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Comparing glycaemic benefits of active versus passive lifestyle intervention in kidney allograft recipients (CAVIAR): a randomised controlled trial

Kulli Kuningas[1], Joanne Driscoll[2], Reena Mair[2], Helen Smith[3], Mary Dutton[1], Edward Day[4], Adnan Sharif[1,5]

[1]Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

[2]Department of Nutrition and Dietetics, Queen Elizabeth Hospital, Birmingham, UK

[3]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

[4]National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[5]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

Corresponding author contact information. Dr. Adnan Sharif, Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2GW, United Kingdom. Phone: (0121 371 5861), Fax: (0121 472 4942), Email: adnan.sharif@uhb.nhs.uk. Orchid ID: 0000-0002-7586-9136

Authorship

Research idea and study design[AS], Study delivery[KK,JD,RM,HS,MD,ED], Data acquisition[KK,HS,MD], Data analysis[KK,HS,AS], Supervision and mentorship[MD,ED.AS], Wrote original draft[AS], Reviewed and approved final draft[ALL AUTHORS]

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Abbreviations:

PTDM – post transplantation diabetes mellitus

BCT – behavior change technique

BAME – black, Asian and minority ethic

Abstract

Background. New-onset diabetes is common after kidney transplantation but the benefit of lifestyle intervention to improve glucose metabolism post transplantation is unproven.

Methods. We conducted a single-center, randomised controlled trial involving 130 nondiabetic kidney transplant recipients with stable function between 3-24 months post transplantation. Participants were randomly assigned in a 1:1 ratio to receive active intervention (lifestyle advice delivered by renal dietitians using behaviour change techniques) versus passive intervention (leaflet advice alone). Primary outcome was six-month change in insulin secretion, insulin sensitivity and disposition index. Secondary outcomes included patient-reported outcomes, cardio-metabolic parameters, clinical outcomes and safety endpoints.

Results. Between August 17th 2015 and December 18th 2017, 130 individuals were recruited of whom 103 completed the study (drop-out rate 20.8%). Active versus passive intervention was not associated with any change in glucose metabolism; insulin secretion (mean difference -446 [95% CI -3184 to 2292], p=0.748), insulin sensitivity (mean difference -0.45 [95% CI -1.34 to 0.44], p=0.319) or disposition index (mean difference -940 [95% CI -5655 to 3775], p=0.693). Clinically, active versus passive lifestyle intervention resulted in reduced incidence of post transplantation diabetes (7.6% versus 15.6% respectively, p=0.123), reduction in fat mass (mean difference -1.537kg [-2.947 to -0.127], p=0.033) and improvement in weight (mean difference -2.47kg [-4.01 to -0.92], p=0.002). No serious adverse events were noted.

Conclusions. Active lifestyle intervention led by renal dietitians did not improve surrogate markers of glucose metabolism. Further investigation is warranted to determine if clinical outcomes can be improved using this methodology.

Trial Registration. Registered with clinicaltrials.org registry (identifier; NCT02233491).

Introduction

Kidney transplantation is the preferred modality of renal replacement therapy for suitable candidates with end-stage kidney failure. However, the need for lifelong immunosuppression to prevent allograft rejection is associated with significant side effects and complications. Cardiovascular disease remains a leading cause of morbidity and mortality after kidney transplantation[1] and its development is linked to both traditional and transplant-specific risk factors.[2] The latter are predominantly due to the constellation of cardio-metabolic side effects attributable to immunosuppression, among which the development of de novo post transplantation diabetes mellitus (PTDM) is most significant.

PTDM is a major complication with underlying aetiology related to both traditional and transplant-specific pathophysiology, and can affect over a third of patients within the first year post transplantation.[3] PTDM is linked to cardiovascular events and all-cause mortality after kidney transplantation[4] and is ranked as a leading concern for recipients themselves.[5] Both generic[6] and PTDM-specific[7] international guidelines strongly advocate lifestyle intervention strategies to minimise the risk of PTDM but lack any strong evidence-base in support.

Previous work has shown the benefit of renal dietitian intervention to attenuate progression of abnormal glucose metabolism after kidney transplantation.[8] However, this was a nonrandomised study with dietitian intervention only offered to recipients with abnormal post prandial glucose metabolism. Clinical trial evidence is lacking to support the efficacy of lifestyle intervention to reduce the risk of PTDM after kidney transplantation, compared to the general population where it is as effective as pharmacological therapy at preventing diabetes.[9] Lifestyle interventions to delay or prevent PTDM have the potential to prolong kidney transplant survival, reduce the burden of healthcare costs and improve the health and wellbeing of the kidney transplant population.

