Global Trials Focus October - November 2024

The ISN-ACT (Advancing Clinical Trials) team presents this bi-monthly round up of randomized trials in nephrology. Trials are selected not just for impact, but also to showcase the diversity of research produced by the global nephrology community. Each trial is reviewed in context and has a risk of bias assessment. We hope to drive improvement in trial quality and promote greater engagement in trial activity.

Key to risk of bias assessment

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

High risk
Uncertain risk / not stated
Low risk

Do you agree with our trial of the month? Tell us what you think!
@ISNeducation

Want to run your own trial?
ISN-ACT Clinical Trials Toolkit
www.theisn.org/isn-act-toolkit

Would you like to write your own reviews?
Join the GTF team.
Contact us at research@theisn.org

ISN Academy: Transplant

ACTivity and healthy diet after kidney transplantation: a challenge

Effect of an exercise intervention or combined exercise and diet intervention on health-related quality of life-physical functioning after kidney transplantation: the Active Care after Transplantation (ACT) multi-centre randomised controlled trial

Knobbe et al., Lancet Healthy Longev. (2024).

R A BP BO CD CR B

Reviewed by Anastasiia Zykova

Summary: This multi-center trial aimed to provide robust evidence that a diet and exercise program improves kidney transplant recipients' health-related quality of life (HRQoL). Two hundred twenty-one participants were randomized (1:1:1) to receive either usual care, exercise, or a combined exercise and diet intervention. The exercise program consisted of twice-weekly exercise sessions for 3 months (30 minutes of dynamic resistance and muscle endurance training, 30 minutes of aerobic training, 30 minutes of rest, and 30 minutes of supervised sports activity). The dietary intervention involved 12 sessions of dietary counselling by a kidney dietician. Lifestyle advice was given throughout the study. The primary outcome was HRQoL-domain physical functioning, assessed by the 36-item Short Form Survey at 15 months. The mean age of participants was 52.5 years (SD 13.5), 62% were male, 29% received a pre-emptive transplant, with a median post-transplant time of 5.5 months (IQR 3.6-8.4), mean GFR of 50.4 ml/min/1.73m^2 (SD 16.6), and 89% of participants received triple immunosuppressive therapy. At 15 months, there was no significant difference in the HRQoL domain of physical functioning for either the exercise group (5.3 arbitrary units, 95% CI -4.2 to 14.9; p=0.27) or the combined exercise with diet group (5.9 arbitrary units, 95% CI -4.1 to 16.0; p=0.25) when compared with the control group. However, at 3 months, following the period of supervised exercise, the exercise group showed a statistically significant improvement in the HRQoL physical functioning domain compared to the control group (mean difference 7.3 arbitrary units, 95% CI 1.2 to 13.3; p=0·018), while in the exercise plus diet group, this between-group difference was not statistically significant. Secondary endpoints such as total muscle strength, peak oxygen uptake and peak cycling power significantly improved in the exercise group compared to the control group. There were no safety concerns during the study.

Comment: The association between physical activity and reduction in cardiovascular and metabolic risks is well-established in the general population. However, kidney transplant recipients are at risk of low physical activity, given their numerous health challenges, putting them at increased risk of mortality. Despite the need for good-quality evidence to guide physical exercise and diet interventions in those at high risk of CVD, conducting large trials to test these programs in kidney transplant recipients poses significant challenges. These include low compliance, high dropout rates, difficulty maintaining engagement with exercise regimens, the variety of exercise programs and dietary interventions available, and the difficulties of measuring HRQoL. This study shows significant gains in the short term, which were not sustained at 15 months. The results are consistent with studies in other kidney populations. The study gives impetus to the value of organized exercise and diet programs but raises the question of how to implement a sustainable program that maintains those gains. Future studies involving implementation scientists are required for complex behavioral interventions so that the findings of this study over the short term can be demonstrated over the longer term, using robust methodology.

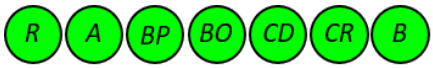
---

*ISN Academy: **Glomerular diseases***

An APPLAUSE for Iptacopan therapy for IgA-nephropathy

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

Perkovic et al., N Engl J Med. (2024).



