Hydrochlorothiazide unsuccessful in preventing reoccurrence of kidney stones: Data from the NOSTONE trial.


Reviewed by Anastasiia Zykova

Summary: NOSTONE trial was a multiarm placebo-controlled trial in which 416 patients with recurrent calcium-containing kidney stones were randomized to receive hydrochlorothiazide (HCTZ, 12.5mg, 25mg, or 50mg once daily) or placebo. All patients had dietary consultations based on current guidelines. The median age was 49 years, 99% of participants were white and there was a significant male predominance (80%). Patients with secondary causes of nephrolithiasis such as cystinuria, severe gout or sarcoidosis were excluded, but 63% of patients had idiopathic hypercalciuria (defined as an excretion rate more than 200 mg/day). Over a median follow-up of duration 2.9 years, the primary outcome of symptomatic or radiologic recurrence showed no statistically significant relationship to hydrochlorothiazide dosing compared to placebo, with rates of 59% with 12.5mg hydrochlorothiazide, 56% with 25mg hydrochlorothiazide, and 49% with 50mg hydrochlorothiazide, compared to 59% with placebo (P=0.66). Rates of radiological recurrence, as the secondary outcome, were lower with 25mg HCTZ (odds ratio [OR] vs placebo 0.49; 95% confidence interval [CI], 0.27 to 0.8) and 50mg HTCZ (OR vs placebo 0.54; 95% CI, 0.29 to 0.98), although the rate of symptomatic recurrence was similar between groups. Hypokalemia, gout, allergic skin reactions and new-onset diabetes mellitus occurred more often in experimental arms and were not dose-dependent, however, the incidence of serious adverse events was similar between the four groups.

Comment: Nephrolithiasis is a common problem and is associated with debilitating symptoms and great impact on health care systems, including a high-cost burden. For decades, thiazides have been a key treatment for the prevention of calcium-containing kidney stones based on observational trials and small randomized controlled trials (RCT). This trial has challenged the common belief in HCTZ efficacy. As discussed by the authors, HCTZ did reduce urinary calcium excretion in the study, but this may have been counteracted by an increase in urinary oxalate excretion from baseline in all four groups, less citrate excretion in the HCTZ groups, and overall high sodium intake. It is interesting to note the numerically lower event rates with higher doses of HCTZ, although the authors determined that the study was well-powered to detect a statistically significant difference between treatment groups, with attainment of the recruitment target and low drop-out rates. It is possible that a longer duration of follow-up may reveal a greater benefit for symptomatic stone events, however the authors note that such a difference would need to be dramatic to alter the overall findings.
Double vaccine dose, heterologous vaccination or discontinuation of mycophenolate is not superior to a single dose booster of Moderna COVID-19 vaccine in kidney transplant recipients

Alternative strategies to increase the immunogenicity of COVID-19 vaccines in kidney transplant recipients not responding to two or three doses of an mRNA vaccine (RECOVAC): a randomised clinical trial


Summary: An open-label RCT between October 2021 and February 2022 compared three alternative strategies to improve COVID-19 vaccine response in kidney transplant recipients (KTRs) who had previously not seroconverted after 2-3 doses of an mRNA vaccine vaccination, nor previously had a COVID-19 infection. There were two cohorts of participants in this trial. In the first cohort, 230 participants were randomized 1:1:1 to single dose of mRNA-1273 (Moderna), double mRNA-1273 vaccine dose, or heterologous vaccination with Ad26.COV2-S (Janssen Biologics). In the second cohort, 103 participants who were receiving triple immunosuppressive therapy (steroids + calcineurin inhibitor + mycophenolate mofetil or mycophenolic acid (MMF-MPA)) were randomized to either continuation of MMF-MPA or discontinuation of MMF-MPA 1 week before and 1 week after receiving a single dose of the mRNA-1273 vaccine. At 28 days after vaccination, the seroresponse rates (SRRs) of participants (defined as the percentage of participants with a spike protein [S1]-specific IgG concentration of at least 10 binding antibody units per ml) between the three alternative strategies was not superior to a single mRNA-1273 vaccine. Specifically, compared to the single mRNA-1273 vaccine, the difference in SRR for double dose vaccination was -0.4% (95% CI -16 to 15; P=0.96); for heterologous vaccination it was -6% (95% CI -21 to 10; P=0.49); and for the discontinued MMF-MPA group it was 13% (95% CI -5 to 31; P=0.15). There were no serious adverse events related to vaccination and no acute rejection occurred.