However, interventions to change health-related behaviours are complex and consist of many interacting components.[10] Promoting lifestyle interventions in kidney transplant recipients is difficult as they compete for attention against a number of kidney- and transplant-specific complications which rank higher for patient concern.[5] The recent development of a taxonomy of behaviour change techniques (BCTs) has identified interventions that are effective at promoting physical activity and healthy eating.[11] Clearly defined BCTs are rarely embedded with clinical interventions after transplantation and have not been used in the development of lifestyle interventions post transplant. In view of the significant clinical burden and patient anxiety related to PTDM, the need for evidence-based interventions to inform clinical practice is imperative. This led us to investigate the benefit of active versus passive lifestyle intervention after kidney transplantation to prevent abnormal glycaemic control, developing a bespoke renal dietitian-led approach underpinned by effective BCTs.

Materials and Methods

Study design and participants

Details of the CAVIAR study objectives, design, methods and analysis have been previously reported.[12] Briefly, participants were recruited from a single transplant center and were eligible for inclusion if they were between 3-24 months after kidney transplantation, had no preexisting diabetes and were deemed to have stable kidney function by their transplant clinician. Potential eligible patients were invited to participate by a member of the research team, who assessed eligibility and obtained written informed consent. Approval was obtained from the local Research Ethics Committee prior to enrolment and the trial was registered with the clinicaltrials.org registry (identifier; NCT02233491).

Randomisation

Patients were randomly assigned (1:1) to receive either active lifestyle intervention with the renal dietitian or passive lifestyle advice with no dietitian involvement. Randomisation was done by the trial coordinator via a web-based randomisation service (www.sealedenevelope.com) stratified by age, body mass index (BMI) and ethnicity in random permutated blocks. In view of the nature of the intervention, patients and clinicians were aware of group allocation.

Procedures

Kidney allograft recipients fulfilling the eligibility criteria and who gave informed consent were subsequently randomised into active versus passive intervention arms.

Active intervention group. This group received active lifestyle modification led by a renal dietitian who facilitated individualised lifestyle intervention advice to prevent the risk of PTDM. These participants received four face-to-face appointments with the dietitian (lasting 45-60 minutes) at baseline, day 30, day 60 and day 120. Brief telephone reviews were conducted between appointments (2-4 weeks after each face-to-face appointment) to review progress and provide additional support during the 6-month active intervention period (some appointments could be substituted with telephone support if requested). Patients had their dietary habits personally reviewed by the renal dietitian and personalised healthy eating advice was given based upon current guidelines issued by Diabetes UK[13] and Public Health England tailored to the individual. Briefly, the guidelines recommend a diet containing less saturated fat and sugar, with more fruit, vegetables, healthy protein sources and wholegrains. Patients were advised to keep food diaries to monitor compliance with initiated changes and were followed up by the renal dietitians prospectively as highlighted to monitor progress and reinforce the advice (running parallel with routine clinic visits). In addition, a graded exercise

program was encouraged to increase physical activity (e.g. endurance exercise such as walking, jogging, swimming) and an exercise diary encouraged to track progress.

Passive Control Group. This group received standard of care, which involved counselling about the risks of PTDM and leaflet advice outlining recommended lifestyle intervention (advice on healthy eating, exercise and the importance of weight loss if required – see supplementary files, SDC, http://links.lww.com/TP/B815). There was no renal dietitian input and no behavioural therapy intervention.

Both groups underwent assessment at baseline and end of the 6-month intervention. If any kidney allograft recipient developed PTDM during the study, they were treated in line with recommended international consensus guidelines[7].

Behaviour change techniques

The active intervention was underpinned by defined BCTs and overseen by a clinician with recognised expertise in behavioural change therapy. After development of the behaviour change intervention in conjunction with the renal dietitians, ongoing support was provided to renal dietitians to support and refine their delivery of personalised interventions to study participants in the active intervention arm.

Research evidence in relation to BCTs for healthy eating and physical activity interventions[10] suggest that interventions that combine self-monitoring with at least one other technique derived from control theory are significantly more effective than other interventions. Therefore, the intervention included the following BCTS:

1. Providing information on the consequences of sub-optimal diet and exercise levels on health in general.
2. Providing specific feedback of personalised information (Body Mass Index, Body Fat Percentage, Waist to Hip Ratio) and comparison with healthy range.

3. Prompting intention formation (i.e. encouraging the patient to make a resolution to change their diet or level of exercise).

4. Setting SMART (Specific, Measurable, Achievable, Relevant, and Time-bound) goals around diet, exercise and weight.

5. Setting graded tasks around the achievement of patient goals.

6. Encouraging self-monitoring of goals through food and exercise diaries and other node-link maps.

7. Regular reviews of specific behavioural goals and reinforcement of progress through praise and encouragement.

8. Reviewing social support available from personal network of family/friends and linking support to the achievement of specific goals.