Reviewed by Anastasiia Zykova

Summary: Iptacopan, an oral, first-in-class inhibitor of Factor B, targets the alternative complement pathway in IgA nephropathy (IgAN) by disrupting the formation of C3 and C5 convertases and the alternative complement pathway loop. In this double-blind, placebo-controlled phase 3 study, 443 participants with biopsy-proven IgAN and significant proteinuria (24-hour urine protein to creatinine ratio [UPCR] >1g/g) despite supportive therapy were randomized to iptacopan (200 mg bd) or placebo. The primary outcome was the change in 24-hour UPCR from baseline at month 9. In this interim efficacy analysis of 250 participants (mean age 39 years, predominantly male, 51.2% from Asia), the treatment and control groups were well balanced at baseline, including eGFR (62.7±26.0 ml/min/1.73m2 and 65.5±26.7 ml/min/1.73m2, respectively), proteinuria (median 24h UPCR 1.81g/g and 1.87g/g), use of SGLT2 inhibitors (14.4% and 11.2%), and renin-angiotensin system inhibitors (>98% in both groups). At nine months, the adjusted geometric mean 24-hour UPCR was 38.3% (95% confidence interval [CI], 26.0 to 48.6) lower in the iptacopan group than in the placebo group (two-sided P<0.001). The most common adverse events were infections, with no increased risk in the treatment group.

Comment: IgA nephropathy is one of the most common forms of glomerulonephritis leading to kidney failure, and it poses significant health risks and burdens healthcare systems. In the last year alone, an increasing number of new agents (atrasentan, atacicept, sparsentan) have shown efficacy in reducing proteinuria in IgAN, in conjunction with SGLT2 inhibitors and renin-angiotensin system blockade. By blocking the alternative complement pathway more proximal than eculizumab (which is used for other complement-mediated diseases like C3 glomerulopathy and aHUS), iptacopan may be associated with a lower risk of infections, and its oral administration is more convenient for patients. However, real-world data are needed to prove the efficacy of iptacopan in preserving kidney function.

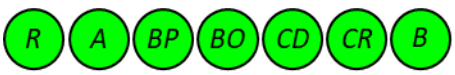
---

*ISN Academy: **Dialysis***

Randomized controlled trial suggests that 5% topical gabapentin cream effectively treats pruritus in dialysis patients

Effectiveness of topical gabapentin cream in treating pruritus in dialysis patients: A randomized controlled trial

Faghihi G, et al. Hemodial Int. (2024).



Reviewed by Rupesh Raina

Summary: This triple-blind clinical study explored the effectiveness and safety of a 5% gabapentin topical cream for treating pruritus in dialysis patients. The study involved a cohort of 80 participants divided into two groups of 40. The intervention group, comprising 92.5% of individuals on hemodialysis, received the 5% gabapentin cream, while the control group was given a placebo. Both groups were instructed to apply their assigned cream daily to the most affected areas over 4 weeks, with re-supplies provided every 2 weeks. The intensity of the itching and its impact on quality of life were evaluated at baseline, 1 month, and 2 months post-treatment, utilizing the Visual Analog Scale (VAS) and the 12-item Pruritus Severity Score (12-PSS). At baseline, the mean ± SD 12-PSS pruritus scores were 12.18 ± 3.89 in the intervention group and 12.47 ± 3.75 in the control group. One month after starting therapy, the intervention group demonstrated a significant reduction in mean pruritus score to 7.55 ± 3.08 ($p < 0.001$), compared to the control group, which showed no significant change. The reduction in VAS score was also significant in the intervention group, decreasing from 7.98 ± 1.56 at the start to 3.98 ± 1.80 after 2 months ($p < 0.001$). In contrast, no significant change was observed in the control group for either score. Itching intensity and its impact on quality of life were significantly improved in the intervention group.

Comment: Side effects, including dizziness, somnolence, ataxia, and fatigue, often constrain the oral administration of gabapentin. Evidence suggests that gabapentin topical creams can be equally effective as oral formulations. Given that gabapentin is solely eliminated through kidney excretion, patients undergoing dialysis face a heightened risk of toxicity. However, there are limited studies on the use of gabapentin topical creams for controlling pruritus. This study evaluated the efficacy of the cold cream containing 5% gabapentin for treating pruritus in patients receiving chronic dialysis therapy. This study found that applying a 5% gabapentin cream over four weeks significantly reduced the severity of pruritus in patients undergoing chronic dialysis therapy. The notable decrease in Visual Analog Scale (VAS) scores and itching intensity was still evident one month after the treatment concluded and none of the patients reported any adverse side effects. As acknowledged by the authors, while this study was conducted with a relatively small cohort, it nonetheless provides valuable insights into a less-explored area of quality-of-life research. Future studies conducted across larger cohort sizes and longer durations would improve the generalizability of these findings.

