LDL cholesterol with statin regimens reduces the risk of myocardial infarction, ischaemic stroke, and the need for coronary revascularisation in people without kidney disease, but its effects in people with moderate-to-severe kidney disease are uncertain. The SHARP trial aimed to assess the efficacy and safety of the combination of simvastatin plus ezetimibe in such patients.
METHODS: This randomised double-blind trial included 9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation. Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. The key prespecified outcome was first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure). All analyses were by intention to treat.
FINDINGS: 4650 patients were assigned to receive simvastatin plus ezetimibe and 4620 to placebo. Allocation to simvastatin plus ezetimibe yielded an average LDL cholesterol difference of 0·85 mmol/L (SE 0·02; with about two-thirds compliance) during a median follow-up of 4·9 years and produced a 17% proportional reduction in major atherosclerotic events (526 [11·3%] simvastatin plus ezetimibe vs 619 [13·4%] placebo; rate ratio [RR] 0·83, 95% CI 0·74-0·94; log-rank p=0·0021). Non-significantly fewer patients allocated to simvastatin plus ezetimibe had a non-fatal myocardial infarction or died from coronary heart disease (213 [4·6%] vs 230 [5·0%]; RR 0·92, 95% CI 0·76-1·11; p=0·37) and there were significant reductions in non-haemorrhagic stroke (131 [2·8%] vs 174 [3·8%]; RR 0·75, 95% CI 0·60-0·94; p=0·01) and arterial revascularisation procedures (284 [6·1%] vs 352 [7·6%]; RR 0·79, 95% CI 0·68-0·93; p=0·0036). After weighting for subgroup-specific reductions in LDL cholesterol, there was no good evidence that the proportional effects on major atherosclerotic events differed from the summary rate ratio in any subgroup examined, and, in particular, they were similar in patients on dialysis and those who were not. The excess risk of myopathy was only two per 10,000 patients per year of treatment with this combination (9 [0·2%] vs 5 [0·1%]). There was no evidence of excess risks of hepatitis (21 [0·5%] vs 18 [0·4%]), gallstones (106 [2·3%] vs 106 [2·3%]), or cancer (438 [9·4%] vs 439 [9·5%], p=0·89) and there was no significant excess of death from any non-vascular cause (668 [14·4%] vs 612 [13·2%], p=0·13).
INTERPRETATION: Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

PMCID: PMC3145073
PMID: 21663949 [PubMed - indexed for MEDLINE]

75. Transplantation. 2011 May 15;91(9):976-83.

Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies).

Vanrenterghem Y, Bresnahan B, Campistol J, Durrbach A, Grinyó J, Neumayer HH, Lang P, Larsen CP, Mancilla-Urrea E, Pestana JM, Block A, Duan T, Glicklich A, Gujrathi S, Vincenti F.
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BACKGROUND: Cardiovascular disease, the most common cause of death with a functioning graft among kidney transplant recipients, can be exacerbated by immunosuppressive drugs, particularly the calcineurin inhibitors. Belatacept, a selective co-stimulation blocker, may provide a better cardiovascular/metabolic risk profile than current immunosuppressants.
METHODS: Cardiovascular and metabolic endpoints from two Phase III studies (BENEFIT and BENEFIT-EXT) of belatacept-based regimens in kidney transplant recipients were assessed at month 12. Each study assessed belatacept in more intensive (MI) and less intensive (LI) regimens versus cyclosporine A (CsA). These secondary endpoints included changes in blood pressure, changes in serum lipids, and the incidence of new-onset diabetes after transplant (NODAT).
RESULTS: A total of 1209 patients were randomized and transplanted across the two studies. Mean systolic blood pressure was 6 to 9 mm Hg lower and mean diastolic blood pressure was 3 to 4 mm Hg lower in the MI and LI groups versus CsA ($P \leq 0.002$) across both studies at month 12. Non-HDL cholesterol was lower in the belatacept groups versus CsA ($P<0.01$ MI or LI vs. CsA in each study). Serum triglycerides were lower in the belatacept groups versus CsA ($P<0.02$ MI or LI vs. CsA in each study). NODAT occurred less often in the belatacept groups versus CsA in a prespecified pooled analysis ($P<0.05$ MI or LI vs. CsA).
CONCLUSIONS: At month 12, belatacept regimens were associated with better cardiovascular and metabolic risk profiles, with lower blood pressure and serum lipids and less NODAT versus CsA. The overall profile of belatacept will continue to be assessed over the 3-year trials.