The intervention incorporated self-regulatory techniques congruent with control theory, encouraging individuals to decide to act (intention formation), prompting specific goal-setting, providing feedback on performance and self-monitoring of behaviour, and continuous review of set goals or intentions. These techniques were combined with two other effective strategies to support the behaviour change intervention; node link mapping (use of visual representation for presenting the intervention) and elements of Social Behaviour and Network Therapy (focus on building social network support for behaviour change). Further details and references are detailed in our CAVIAR methodology paper.[12]

Study investigations

Clinical and biochemical data was collected at baseline (month 0), midway (month 3) and end (month 6). Oral glucose tolerance tests were classified by current International Consensus recommendations for diagnosis of both prediabetes and PTDM[7]. The BioPlex Pro Human Diabetes 10-plex assay (BioRad, California, USA) was used to quantitate a number of diabetes- and obesity-related markers at each study timepoint, checked in a fasting state on

the morning of the oral glucose tolerance test. Recorded outputs were the average of two measurements to improve precision.

The following formulae were utilised for determination of glucose metabolism parameters; insulin sensitivity, insulin secretion and the disposition index. These surrogates were chosen on the basis of previous validation work showing them to be the best surrogates against gold-standard investigations in the setting of kidney transplantation[14,15]:

- *Insulin secretion* = $HOMA_{sec} = Insulin_0 \times [3.33/(glucose_0 - 3.5)]$
- *Insulin sensitivity* = *McAuley's index* = $exp\ [2.63 - (0.28 \times ln\ \{insulin_0 / 6.945\}) - (0.31 \times ln\ trigycerides_0)]$
- *Disposition index* = $HOMA_{sec} \times$ *McAuley's index* = $Insulin_0 \times [3.33/(glucose_0 - 3.5)] \times exp\ [2.63 - (0.28 \times ln\ \{insulin_0 / 6.945\}) - (0.31 \times ln\ trigycerides_0)]$

Outcomes

The primary endpoint for this trial was change in glucose metabolism as measured by change in insulin secretion, insulin sensitivity and disposition index at the end of the 6-month study intervention. These indices were analysed using surrogate measures as previously validated in the setting of kidney transplantation.[14,15] The justification for using these indices as the primary outcome was based on previous work showing benefit of lifestyle intervention on glucose metabolism parameters and change in disposition index being the earliest detected glycaemic abnormality in nondiabetic kidney transplant recipients. On this basis, it was hypothesized that we would be able to determine a beneficial impact of active versus passive lifestyle intervention based on these surrogate outcomes of abnormal glucose metabolism. A number of secondary endpoints relating to cardio-metabolic function and profile, patient-reported outcomes, safety endpoints and clinical outcomes were also collected.

This report deals only with the immediate primary and secondary outcome measurements at 6-months post study commencement. Long-term outcomes at 1-, 3-, 5- and 10-years are planned for collection and will be reported in due course.

Sample size calculation

The principle parameters being examined in this study are changes in insulin sensitivity and insulin secretion. The power calculation was performed with the assumption of a 20% participant drop-out rate. An anticipated change in the primary outcome measure of 5% in the control group and 25% in the intervention group was predicted. These figures are based on intra-subject variability of 25% for insulin secretion and 20% for insulin sensitivity, as observed in our previous work.[16]

Therefore, assuming 80% of the control group demonstrates a 5% change in the primary outcome measure (and 20% drop-outs demonstrate no change), then the average change in the control group is 4%. Similarly, if it is assumed 80% of the intervention group will demonstrate a 25% change in the primary outcome measure (and 20% drop-outs demonstrate no change), then the average change in the intervention group is 20%. To detect this difference of 16% change (assuming standard deviation of change is 25%), it was calculated that a total of 130 patients were required for recruitment (65 per randomised arm) for 95% power (assuming a 5% significance level and a two-sided test) to attain a high-powered sample size. All analyses were undertaken on an intention-to-treat basis.

Statistical analysis

The planned primary analyses were done at the individual level, according to the intention-to-treat principle. For participants who did not attend the 6-month end of study assessment, secondary outcomes of clinical endpoints were determined from healthcare records unless participants had withdrawn consent for this access.

Statistical analysis was performed using SPSS Version 25 (Chicago, IL). Normality of data was assessed using the Kolmogorov-Smirnov tests. Descriptive statistics were used to estimate the frequencies, means (± standard deviation) or medians (± interquartile range) of study variables as required. For continuous variables, Student *t*-test or Mann-Whitney test were used for parametric and nonparametric data respectively. Mean differences between continuous variables for groups were also reported, with 95% confidence intervals of the difference. Difference between groups was assessed with two-sided Fisher's exact test or Pearson chi-square for categorical variables as appropriate. Correlation assessment was made with Pearson's test or Spearman's rank test for parametric and nonparametric variables respectively. A p value <0.05 was considered significant in the statistical analysis.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Study cohort

Between August 17th 2015 and December 18th 2017, 130 individuals were recruited that comprised the intention-to-treat population at the start of the study. At the end of study (26th July 2018) 103 individuals remained and completed follow up investigations, reflecting a drop-out rate of 20.8%. Figure 1 provides a CONSORT flow diagram of the study.