---

*ISN Academy: **Dialysis***

Assessment of the efficacy of sodium zirconium cyclosilicate therapy in reducing the incidence of cardiac arrhythmias in hemodialysis patients

Effects of dialysate potassium concentration of 3.0mEq/l with sodium zirconium cyclosilicate on dialysis-free days versus dialysate potassium concentration of 2.0mEq/l alone on rates of cardiac arrhythmias in hemodialysis patients with hyperkalemia

Charytan DM et al. Kidney Int. (2024).

Reviewed by Chiara Ruotolo

Summary: This prospective, open-label 2×2 crossover trial investigated strategies for maintaining serum potassium homeostasis in hemodialysis patients to prevent arrhythmic complications. Eighty-eight participants on maintenance hemodialysis with a history of elevated blood potassium (pre-dialysis serum potassium [sK+] 5.1-6.5mEq/l) were randomly assigned to receive either 8 weeks of a 3.0 mEq/l dialysate potassium in combination with sodium zirconium cyclosilicate (SZC), an oral potassium binder, on non-dialysis days to maintain a pre-dialysis sK+ within 4.0–5.5 mEq/l (3.0K+/SZC) or, to 8 weeks of 2 mEq/l dialysate potassium without SZC (2.0K+/noSZC). Following a 2-week wash-out period, participants then received the other intervention. All participants had an implantable cardiac loop recorder to assess any arrhythmias during this period. The mean age of participants was 57.1 years, and 51% were male. The mean pre-dialysis sK+ at baseline was 5.5 mEq/l, and 8.0% had a history of atrial fibrillation (AF). This study found that 3.0K+/SZC significantly reduced the incidence rate of AF events (duration >= 2 minutes) compared with 2.0K+/noSZC. The unadjusted mean annual incidence rate (95% CI) of AF was 9.8 (8.0 to 11.5) with 3.0K+/SZC and 13.4 (11.4 to 15.5) with 2.0K+/no SZC. The modelled rate ratio (mRR) calculated using a quasi-Poisson model was 0.52 (0.41 to 0.65:

P<0.001). There were also fewer clinically significant arrhythmias with 3.0K+/SZC compared to 2.0 K+/noSZC, with a mean annual incidence rate of 6.8 vs 10.2 (mRR 0.47; P < 0.001). Further, 3.0K+/SZC reduced the odds of sK+ being outside the optimal window; modelled odds ratio (0.27; 0.21 to 0.35). Post-dialysis hypokalemia was also less frequent with 3.0K+/SZC (33 participants) than 2.0K+/noSZC (58 participants).

Comment: Historically, the primary approach towards preventing hyperkalemia in hemodialysis patients has been using low dialysate potassium (dK+) to maximize potassium removal. However, rapid electrolyte removal with low dK+ may increase the risk of peri-dialytic hypokalemia and associated arrhythmias. Abnormal potassium concentrations, whether high or low, increase the risk of sudden death and arrhythmias such as AF in this population. Therefore, maintaining serum potassium (sK+) within a physiological range between hemodialysis sessions is crucial. Potassium binders may help prevent potassium buildup during interdialytic intervals, thereby reducing the need for rapid dialytic removal and permitting higher dK+, potentially lowering the risk of hypokalemia-induced arrhythmia like AF. This trial demonstrates that a 3.0 mEq/l potassium dialysate with SZC (an intestinal potassium binder) on non-dialysis days titrated to a target pre-dialysis sK+, can be safely implemented. Limitations include a small sample size, short treatment duration (8 weeks), and unblinded treatment assignments. In addition, the study's young population (mean age 57 years) and limited AF cases (only 9 of 88 participants) further limited the power to detect a difference in clinical endpoints. Additional larger and longer studies are needed to assess whether the 3.0K+/SZC strategy would reduce morbidity and mortality.

---

*ISN Academy: **Chronic Kidney Disease***

Semaglutide lowers the urine albumin-to-creatinine ratio in non-diabetic CKD individuals who are overweight or obese

Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial

Apperloo EM, et al. Nat Med. (2024).