PMID: 21372756 [PubMed - indexed for MEDLINE]

76. Transplant Proc. 2011 Mar;43(2):530-2.

Nocturnal nondipping hypertension is related to dyslipidemia and increased renal resistivity index in renal transplant patients.

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BACKGROUND: There are limited data about ambulatory blood pressure monitoring (ABPM) in renal transplantation patients. We sought to evaluate the clinical outcomes, and success of antihypertensive therapy based upon ABPM data.
METHODS: We performed ABPM on 82 recipients between 2000 and 2006 including 27 females of overall age of 37.3±10.8 years who displayed mild to moderate hypertension (HT). We evaluated demographic blood pressure, proteinuria, and laboratory values, as well as renal resistive index (RRI) estimated by Doppler ultrasonography.
RESULTS: There were 65% of subjects who were "nondippers". Nighttime systolic and diastolic blood pressures correlated with phosphorus (r=0.32; P=.04) and proteinuria (r=0.35; P=.01). The incidence of increased RRI was greater among nondipper than dipper patients (52% vs 24%; P<.01). Comparison of variables between dipping and nondipping patients were total cholesterol, low-density lipoprotein cholesterol triglyceride, and C-reactive protein values (P=.04, .03, .001, and .001, respectively). Regression analysis revealed increased RRI (<0.7) and total cholesterol (>240 mg/dL) to be the main risk factors for a nondipping pattern (P<.001 and .05 respectively).
CONCLUSION: Nondipping HT is common after transplantation. ABPM may be a useful tool to optimize treatment strategies to reduce cardiovascular events and chronic graft dysfunction. An high RRI seemed to be a strong determinate of nondipper status.

PMID: 21440752 [PubMed - indexed for MEDLINE]

77. Transplantation. 2011 Jan 27;91(2):225-30.

Cause of death with graft function among renal transplant recipients in an integrated healthcare system.

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BACKGROUND: Cardiovascular disease (CVD) is the leading cause of death in renal transplant recipients with a functioning allograft. Modification of CVD risk factors may, therefore, decrease overall mortality in this patient population. We studied renal transplant recipients within an integrated healthcare system (IHS) that uses case management and electronic health records to determine mortality from CVD.
METHODS: We retrospectively collected data on all renal transplant recipients over a 10-year period. The primary endpoint was death with graft function (DWGF). Cardiovascular events were used as secondary endpoints. We determined the cause of death and collected laboratory data. The data were analyzed using Student's t test for continuous data, chi square for categorical data, and multivariate logistic regression. Survival was determined using the Kaplan-Meier product-limit method.
RESULTS: Death from "other" causes accounted for 29%. This was followed by CVD (24%), infection (16%), and malignancy (12%). The most common "other" causes were diabetes mellitus and end-stage renal disease. Overall, lower hemoglobin, uncontrolled blood pressure, and lower albumin levels were associated with DWGF. There were 184 cardiovascular events in total. Low-density lipid levels were lower in the group with cardiovascular events and DWGF. The use of antihypertensive and antihyperlipidemic agents was similar between the two groups with the exception of diuretics, which were used more often in the DWGF group.
CONCLUSIONS: There was a low rate of DWGF because of CVD within this IHS. It is possible that coordinated care within an IHS leads to improved cardiovascular mortality.

PMID: 21048529 [PubMed - indexed for MEDLINE]

78. BMC Cardiovasc Disord. 2011 Jan 10;11(1):2.

Incidence of cardiovascular events after kidney transplantation and cardiovascular risk scores: study protocol.

Pita-Fernandez S, Pertega-Diaz S, Valdes-Canedo F, Seijo-Bestilleiro R, Seoane-Pillado T, Fernandez-Rivera C, Alonso-Hernandez A, Lorenzo-Aguiar D, Lopez-Calvino B, Lopez-Muniz A.