Comment: COVID-19 vaccine response in KTRs is suboptimal. Vaccination with a single dose booster of mRNA-1273 vaccine appears to be a successful strategy to achieve a humoral immune response in KTRs who remain seronegative even after 2-3 doses of a COVID-19 mRNA vaccine, achieving seroresponse in 68% of participants, while none of the three alternative approaches demonstrated superiority. It is important to note that the study didn’t reach the target sample size, resulting in wide confidence intervals for the difference between approaches, and the study population consisted mostly of white males, which may limit generalizability of the results to other populations. The short follow up period (28 days) may not be sufficient to assess the long-term efficacy and safety of the alternative strategies. Further studies with larger sample sizes and longer follow up periods are needed to confirm and extend these findings.

Low dose anti-thymocyte globulin induction shows higher rejection rates among Asian kidney transplant recipients

A prospective, randomized, non-blinded, non-inferiority pilot study to assess the effect of low-dose antithymocyte globulin with low-dose tacrolimus and early steroid withdrawal on clinical outcomes in non-sensitized living-donor kidney recipients

Ko et al. PLOS ONE 18(3) (2023).

Summary: In this prospective open-label non-inferiority trial from one Korean medical center, 36 living-donor kidney transplant recipients were randomized to receive 4.5mg/kg or 6.0mg/kg of anti-thymocyte globulin (ATG) at induction. The maintenance immunosuppressive regimen consisted of tacrolimus (0.05mg/kg twice a day with target trough level of 6-8ng/ml until 12 months post-transplant), mycophenolate mofetil (750mg twice a day), and high-dose intravenous methylprednisone with a total seven-day corticosteroid taper. Baseline characteristics of recipients and donors were similar between the groups, including HLA-A, B, DR, and DQ mismatches. After 12 months post-transplant, biopsy-proven acute rejection (BPAR) was more common in the low-dose ATG group (21.1% vs 0%, log-rank test; P=0.048). Importantly, the composite end point of BPAR, de novo donor specific antibody (DSA) formation and death-censored graft failure was significantly higher in low-dose ATG group (36.8% vs 0%, log-rank test, P=0.006). There were no cases of delayed graft function during the first week post-transplant in both groups. There were no differences in renal function and adverse events, including leukopenia and thrombocytopenia, between the two groups during follow-up. The proportion of natural killer (NK) and NK-T cells among lymphocytes were significantly higher in the low-dose ATG
group, whereas those of T, B, and monocytes were similar and had reached baseline values at six-months post-transplant.

**Comment**: ATG is a common induction agent for kidney transplant recipients, however, data for dose optimization in Asian kidney recipients is limited. The aim of this study was to compare efficacy of 4.5mg/kg ATG and 6.0mg/kg ATG in living-donor Asian kidney recipients. However, the main limitation of this trial as acknowledged by the authors is that it was prematurely stopped by the data safety monitoring board due to the more frequently observed composite events of biopsy-proven acute rejection and de novo DSAs after kidney transplantation in the low-dose ATG group. While the small sample size and small number of outcome events may reduce the certainty of the conclusion, the safety profile of the low dose ATG approach is concerning, and further use of low dose ATG in clinical care or research studies should be approached with caution.

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**Phylloquinone treatment improves Vitamin K status in hemodialysis patients and a fully powered RCT is feasible to assess impact on coronary artery calcification**

*Inhibit progression of coronary artery calcification with vitamin K in hemodialysis patients (the iPACK-HD study): a randomized, placebo-controlled multi-center, pilot trial*

*Holden et al. Nephrol Dial Transplant (2023)*

**Summary**: In this multi-center pilot RCT, 86 adult participants on maintenance hemodialysis (HD) with a coronary artery calcification (CAC) score ≥30 Agatston Units were randomized to receive phylloquinone (Vitamin K1) 10mg thrice per week (administered post-HD) or matching placebo over 12 months. The primary outcome was the feasibility to conduct an adequately powered trial in the future. Three out of four pre-specified feasibility outcomes were achieved: recruitment rate was 4.4 participants per month (target: ≥4.17 per month), study medication compliance was 96% (target: ≥90% doses) and study completion was 80% (target ≥80%), however, only 74% adhered to the study protocol (target ≥80%). As expected, compared to placebo, participants randomized to phylloquinone had improved Vitamin K status as demonstrated by a significant increase in serum phylloquinone (absolute % change from baseline: 481.8 [95% CI 227.2 to 933.3]; P<0.01), and a significant decrease in dephospho-uncarboxylated matrix Gla-protein (MGP; absolute % change from baseline: -86.1 [95% CI -90.8 to -69.3%]; P<0.01). There was no significant difference in the absolute (12.7 [95% CI -187.1 to 96.1]; P>0.001) or relative (4 [95% CI -29, 19]; P<0.001) change in the CAC score between the groups at the end of the study. In terms of safety, the adverse event rates and cardiovascular events were comparable between the two groups.