R A BP BO CD CR B

Reviewed by Nikolina Basic-Jukic

Summary: A randomized, double-blind, placebo-controlled trial was performed in overweight or obese participants (body mass index >= 27kg/m2) with non-diabetic chronic kidney disease (CKD; eGFR >= 25ml/min/1.73m2 and urine albumin-to-creatinine ratio [UACR) between 30 and <3500 mg/g). Of the 125 participants screened, 101 were randomized to semaglutide (2.4mg once-weekly subcutaneously, n = 51) or matched placebo (n = 50) for 24 weeks. Baseline characteristics were well balanced between the groups (mean age 56 years, predominantly male and White, mean eGFR 65ml/min/1.73m^2, median UACR 251mg/g, mean BMI 36.2kg/m2; 86% used renin-angiotensin system inhibitors, and 19% used SGLT2 inhibitors). At week 24, compared to placebo, treatment with semaglutide reduced UACR by -52.1% (95% CI -65.5 to -33.4; P < 0.0001). There was no significant difference in creatinine eGFR between the groups at week 24 (mean difference semaglutide versus placebo −1.1 ml/min/1.73 m^2; 95% CI −4.8 to 2.6; *P* = 0.57). Semaglutide also resulted in placebo-corrected changes of −9.1 kg in body weight (95% CI −11.0 to −7.2; *P* < 0.0001) and −4.4 cm in waist circumference (95% CI −8.4 to −0.3; *P* = 0.04) from baseline. Gastrointestinal adverse events were the most common adverse events during treatment with semaglutide.

Comment: The rising global rates of overweight and obesity represent a significant public health challenge, increasing the risk of type 2 diabetes, CKD, heart failure, and other cardiovascular diseases. SGLT2 inhibitors have emerged as transformative treatments for patients with cardio-kidney-metabolic syndrome, supported by extensive evidence from randomized trials in diverse populations, including patients with heart failure, type 2 diabetes mellitus, and CKD. However, despite the benefits of SGLT2 inhibitors in reducing kidney and cardiovascular risks, many patients remain at risk of progressive kidney function loss, often linked to increased albuminuria. This highlights the need for additional therapies, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which can simultaneously reduce body weight and albuminuria. The present study found that semaglutide (a GLP-1 RA) significantly reduced UACR compared to placebo in patients with non-diabetic CKD, highlighting the potential usefulness of semaglutide across the spectrum

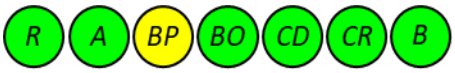
of cardiovascular, kidney, and metabolic diseases. However, the predominance of White participants limits the generalizability of the findings. Additionally, as the primary outcome is a surrogate marker of kidney function (UACR), further studies with longer follow-ups are required to determine the long-term benefits of semaglutide in overweight or obese patients with CKD.

ISN Academy: Dialysis

Clinical vs Ultrasound-Guided Assessment of Ultra-filtration Volume in Patients with AKI Requiring Dialysis

Does lung ultrasound-guided ultrafiltration lead to better outcomes in acute kidney injury requiring intermittent hemodialysis: A randomized control trial

Zachariah VK et al. Hemodial Int. (2024).



Reviewed by Ahad Qayyum

Summary: In this single-center, single-blind, parallel-group trial, 74 participants with acute kidney injury (AKI) requiring hemodialysis were included to compare the effect of ultrafiltration volume prescriptions assessed clinically by a nephrologist versus lung ultrasound-guided prescriptions. Eligible participants were not on ventilatory or inotropic support and had no significant co-morbidity like heart failure, decompensated liver disease or kidney failure requiring maintenance dialysis. For all participants, a target ultrafiltration volume was prescribed by a nephrologist based on clinical assessment, and a 28-site lung ultrasound for B-line scores was performed before each dialysis session. Participants were then randomized into two groups: in the intervention group, the dialysis prescription was modified using a sliding scale based on the predialysis B-line score, while in the control group, ultrafiltration was modified only in response to an intradialytic adverse event. Post-dialysis lung ultrasound was performed in both groups to determine how many patients achieved a B-line score of less than 5 (the primary endpoint). After the end of the first dialysis session, there was no difference in the B-line score between the intervention and control group (91.8% vs 83.8%; P=0.28). However, there were more intra-dialytic adverse events encountered in the control group (32.4%) compared to the intervention group (10.8%; P=0.024).

Comment: This study demonstrates the potential value of lung ultrasound in terms of intra-dialytic adverse events in patients with AKI requiring hemodialysis, although the primary endpoint was no different between the groups. The integration of lung ultrasound findings with clinical volume assessment minimizes intradialytic events such as SBP fall, cramps and the need to change dialysis parameters. However, the single-center and small sample size limited the ability to detect not only the difference in the primary outcome, but also the difference in mortality between the study arms. In addition, lung ultrasound expertise may vary between operators. Larger studies should be designed in the future to investigate the intradialytic tolerance and potential survival benefits of using pulmonary ultrasound-guided ultrafiltration in patients with AKI requiring dialysis.

Edited by Neeru Agarwal, Megan Borkum, Mohamed Elrgal, Michele Provenzano, and Anastasiia Zykova