Table 1 outlines the baseline demographics of the study cohort, reflecting well matched active and passive intervention groups. Of particular note, 32.3% of recruitment was from individuals of the Black, Asian and Minority Ethnic community.

Change in metabolic parameters

Table 2 shows metabolic surrogate outcomes for the study cohort. Active versus passive lifestyle intervention after kidney transplantation was not associated with any change in glucose metabolism such as insulin secretion (mean difference -446 [-3,184 to 2,292], p=0.748), insulin sensitivity (mean difference -0.45 [-1.34 to 0.44], p=0.319) or disposition index (mean difference -940 [-5,655 to 3,775], p=0.693). We did not observe any significant difference in diabetes- and/or obesity-related immunoassays.

In the total study cohort, fasting glucose levels (in mmol/l) after active versus passive lifestyle intervention at baseline was 5.5 versus 5.6 respectively (p=0.566) and after 6-months was 5.4 versus 5.5 respectively (p=0.795). Postprandial glucose levels (in mmol/l) after active versus passive lifestyle intervention at baseline was 7.5 versus 7.3 respectively (p=0.603) and after 6-months was 7.1 versus 7.1 respectively (0.992).

Change in post prandial glucose levels had weak correlation with change in insulin secretion (-0.288, p=0.011) and disposition index (-2.23, p=0.050), but not significantly for insulin sensitivity (-0.125, p=0.277). There was no significant correlation between change in fasting glucose levels with change in insulin secretion (-0.111, p=0.266), insulin sensitivity (-0.077, p=0.440) and disposition index (-0.143, p=0.152).

Patient-reported outcomes

Table 3 outlines change in patient-reported outcomes including change in physical activity (Duke Activity Status Index and GP Physical Activity Questionnaire) and psychological wellbeing (EQ5D; quality of life and health status; Beck Depression Inventory; specific tool for depression; Situational Motivational Score; specific tool for assessment of situational motivation). No significant difference was observed at 6-months between the cohorts.

Safety and clinical outcomes

No significant safety concerns were identified when comparing the two cohorts and no deaths or graft losses occurred over the 6-month study period (see Table 4). Immunosuppression was no different between the groups. Tacrolimus trough levels in ng/ml (± standard deviation) were similar for active versus passive groups at baseline (8.0 ± 3.2 versus 7.2 ± 2.5 respectively, p=0.197) and 6-months (7.5 ± 3.5 versus 7.0 ± 1.7 respectively, p=0.466). There was no difference in cumulative exposure to mycophenolate or corticosteroids over the study period.

From a clinical perspective, active lifestyle intervention was associated with a significant difference in weight change over the course of the 6-month follow up (mean difference -2.47kg [-.401 to -0.92], p=0.002). Overall, weight loss was observed in 60.0% versus 38.3% of participants in active versus passive intervention arms (p=0.023). There was a trend towards a significant difference in fat-free mass (mean difference -1.540kg [-3.24 to 0.16], p=0.075) and a significant difference in fat mass (mean difference -1.537kg [-2.947 to -0.127], p=0.033) over the course of the 6-month follow up favouring active intervention.

Rates of new-onset post transplantation diabetes were halved in the group receiving active intervention compared to standard of care (7·6% versus 15·6% respectively, p=0·123), a clinically significant reduction but which failed to achieve statistical significance. Sub-analyses of our recruited cohort (Supplementary document, SDC, http://links.lww.com/TP/B815) showed a more pronounced clinical difference in PTDM rates for recruits within 12-months of kidney transplantation (n=82; 9.8% versus 18.4% respectively, p=0.216) or BMI 25 mg/m^2 or higher (n=73; 11.1% versus 24.2% respectively, p=0.131) or both (n=55; 10.7% versus 25.9% respectively, p=0.133).

Discussion

This study demonstrates kidney transplant recipients can be encouraged to undertake lifestyle modification under the supervision of a renal dietitian with pro-active intervention, underpinned by defined BCTs, which may improve their cardio-metabolic risk profile. Our study did not identify any influence of active versus passive lifestyle intervention on our primary outcome of surrogate glucose metabolism measures, but there were encouraging improvements in secondary outcomes such as weight difference, fat mass and trend towards less PTDM between study arms. This study is the first lifestyle intervention trial designed to improve glycaemic metabolism after kidney transplantation, and introduces the concept of incorporating evidence-based BCTs into post transplant care, but further research investigation is warranted to determine beneficial effects on clinical outcomes.