ABSTRACT: BACKGROUND: Cardiovascular disease (CVD) is the major cause of death after renal transplantation. Not only conventional CVD risk factors, but also transplant-specific risk factors can influence the development of CVD in kidney transplant recipients. The main objective of this study will be to determine the incidence of post-transplant CVD after renal transplantation and related factors. A secondary objective will be to examine the ability of standard cardiovascular risk scores (Framingham, REGICOR, SCORE, and DORICA) to predict post-transplantation cardiovascular events in renal transplant recipients, and to develop a new score for predicting the risk of CVD after kidney transplantation.
METHODS: Observational prospective cohort study of all kidney transplant recipients in the A Coruna Hospital (Spain) in the period 1981-2008 (2059 transplants corresponding to 1794 patients). The variables included will be: donor and recipient characteristics, chronic kidney disease-related risk factors, pre-transplant and post-transplant cardiovascular risk factors, routine biochemistry, and immunosuppressive, antihypertensive and lipid-lowering treatment. The events studied in the follow-up will be: patient and graft survival, acute rejection episodes and cardiovascular events (myocardial infarction, invasive coronary artery therapy, cerebral vascular events, new-onset angina, congestive heart failure, rhythm disturbances and peripheral vascular disease). Four cardiovascular risk scores were calculated at the time of transplantation: the Framingham score, the European Systematic Coronary Risk Evaluation (SCORE) equation, and the REGICOR (Registre Gironi del COR (Gerona Heart Registry)), and DORICA (Dyslipidemia, Obesity, and Cardiovascular Risk) functions. The cumulative incidence of cardiovascular events will be analyzed by competing risk survival methods. The clinical relevance of different variables will be calculated using the ARR (Absolute Risk Reduction), RRR (Relative Risk Reduction) and NNT (Number Needed to Treat). The ability of different cardiovascular risk scores to predict cardiovascular events will be analyzed by using the c index and the area under ROC curves. Based on the competing risks analysis, a nomogram to predict the probability of cardiovascular events after kidney transplantation will be developed.
DISCUSSION: This study will make it possible to determine the post-transplant incidence of cardiovascular events in a large cohort of renal transplant recipients in Spain, to confirm the relationship between traditional and transplant-specific cardiovascular risk factors and CVD, and to develop a score to predict the risk of CVD in these patients.

PMCID: PMC3022886
PMID: 21639867 [PubMed - as supplied by publisher]

79. Nephron Clin Pract. 2011;119(3):c227-35.

Traditional and nontraditional cardiovascular risk factors and estimated risk for coronary artery disease in renal transplant recipients: a single-center experience.

Banas MC, Banas B, Orth SR, Langer V, Reinhold SW, Weingart C, Jung B, Krüger B, Krämer BK.

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BACKGROUND/AIMS: The prevalence of cardiovascular disease in renal transplant recipients is markedly higher than in the general population due to the high prevalence of traditional cardiovascular risk factors, renal transplant function impairment and treatment with immunosuppressive drugs that affect blood pressure, cholesterol and blood glucose levels.
METHODS: Cross-sectional analysis using our renal transplant clinic cohort investigating (1) the cardiovascular risk factors present in this cohort, and (2) estimating their impact on the risk of coronary artery disease (CAD) by using the Framingham algorithm.
RESULTS: Control of modifiable cardiovascular risk factors in 231 renal transplant recipients is suboptimal, i.e. 47.2% of patients are hypertensive, 10.3% actively smoke, 39.4% have serum cholesterol concentrations >200 mg/dl, and 19.7% have diabetes mellitus. Blood pressure, age, hyperlipidemia, smoking and diabetes modulate the estimated CAD risk in males and females. Furthermore, a short time period (less than 1 year) since transplantation and increased serum creatinine levels negatively influenced the CAD risk in this patient population.
CONCLUSION: According to current guidelines, the control of modifiable cardiovascular risk factors in renal transplant recipients is suboptimal. The decreasing CAD risk over time after transplantation may be due to the reduction of immunosuppressive drugs with time and survival bias.

PMID: 21849798 [PubMed - indexed for MEDLINE]

80. Kidney Int Suppl. 2010 Sep;(118):S8-14.

The metabolic syndrome following kidney transplantation.