**Comment**: Vascular calcification is common in patients with kidney failure. It is postulated that vitamin K may exert a cardioprotective effect that is mediated by vitamin K-dependent carboxylation on MGP, which is a potent inhibitor of vascular calcification. This is particularly relevant to kidney failure patients, in whom subclinical vitamin K deficiency is prevalent. The effect of vitamin K2, K3 and K4, such as the use of vitamin K4 among kidney transplant recipients in the ViKTORIES trial, have shown underwhelming results, but vitamin K1 may yet yield a meaningful benefit. The results of the iPACK-HD study confirm the feasibility to perform a larger-scale clinical trial to evaluate the efficacy of phylloquinone (vitamin K1) in delaying vascular calcification in people on dialysis. However, there are some limitations in this study, including its small sample size which resulted in imbalances in baseline characteristics such as the treatment group having more males, more participants with type 2 diabetes, a shorter dialysis vintage and a higher CAC score. These are all prognostic variables which may have resulted in the lack of observed difference between the groups in vascular calcification, although this study was not powered to detect any differences. Therefore, the value of routine supplementation of vitamin K with phylloquinone to prevent cardiovascular disease in kidney failure patients remains uncertain until a fully powered RCT is carried out.

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**Tolvaptan-Octreotide long-acting combination: a New TOOL to treat ADPKD**

*Effects of octreotide-long-acting release added-on tolvaptan in patients with autosomal dominant polycystic kidney disease: pilot, randomized, placebo-controlled, cross-over trial*


**Summary**: Analyses of efficacy and safety data for dose optimization in ADPKD patients demonstrated that the combination of tolvaptan and long-acting octreotide was beneficial compared to placebo. The results of this pilot trial will serve as a basis for planning a larger, adequately powered RCT. The main limitation of this study is the small sample size which resulted in imbalances in baseline characteristics such as the treatment group having more males, more participants with type 2 diabetes, a shorter dialysis vintage and a higher CAC score. These are all prognostic variables which may have resulted in the lack of observed difference between the groups in vascular calcification, although this study was not powered to detect any differences. Therefore, the value of routine supplementation of vitamin K with phylloquinone to prevent cardiovascular disease in kidney failure patients remains uncertain until a fully powered RCT is carried out.
Summary: Previous experimental studies in autosomal dominant polycystic kidney disease (ADPKD) have demonstrated a synergistic effect of vasopressin antagonists and somatostatin analogues in reducing kidney cyclic adenosine monophosphate (cAMP) levels and thereby reducing kidney tubular cell proliferation and cyst growth. Experimental studies have demonstrated an acute and reversible GFR decline, followed by a slower GFR decline and smaller increase in total kidney volume (TKV) in the long-term. In this phase II cross-over, placebo-controlled study 19 participants with ADPKD who received tolvaptan therapy (up-titrated as tolerated to a maximum of 90mg in the morning and 30mg in the afternoon) for one month prior to the intervention, were randomized to receive either two 20 mg intramuscular (IM) injections of octreotide-long-acting-release (LAR) or placebo (two IM 0.9% saline solution injections) for 4 weeks, followed by a 4-week washout period, after which they crossed over to the alternate treatment for another 4 weeks. GFR as measured by iohexol plasma clearance was significantly decreased in the tolvaptan and octreotide-LAR treatment period at 4 weeks by 7mL/min/1.73m^2 (standard deviation [SD] 3–14; P=0.03), and by 3mL/min/1.73m^2 (SD -1 to 5) in the tolvaptan and placebo treatment period (P=0.01), with no statistically significant difference between the two treatment periods. Notably the difference in GFR reduction at 1 week after treatment with tolvaptan and octreotide-LAR compared to tolvaptan and placebo was significant (3mL/min/1.73m^2 lower with dual treatment [SD 0–12]; P=0.01). Total kidney volume (TKV) decreased by 41mL (SD 25–77) during the tolvaptan and octreotide-LAR treatment period (P<0.001) only. Twenty-four hour urine output was increased during both treatment periods, however it was more in the tolvaptan and placebo treatment period by 1193ml/24hr (SD -183 to 1925; P=0.02). The treatment was well tolerated, and adverse events were similar in both treatment groups.

Comment: ADPKD is a major cause of kidney failure. TOOL is the first randomized control trial to compare the efficacy of octreotide-LAR and tolvaptan dual therapy against tolvaptan monotherapy in patients with ADPKD. The results demonstrated that treatment with octreotide-LAR and tolvaptan reduced GFR more than tolvaptan alone at week 1, which may suggest a more prominent nephroprotective effect initially via the reduction of hyperfiltration. Octreotide-LAR and tolvaptan together also reduced TKV and total cystic volume at week 4, which may have attenuated the aquaretic effect of tolvaptan. This study is limited by the relatively small sample size and a short treatment duration. Larger trials are needed to confirm these findings as well as to assess the long-term efficacy and safety of the octreotide-LAR-tolvaptan dual therapy in this population.

Edited by Daniel O’Hara, Michele Provenzano, Neeru Agarwal and Anastasiia Zykova