The immediate interpretation of our 'negative' study suggests one of three conclusions; 1) active lifestyle intervention was ineffective; 2) study intervention was too short, or; 3) the chosen primary outcome for analysis was inappropriate. It is possible the study intervention period was too short and longer exposure could convert observed trends into significant differences with longer follow up. A recent systematic review of clinical trials suggests time-limited lifestyle interventions may have variable efficacy for prevention of diabetes.[17] With regards to the primary outcome, the negligible effects of active lifestyle intervention on glucose metabolism appear to contrast with clinically meaningful reduction in PTDM rates. This paradoxical observation appears contradictory and requires explanation. Firstly, previous work validating use of surrogate measures of glucose metabolism was conducted exclusively in kidney transplant recipients of white ethnicity,[14,15] while approximately a third of our study participants were non white. High participation rates from BAME individuals is a significant strength of this study but may have an impact on the final analysis. Kodama et al., in their systematic review and meta-analysis of 74 study cohorts, demonstrated significant

differences in the hypothesized hyperbolic relationship between insulin secretion and sensitivity among Africans, Caucasians and East-Asian individuals.[18] Rasouli et al. also observed African-American individuals paradoxically have an approximate 25% increase in DI compared to white individuals (secondary to greater compensatory increase in insulin secretion in relation to increased insulin resistance).[19] Another limitation to the interpretation of insulin-based parameters in this study is the lack of data relating to influences which impact upon circulating insulin levels such as hepatic insulin extraction. The complex interplay between insulin secretion, insulin sensitivity and hepatic insulin extraction has led to significant debate about the strengths and limitations of calculating the disposition index. While the hyperbolic relationship between insulin secretion and sensitivity remains a convenient conceptual framework, it continues to be refined in light of emerging research evidence. In addition, the power calculation was not adjusted for baseline glucose metabolism, which may have interfered in our sample size estimation. Therefore, it is possible that the observed power may have differed from assumed power, leading to an under-powered sample.

The lack of improvement in surrogates of glucose metabolism may also reflect the volatile nature of post transplantation glycemia. Firstly, postoperative hyperglycaemia consistent with diagnostic criteria for diabetes is ubiquitous post kidney transplantation among nondiabetic recipients.[20] While this frequently improves, approximately half of kidney transplant recipients remain with PTDM or prediabetes as demonstrated in a Spanish cohort study of 672 kidney transplant recipients.[21] The dynamic and bimodal nature of post transplant glycaemia may explain the lack of significant change in short-term glucose metabolism indices in our study. We relied on surrogates assessing baseline glucose metabolism, rather than postprandial glucose metabolism, due to previously validated work but this reliance on static versus dynamic measurements may underestimate intervention benefits. The utility of

the disposition index has also been questioned in recent studies, with beta-cell sensitivity and/or beta-cell response to rate of change in plasma glucose concentration competing for importance as determinants of beta-cell function.[22,23] It is clear from this study that our understanding of the pathophysiology of PTDM remains sub-optimal and requires further investigation, especially in light of fundamental differences compared to alternative forms of diabetes[24] and justifies PTDM to be considered as a unique subset within diabetes classification systems.

This study area is important as cardiovascular disease remains a leading cause of morbidity and mortality after kidney transplantation[1] and evidence-based strategies to attenuate cardio-metabolic risk profiles are limited.[2] Only two randomised controlled trials to reduce cardiovascular risk post transplantation have ever been conducted, ALERT[25] and FAVORIT,[26] but the benefit of lifestyle modification post transplantation has never been robustly explored. In the general population, lifestyle intervention is effective at preventing type 2 diabetes but does not reduce all-cause mortality among individuals with type 2 diabetes.[27] Trials exploring the benefits of lifestyle intervention after kidney transplantation are limited. The INTENT (Intensive Nutrition Interventions on Weight Gain after Kidney Transplantation) study compared early intensive nutritional/exercise advice versus standard of care in 36 kidney transplant recipients in New Zealand, with the primary outcome change in weight after 6-months.[28] No difference was observed between the cohorts at 6-months, which differs from our study results. This could be explained by methodological variations in the intervention, higher-than-expected attrition rate for study participation and different behaviour change components. The ACT (Active Care after Transplantation) study is a multicenter randomised controlled trial currently in progress across three centers in the Netherlands, comparing three arms (exercise versus exercise/diet versus standard of care) among 219 kidney transplant recipients, with the primary outcome change in physical

functioning of quality of life.[29] Lifestyle counselling and motivational techniques, in line with the self-determination theory, will underpin the delivery of interventions. Recently published taxonomy of BCT has assessed the effectiveness of behaviour change intervention to promote healthy eating and physical activity.[10] With this knowledge in mind, CAVIAR incorporated self-regulatory techniques congruent with Control Theory, combined with node-link mapping and elements of social behaviour and network therapy in support. While the pharmacological management of PTDM is slowly developing a growing evidence base,[30] we believe behaviour change and lifestyle intervention remains critical after kidney transplantation and seeking clinical evidence for its efficacy remains desirable.