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The metabolic syndrome is a constellation of defined cardiovascular risk factors occurring simultaneously in a single individual. The result of dysregulated glucose and vascular metabolism, the syndrome has been identified as a significant risk factor for cardiovascular morbidity in the general population. More recently, a relatively high prevalence of the metabolic syndrome has been recognized among kidney transplant recipients. The prevalence, risk factors, pathophysiology, and potential consequences of the metabolic syndrome in the general population and in kidney transplant recipients are reviewed. The definitions and clinical utility of the metabolic syndrome as a medical condition continue to be debated. Nevertheless, the burden of risk increases with the presence of multiple components, including insulin resistance, abdominal obesity, and dysregulated lipid metabolism. Risk factors specific to transplant recipients include the duration of pretransplant dialysis and posttransplant immunosuppression and weight gain. The metabolic syndrome is emerging as a significant surveillance target following kidney transplantation. Control of body mass index, blood glucose and lipid levels, as well as blood pressure, is required to prevent the consequences of the metabolic syndrome, including cardiovascular events and cardiovascular death. Immunosuppressive regimens should be designed to limit exacerbation of components of the metabolic syndrome.

PMID: 20706225 [PubMed - indexed for MEDLINE]

81. Iran J Kidney Dis. 2010 Jul;4(3):237-43.

Evaluation of arterial stiffness and pulse wave reflection for cardiovascular risk assessment in diabetic and nondiabetic kidney transplant recipients.

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INTRODUCTION: Evidence demonstrates that cardiovascular risk reduces after kidney transplantation, but is still a major cause of death. With increasing inclusion of diabetic patients for kidney transplantation, the evaluation of cardiovascular disease in this population becomes more important. We compared arterial stiffness and pulse wave reflection as well as other cardiovascular risk factors in kidney transplant patients with and without diabetes mellitus.
MATERIALS AND METHODS: One hundred kidney transplant recipients, including 33 diabetic patients, were evaluated for their renal-cardiovascular risk factors, including blood pressure, lipids, glucose control, homocysteine, and arterial stiffness indexes. The tests were repeated after 1 year in 47 individuals.
RESULTS: There was no significant difference in pulse wave velocity (PWV) between the diabetic and nondiabetic groups, despite a greater augmentation index (AI) in the diabetic group (20.5 +/- 2.3 versus 13.1 +/- 2.2). Multivariable analysis revealed that diabetes mellitus was a significant determinant for AI independently of age, blood pressure, posttransplant time, gender, and glomerular filtration rate (R2 = 39%). Repeated test after 1 year demonstrated a significant reduction in the carotid-femoral PWV (P = .03) and systolic blood pressure (P = .007).
CONCLUSIONS: In contrast to nontransplant groups, AI was significantly greater in diabetic kidney transplant patients compared to their nondiabetic counterparts, despite a comparable PWV. However, carotid-femoral PWV improved after 1 year. These may reflect progressive ventricular and large arterial function improvement despite remained small arterial defects after transplantation. It also suggests potential role of arterial evaluation in risk assessment among kidney transplant patients.

PMID: 20622314 [PubMed - indexed for MEDLINE]

82. Nephrol Dial Transplant. 2010 Feb;25(2):617-24.

Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation.

Höcker B, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, Pohl M, Zimmering M, Fründ S, Klaus G, Wühl E, Tönshoff B.

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BACKGROUND: Long-term corticosteroid treatment impairs growth and increases cardiovascular risk factors. Hence, steroid withdrawal constitutes a major topic in paediatric renal transplantation and maintenance immunosuppression.
METHODS: The lack of data from randomised controlled trials caused us to conduct the first prospective, randomised, multicentre study on late steroid withdrawal among paediatric kidney allograft recipients treated with standard-dose cyclosporine microemulsion (CsA) and mycophenolate mofetil (MMF) for 2 years. Forty-two low- or regular-immunologic risk patients were randomly assigned, >or=1 year post-transplant, to continue taking or to withdraw steroids over 3 months.
RESULTS: Two years after steroid withdrawal, they showed a longitudinal growth superior to controls [mean height standard deviation score (SDS) gain, 0.6 +/- 0.1 SDS versus -0.2 +/- 0.1 SDS ($P < 0.001$)]. The prevalence of the metabolic syndrome declined significantly ($P < 0.05$), 2 years after steroid withdrawal, from 39% (9/23) to 6% (1/16). Steroid-free patients had less frequent arterial hypertension (50% versus 93% ($P < 0.05$)) and required fewer antihypertensive drugs [0.6 +/- 0.2 versus 1.5 +/- 0.3 ($P < 0.05$ versus control)]. Additionally, they had a significantly improved carbohydrate and lipid metabolism with fewer hypercholesterolaemia and hypertriglyceridaemia ($P < 0.05$ versus control). Patient and graft survival amounted to 100%. Allograft function remained stable 2 years after steroid withdrawal. The incidence of acute rejections was similar in the steroid-withdrawal group (1/23, 4%) and controls (2/19, 11%).
CONCLUSION: Late steroid withdrawal in selected CsA- and MMF-treated paediatric kidney transplant recipients improves growth, mitigates cardiovascular risk factors and reduces the prevalence of the metabolic syndrome, at no increased risk of acute rejection or unstable graft function.

PMID: 19793929 [PubMed - indexed for MEDLINE]

83. Pediatr Nephrol. 2010 Feb;25(2):343-8.

Subclinical atherosclerosis and related risk factors in renal transplant recipients.

Basiratnia M, Fazel M, Lotfi M, Hosseini Al-Hashemi G, Fallahzadeh MH, Derakhshan A, Salehipour M.

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Long-term survival after successful renal transplantation is shortened by cardiovascular disease. Cardiovascular disease is a main cause of morbidity and death among children and young adults after renal transplantation. The aim of our study was to measure the carotid intima media thickness (cIMT) and determine its relationship to the risk factors for early arteriopathy in renal transplant recipients. Sixty-six stable renal transplant patients (36 female and 30 male), 7-25 years of age (mean 18.3 +/- 4.5 years) were enrolled in this study. The cIMT was measured by high-resolution B mode ultrasonography in multiple projections. The results were correlated with clinical and paraclinical parameters, including age, gender, body mass index (BMI), blood pressure, glomerular filtration rate (GFR), duration of dialysis, duration of chronic kidney disease (CKD), post-transplantation interval, calcium-phosphate (CaxP) product, cumulative dose of Ca-based P binder and calcitriol, lipid profile, uric acid, and cyclosporine level. The mean post-transplantation follow-up period was 64 +/- 40 months. The mean cIMT standard deviation score (SDS) of the patients and the control group was 0.60 +/- 0.81 mm (range -1.10 mm to 2.75 mm) and -1.25 +/- 0.95 mm (range -3.23 mm to 0.26 mm), respectively. Renal transplant recipients had a significantly greater cIMT than that of the controls ($P < 0.001$). Among several risk factors, there were positive correlations between cIMT SDS and gender, and cumulative dose of calcitriol ($P = 0.02$ and $P = 0.02$, respectively). In conclusion, subclinical atherosclerosis is present in young transplant recipients. Non-invasive monitoring of cIMT in renal transplant patients for the detection of early vascular lesions might be of value in preventing cardiovascular disease. Further studies are needed to see if proper monitoring of vitamin D therapy before and after transplantation could be helpful in the prevention of arteriopathy in renal transplant recipients.

PMID: 19911201 [PubMed - indexed for MEDLINE]

84. J Nephrol. 2009 Sep-Oct;22(5):598-609.

Statin treatment for dyslipidemia in chronic kidney disease and renal transplantation: a review of the evidence.

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Patients with chronic kidney disease (CKD) have significantly increased risks of cardiovascular (CV) morbidity and mortality. Dyslipidemia is a common disorder in CKD patients. CKD patients have a different lipid profile with increased atherogenic lipid fractions, and serum low-density lipoprotein cholesterol (LDL-C) levels may underestimate the atherogenic effect of LDL-C in these patients. Dyslipidemia may contribute to the increased CV morbidity and mortality, and to the progression of kidney disease in CKD patients. Currently, statins are the pharmacologic intervention of first choice, if lifestyle changes fail adequately to lower LDL-C levels in the setting of normal or moderately elevated triglycerides. Statins have been extensively studied in a large variety of patient populations and have proven efficacy in the treatment of dyslipidemia, and in reducing CV mortality. Although much evidence supports the CV benefits of statins in patients with normal renal function, there are contradictory results for the beneficial effect of statin therapy on CV morbidity and mortality in CKD patients. While post hoc subgroup analyses of multiple randomized trials support statin use in early CKD patients, the only randomized trial conducted in diabetic dialysis patients found no evidence of benefit in overall mortality. Post transplant there is some definite CV benefit, albeit in a patient cohort selected to be at reduced CV risk by virtue of being eligible for organ transplant. The results from the AURORA and SHARP studies are awaited anxiously.