Additional limitations of this study, distinct from the methodological considerations already discussed regarding study intervention period and primary outcome, should be noted. The study participant attrition rate of 20.8% was marginally above our estimated 20.0% that was factored into our power calculations (aiming for 95% power). However, it is unlikely to have made any significant difference to the final analysis. The active intervention arm was designed pragmatically in an attempt to minimise participant attrition rates, with flexibility for some study visits to be telephone-based, but post trial participant feedback will help to develop any refinements or improvements to future work. While an excellent proportion of non white kidney transplant recipients was achieved, a number of potential recruits could not be recruited due to language barriers and it is important to overcome such inequalities in access to research to ensure study findings are genuinely representative of patient cohorts.

Despite our frank discussion of limitations, we believe this study identifies potential benefits of active lifestyle modification and supports the encouragement of active lifestyles after transplantation. However, in line with a recent meeting report on the benefits of sport and exercise post transplantation,[31] evidence for improved hard clinical outcomes remain lacking. Our experience should not dissuade further research but guide methodological considerations

for future work. For example, the active intervention may require more frequent visits to improve intensity (but needs balancing against risk for drop outs). Future study recruitment should also select an at-risk group for development of PTDM (e.g. older age, non white ethnicity, overweight, family history) for investigation. Assessing change in dynamic glucose metabolism (using postprandial samples) rather than static physiological markers may be more beneficial. However, this study will allow adequate power calculations to be made for clinically meaningful outcomes like development of PTDM.

In conclusion, our renal dietitian-led lifestyle intervention utilizing defined BCTs after kidney transplantation failed to demonstrate improvement in parameters of glucose metabolism but conflictingly suggested some improvement in clinical outcomes such as weight and risk for PTDM. Rather than failing to show the benefit of active lifestyle intervention, we believe our work highlights methodological considerations that should be corrected for any future work in this area. Further research is needed to determine if lifestyle modification after kidney transplantation has benefit upon clinical outcomes such as prevention of PTDM and this study provides adequate event rates and practical experience to develop a more refined well-powered clinical trial across multiple centers.

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Figure legends

Figure 1. CONSORT flow chart for CAVIAR study profile

Table 1. Baseline demographics of study cohort

Parameter		Active	Passive
Number		66	64
Age in years (± SD)		47·7 ± 13·3	47·4 ± 13·7
Male sex		31 (43·7%)	40 (56·3%)
Ethnicity	White	46 (69·7%)	42 (65·6%)
	Black	8 (12·1%)	6 (9·4%)
	South Asian	12 (18·2%)	13 (20·3%)
	Chinese	0 (0·0%)	1 (1·6%)
	Mixed race	0 (0·0%)	1 (1·6%)
	Other	0 (0·0%)	1 (1·6%)
Cytomegalovirus serostatus positive		26 (39·4%)	27 (42·2%)
Hepatitis C positive		0 (0·0%)	0 (0·0%)
Family history of diabetes		20 (37·0%)	18 (36·7%)
Repeat kidney transplant		7 (12·5%)	6 (12·2%)
Post transplant time in days (±SD)		269 ± 181	249 ± 150
Polycystic kidney disease		11 (16.7%)	11 (17.2%)
Immunosuppression	Tacrolimus	66 (100·0%)	64 (100·0%)
	Mycophenolate Mofetil	57 (86·4%)	57 (89·0%)
	Mycophenolic Acid	7 (10·6%)	5 (7·8%)
	Azathioprine	2 (3·0%)	2 (3·2%)
	Prednisolone	66 (100·0%)	64 (100·0%)
Body mass index (kg/m^2) (± SD)		27·8 ± 4.4	27·7 ± 4.4