PMID: 19809992 [PubMed - indexed for MEDLINE]

85. Curr Diab Rep. 2009 Aug;9(4):305-11.

Dyslipidemia following kidney transplantation: diagnosis and treatment.

Badiou S, Cristol JP, Mourad G.

Lipid abnormalities are a common complication of kidney transplantation, occurring in up to 60% of patients. In fact, impairment of lipid metabolism is often present before renal transplantation due to the uremic state. After transplantation and recovery of renal function, lipid disturbances usually persist but show a different profile due to the various effects of immunosuppressive drugs on lipid metabolism. Actually, steroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors usually lead to quantitative and qualitative abnormalities of very low-density, low-density, and high-density lipoproteins. As cardiovascular diseases remain the leading cause of death in renal transplant recipients, management of dyslipidemia and other traditional risk factors, such as smoking, arterial hypertension, diabetes mellitus, and obesity, is of great importance to prevent cardiovascular complications and chronic allograft dysfunction. This review addresses the causes of dyslipidemia, the role of immunosuppressive drugs, and current recommendations to manage lipid disorders in renal transplant recipients.

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86. Transplant Proc. 2009 Jul-Aug;41(6):2151-5.

Prevalence evolution and impact of cardiovascular risk factors on allograft and renal transplant patient survival.

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OBJECTIVE: The prevalence of traditional cardiovascular risk factors in renal transplantation is high. Studying the evolution of cardiovascular risk factors over time may help us to design better strategies to control them. The relative impact of traditional cardiovascular risk factors on allograft survival and mortality in transplant recipients is not clear. This study was performed to determine the incidence and risk factors for allograft survival and mortality among renal transplant patients.
PATIENTS AND METHODS: We enrolled 250 patients who had undergone transplantation between 1980 and 2004. They were followed for various periods, and we analyzed the impact of traditional and nontraditional risk factors on renal allograft survival.
RESULTS: The prevalence of hypertension was >80% during all the follow-up periods. Blood pressure diminished, antihypertensive drug prescription increased, and 15% of patients had adequate blood pressure control during follow-up. The prevalence of pretransplant diabetes mellitus was 6.8%; the incidence of posttransplant diabetes mellitus (PTDM) was 14.2%. The prevalence of PTDM increased over the course of patient evolution. The prevalence of dyslipidemia was in all cases >70%; total cholesterol and low-density lipoprotein (LDL)-cholesterol decreased; prescription of statins increased; and the percentage of patients with good lipid control also increased. The 25% prevalence of active smoking at the time of transplantation decreased to 13.6% at 10 years posttransplantation. The mean patient follow-up was 8 +/- 4.6 years. Sixty-five patients (26%) lost their grafts and 40 (16%) died during follow-up. Donor age, exercise, diastolic blood pressure, renal function, and albumin levels were independent risk factors for graft loss. Charlson comorbidity index at transplantation, recipient and donor ages, exercise, diastolic blood pressure, and LDL-cholesterol posttransplantation were independent risk factors for mortality among renal transplant recipients.
CONCLUSION: Blood pressure and lipid control improved during follow-up, however, insufficiently among renal transplant patients. The prevalence of diabetes gradually increased, and the incidence of smoking cessation was low. Diastolic blood pressure, exercise, and albuminemia were the most significant modifiable cardiovascular risk factors for renal allograft survival. Diastolic blood pressure, LDL-cholesterol level, and exercise were the most relevant modifiable cardiovascular risk factors for the survival of renal transplant patients.

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87. Transplant Proc. 2009 May;41(4):1178-82.

Immunosuppressive agents and metabolic factors of cardiovascular risk in renal transplant recipients.

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Cardiovascular disease (CVD) accounts for 35% to 50% of deaths among renal transplant recipients. Beside the atherogenic risk factors related to hemodialysis, renal function, and use of immunosuppressive agents, other relevant risk factors for CVD include acute rejection episodes, microalbuminuria (muAlb), diabetes, arterial hypertension, lipid disorders, inflammatory triggers, hyperhomocysteinemia, anemia, erythrocytosis, obesity, and hyperuricemia. We studied the prevalence of risk factors and the impact of various drugs on CVD among 103 renal transplant recipients with measured glomerular filtration rates showing values >45 mL/min. We measured uric acid, triglycerides (TG), low-density lipoprotein (LDL)/high-density lipoprotein (HDL) LDL/HDL ratio, homocysteine (HOMO), insulin resistance, muAlb, C-reactive protein (CRP), and fibrinogen. Subsequently, patients were divided into 8 groups based on the immunosuppressive protocol to evaluate its impact on CVD risk factors. Insulin resistance and hyperhomocysteinemia were present in >2/3 of patients. Considering the impact of protocols, the combination of cyclosporine (CsA) + everolimus (EVL) resulted in the most favorable profile in terms of reduction of hyperuricemia, hyperlipidemia, and hyperhomocysteinemia. Insulin resistance tended to be more frequent among patients treated with protocols including calcineurin inhibitors (CNI) and steroids. The prevalence of hyperhomocyteinemia was similar among patients on CsA and on tacrolimus (Tac). Sirolimus (SRL) was associated with higher levels of HOMO. The combination of CNI and proliferative signal inhibitors (PSI) seemed to be the most promising one to reduce the impact of CVD risk factors. The reduction in CVD morbidity can improve expectancy and quality of life, as well as graft function and survival among renal transplant patients.

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88. Curr Med Res Opin. 2009 Jan;25(1):271-85.

Cardiovascular disease in patients with renal disease: the role of statins.

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OBJECTIVES: Atherosclerosis is common in patients with chronic kidney disease (CKD), and cardiovascular disease (CVD) represents a major cause of death. The National Kidney Foundation guidelines favour the use of statin therapy for treatment of dyslipidaemia in patients with CKD. Much evidence supports statin therapy for reducing CVD and improving outcomes in the general population, but there is less evidence in patients with CKD. Consequently, prevention of CVD in CKD is based primarily on extrapolation from non-CKD trials. Significantly, in trials specifically designed to investigate patients with CKD, evidence is emerging for improved cardiovascular outcomes with statin therapy. This review describes available data relating to cardiovascular outcomes and the role of statins in patients with CKD, including pre-dialysis, dialysis, and renal transplant patients.
RESEARCH DESIGN AND METHODS: The PubMed database was searched (1998-present) to ensure comprehensive identification of publications (including randomized clinical trials) relevant to CKD patients, patterns of cardiovascular outcome in such patients and their relationship to lipid profile, and the role of statins for the prevention and treatment of cardiovascular complications.
RESULTS: There are conflicting data on the relationship between dyslipidaemia and cardiovascular outcomes, with one major study of statin therapy (4D—Deutsche Diabetes Dialyse Studie) providing equivocal results. Further studies, including AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events; NCT00240331) in patients receiving haemodialysis, and SHARP (Study of Heart And Renal Protection; NCT00125593) in patients with CKD including those on dialysis, should help to clarify the role of statin therapy in these populations.
CONCLUSIONS: More studies are needed to elucidate the role of statins in improving cardiovascular outcomes for CKD patients. It is anticipated that ongoing clinical trials geared towards the optimal prevention and treatment of CVD in patients with CKD will help guide clinicians in the management of CKD.

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89. Transplant Proc. 2008 Apr;40(3):761-3.

Insulin resistance, body fat percentage, and lipid abnormalities as risk factors for cardiovascular diseases in renal transplant recipients: a 1-year analysis.