Table 2. Metabolic surrogate outcomes between baseline and 6-month study end

Parameter		Active	Passive	Mean difference	P value
Insulin secretion ± SD	Baseline	1344 ± 2506	1935 ± 5667	-446 [-3184 to 2292]	0·748
	Follow up	3517 ± 4967	4554 ± 0132		
	Δ change	+2173 ± 4457	+2619 ± 10292		
Insulin sensitivity ± SD	Baseline	4·45 ± 2·00	4·16 ± 1·67	-0·45 [-1·34 to 0·44]	0·319
	Follow up	3·43 ± 1·46	3·65 ± 1·94		
	Δ change	-1·02 ± 2·24	-0·57 ± 2·27		
Disposition index ± SD	Baseline	4339 ± 5518	5476 ± 8074	-940 [-5655 to 3775]	0·693
	Follow up	9551 ± 9954	11625 ± 13546		
	Δ change	+5212 ± 8780	+6152 ± 14926		
	Follow up	39·0 ± 6·0	40·6 ± 6·8		
	Δ change	+0·32 ± 4·01	+0·78 ± 4·08		
C-peptide (nmol/L) ± SD	Baseline	2374 ± 2196	2284 ± 1912	-11·57 [-1194·90 to 1171·76]	0·985
	Follow up	4186 ± 3349	4140 ± 3656		
	Δ change	+1819 ± 2502	+1830 ± 3477		
Ghrelin (pg/mL) ± SD	Baseline	4293 ± 7027	4323 ± 5850	-488·31 [-3692·98 to -2716·35]	0·763
	Follow up	6935 ± 6878	7645 ± 7732		
	Δ change	+2642 ± 9104	+3131 ± 6717		
Gastric inhibitory peptide (pmol/L) ± SD	Baseline	225 ± 318	160 ± 148	-60·35 [-160·09 to 39·40]	0·233
	Follow up	155 ± 184	151 ± 214		
	Δ change	-70 ± 251	-10 ± 254		
Glucagon like peptide-1 (pmol/L) ± SD	Baseline	143 ± 98	137 ± 95	+20·29 [-46·87 to 87·46]	0·549
	Follow up	175 ± 94	159 ± 91		
	Δ change	+34 ± 156	+14 ± 126		
Glucagon (pmol/L) ± SD	Baseline	262 ± 230	230 ± 196	-3·01 [-109·51 to 103·49]	0·955
	Follow up	197 ± 152	178 ± 138		
	Δ change	-61 ± 295	-58 ± 228		
Insulin (pmol/L) ± SD	Baseline	852 ± 1773	1498 ± 3489	-227·28 [-1901·25 to 1446·69]	0·788
	Follow up	1946 ± 2276	2824 ± 5188		
	Δ change	+1094 ± 2177	+1321 ± 5845		
Leptin (ng/mL) ± SD	Baseline	18359 ± 23678	13125 ± 15265	-8554·29 [-20963·86 to 3855·28]	0·174
	Follow up	19809 ± 22717	22627 ± 28508		
	Δ change	+1449 ± 30906	+10003 ± 32067		
Total plasminogen activator	Baseline	121400 ± 250032	139012 ± 280423	+11097·53 [-130165·31 to 152360·37]	0·876
	Follow up	106596 ± 170161	76755 ± 49355		

inhibitor-1 ± SD	Δ change	-26895 ± 332965	-37993 ± 214004		
Resistin (ng/mL) ± SD	Baseline	8812 ± 9439	7272 ± 7979	+3254·65 [-3588·08 to 10097·38]	0·347
	Follow up	17526 ± 15761	15174 ± 14472		
	Δ change	+9168 ± 16765	+5913 + 15068		
Visfatin (pg/mL) ± SD	Baseline	2635 ± 1928	2563 ± 1633	-17·13 [-1210·78 to 1176·52]	0·977
	Follow up	2764 ± 1626	2771 ± 2854		
	Δ change	+129 ± 2545	+146 ± 3521		
Adiponectin (µg/mL) ± SD	Baseline	15886260 ± 13598455	18405572 ± 19960549	+3829379·22 [-2358346·86 to 10017105·29]	0·222
	Follow up	14389394 ± 13672231	11613250 ± 12149738		
	Δ change	-1992294 ± 13966431	-5821673 ± 16736319		

Δ change among paired samples only (n=103)

Table 3. Patient-reported outcome measures between baseline and 6-month study end

Parameter		Active	Passive	Mean difference	P value
GP Activity Score	Baseline	1·61 ± 1·11	1·84 ± 1·18	+0·36 (-0·19 to 0·90)	0·201
	Follow up	2·41 ± 1·20	2·18 ± 1·21		
	Δ change	+0·77 ± 1·57	+0·41 ± 1·02		
Duke Activity Score	Baseline	40·62 ± 15·77	44·70 ± 13·87	+1·60 (-2·82 to 6·02)	0·474
	Follow up	43·83 ± 15·74	43·56 ± 15·07		
	Δ change	+2·58 ± 11·77	+0·98 ± 9·32		
SMS[1] intrinsic motivation score	Baseline	4·72 ± 1·31	4·51 ± 1·60	+0·17 (-0·37 to 0·71)	0·540
	Follow up	4·82 ± 1·45	4·44 ± 1·56		
	Δ change	+0·08 ± 1·24	-0·09 ± 1·38		
SMS[1] intrinsic regulation score	Baseline	5·99 ± 1·24	5·72 ± 1·38	+0·15 (-0·36 to 0·67)	0·557
	Follow up	5·90 ± 1·28	5·58 ± 1·40		
	Δ change	-0·06 ± 1·17	-2·1 ± 1·36		
SMS[1] extrinsic regulation score	Baseline	2·00 ± 1·32	1·86 ± 1·25	+0·14 (-0·48 to 0·75)	0·665
	Follow up	2·14 ± 1·52	1·94 ± 1·29		
	Δ change	+0·14 ± 1·47	0·00 ± 1·52		
SMS[1] amotivation score	Baseline	1·75 ±1·11	1·52 ± 0·81	-0·11 (-0·59 to 0·38)	0·668
	Follow up	1·96 ± 1·53	1·87 ± 1·24		
	Δ change	+0·22 ± 1·32	+0·33 ± 0·99		
EQ-5D[2] score	Baseline	73·37 ± 14·43	75·06 ± 18·02	+0·77 (-5·16 to 6·69)	0·797
	Follow up	80·57 ± 15·40	80·41 ± 15·30		
	Δ change	+7·02 ± 13·51	+6·25 ± 15·58		
Beck depression inventory score	Baseline	8·96 ± 8·66	7·84 ± 7·53	-0·38 (-3·00 to 2·23)	0·772
	Follow up	6·65 ± 9·53	6·40 ± 7·28		
	Δ change	-1·94 ± 7·99	-1·56 ± 3·53		