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The aim of this study was to evaluate changes in body mass index (BMI), body fat percentage (BF%), insulin resistance, and lipid profile in 32 patients during the first year after renal transplantation by anthropometric measures. The homeostasis model assessment index (HOMA) was calculated for insulin resistance estimation. Anthropometric measures and biochemical markers were evaluated at the time of transplantation (T(0)), and prospectively at 3 (T(3)), 6 (T(6)), 9 (T(9)), and 12 (T(12)) months posttransplantation. The HOMA index decreased significantly at 3 months after transplantation (T(3)) (2.4 +/- 1.5 vs 1.5 +/- 1.1; P < .01); however, an increment was observed at T(6) and T(9) (1.8 +/- 0.8 and 2 +/- 1.5, respectively), remaining stable at T(12) (2 +/- 1.7). BMI and BF% increased significantly over 12 months (23.3 +/- 2.7 vs 24.4 +/- 2.7 kg/m(2); P = .001 and 23.7 +/- 7.8 vs 25.6 +/- 7.7 %; P = .002). Total cholesterol, low-density lipoprotein cholesterol and triglyceride levels showed significant increases starting at T(3). In conclusion, insulin resistance decreased transitorily post-renal transplantation. BMI, BF%, and lipid profile showed unfavorable changes during the first year post-renal transplantation.

PMID: 18455009 [PubMed - indexed for MEDLINE]

90. Am J Transplant. 2005 Dec;5(12):2929-36.

Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study.

Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Grönhagen-Riska C, Neumayer HH, Maes B, Ambühl P, Hartmann A, Staffler B, Jardine AG; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators.

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Renal transplant recipients (RTR) have an increased risk of premature cardiovascular disease. The ALERT study is the first trial to evaluate the effect of statin therapy on cardiac outcomes following renal transplantation. Patients initially randomized to fluvastatin or placebo in the 5-6 year ALERT study were offered open-label fluvastatin XL 80 mg/day in a 2-year extension to the original study. The primary endpoint was time to first major adverse cardiac event (MACE). Of 1787 patients who completed ALERT, 1652 (92%) were followed in the extension. Mean total follow-up was 6.7 years. Mean LDL-cholesterol was 98 mg/dL (2.5 mmol/L) at last follow-up compared to a pre-study level of 159 mg/dL (4.1 mmol/L). Patients randomized to fluvastatin had a reduced risk of MACE (hazards ratio [HR] 0.79, 95% CI 0.63-0.99, p = 0.036), and a 29% reduction in cardiac death or definite non-fatal MI (HR 0.71, 95% CI 0.55-0.93, p = 0.014). Total mortality and graft loss did not differ significantly between groups. Fluvastatin produces a safe and effective reduction in LDL-cholesterol associated with reduced risk of MACE in RTR. The lipid-lowering and cardiovascular benefits of fluvastatin are comparable to those of statins in other patient groups, and support use of fluvastatin in RTR.

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91. Lancet. 2003 Jun 14;361(9374):2024-31.

Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial.

Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators.

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BACKGROUND: Renal transplant recipients are at increased risk of premature cardiovascular disease. Although statins reduce cardiovascular risk in the general population, their efficacy and safety in renal transplant recipients have not been established. We investigated the effects of fluvastatin on cardiac and renal endpoints in this population.
METHODS: We did a multicentre, randomised, double-blind, placebo-controlled trial in 2102 renal transplant recipients with total cholesterol 4.0-9.0 mmol/L. We randomly assigned patients fluvastatin (n=1050) or placebo (n=1052) and follow up was for 5-6 years. The primary endpoint was the occurrence of a major adverse cardiac event, defined as cardiac death, non-fatal myocardial infarction (MI), or coronary intervention procedure. Secondary endpoints were individual cardiac events, combined cardiac death or non-fatal MI, cerebrovascular events, non-cardiovascular death, all-cause mortality, and graft loss or doubling of serum creatinine. Analysis was by intention to treat.
FINDINGS: After a mean follow-up of 5.1 years, fluvastatin lowered LDL cholesterol concentrations by 32%. Risk reduction with fluvastatin for the primary endpoint (risk ratio 0.83 [95% CI 0.64-1.06], p=0.139) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs 104, 0.65 [0.48-0.88] p=0.005) in the fluvastatin group than in the placebo group. Coronary intervention procedures and other secondary endpoints did not differ significantly between groups.
INTERPRETATION: Although cardiac deaths and non-fatal MI seemed to be reduced, fluvastatin did not generally reduce rates of coronary intervention procedures or mortality. Overall effects of fluvastatin were similar to those of statins in other populations.

PMID: 12814712 [PubMed - indexed for MEDLINE]

93. Fluvastatinin the Prevention of Renal Transplant Vasculopathy: Resultsof a Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

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