[1]Situational Motivation Score

Δ change among paired samples only (n=103)

Table 4. Clinical outcomes at 6-months

Parameter		Active	Passive	Mean difference	P value
Estimated glomerular filtration rate (ml/min)	Baseline	48·44 ± 13·35	51·93 ± 16·15	-1·08 (-3·63 to 1·46)	0·400
	Follow up	48·22 + 13·78	50·76 ± 15·07		
	Δ change	-0·82 ± 6·00	+0·27 ± 6·36		
Urine albumin-creatinine ratio (mg/mol)	Baseline	5·82 ± 6·58	18·98 ± 69·43	-5·78 (-11·92 to 0·36)	0·065
	Follow up	4·80 ± 5·37	11·91 ± 34·63		
	Δ change	-1·35 ± 7·00	+4·44 ± 18·42		
Weight (kg) ± SD	Baseline	79·03 ± 16·10	81·28 ± 14·73	-2·47 [-4·01 to -0·92]	0·002
	Follow up	77·91 ± 16·50	82·66 ± 14·72		
	Δ change	-1·20 ± 4·38	+1·26 ± 3·32		
Waist-hip ratio ± SD	Baseline	0·947 ± 0·102	0·950 ± 0·086	-0·007 [-0·032 to 0·017]	0·552
	Follow up	0·940 ± 0·098	0·948 ± 0·095		
	Δ change	-0·011 ± 0·063	-0·004 ±0·057		
Systolic BP (mmHg) ± SD	Baseline	128·3+ 18·5	124·8 ± 10·9	-1·7 [-7·6 to 4·1]	0·555
	Follow up	126·0 ± 14·5	125·7 ± 14·5		
	Δ change	-1·5 ± 14·9	+0·2 ± 13·9		
Diastolic BP (mmHg) ± SD	Baseline	79·6 ± 10·4	79·4 ± 7·4	-0·12- [-3·89 to 3·64]	0·948
	Follow up	80·3 ± 9·3	79·7 ± 9·3		
	Δ change	+0·45 ± 10·24	+0·58 ± 8·18		
Total cholesterol (mmol/L) ± SD	Baseline	4.8 ± 1.9	5.0 ± 2.1	-0.1 [-0.6 to 0.4]	0.534
	Follow up	4.2 ± 1.9	4.5 ± 2.0		
	Δ change	-0.6 ± 3.2	-0.5 ± 3.7		
Triglycerides (mmol/L) ± SD	Baseline	1.72 ± 0.75	1.62 ± 0.68	+0.19 [-0.55 to 0.91]	0.629
	Follow up	2.09 ± 2.80	1.79 ± 0.81		
	Δ change	+0.37 ± 2.42	+0.19 ± 0.79		
Skinfold thickness (mm) ± SD	Baseline	16·1 ± 6·0	15·1 ± 6·3	-2·07 [-5·12 to 0·98]	0·181
	Follow up	14·6 ± 5·9	16·5 ± 6·9		
	Δ change	-1·06 ± 7·21	+1·01 ± 7·75		
Fat-free mass (kg) ± SD	Baseline	54·5 ± 11·2	56·9 ± 11·3	-1·540 [-3·236 to 0·156]	0·075
	Follow up	54·2 ± 11·9	57·1 ± 10·6		
	Δ change	-0·644 ± 2·347	+0·895 ± 5·597		
Fat mass (kg) ± SD	Baseline	24.8 ± 9.7	23.7 ± 10.5	-1.537 [-2.947 to -0.127]	0.033
	Follow up	23.6 ± 9.5	25.4 ± 9.9		
	Δ change	-0.667 ± 4.140	+0.870 ± 2.337		
Total body water (kg) ±	Baseline	39·9 ± 8·2	42·2 ± 8·2	-0·485 [-1·121 to 0·151]	0·133

SD	Follow up	39·6 ± 8·7	41·7 ± 7·7		
	Δ change	-0·483 ± 1·715	+0·002 ± 1·331		
HbA1c (mmol/mol) ± SD	Baseline	38·7 ± 5·2	39·7 ± 5·9	-0·46 [-2·08 to 1·16]	0·572
	Follow up	39·0 ± 6·0	40·6 ± 6·8		
	Δ change	+0·32 ± 4·01	+0·78 ± 4·08		
Impaired fasting glucose		18 (32·1%)	15 (31·9%)	-	0.575
Impaired glucose tolerance		10 (22·7%)	9 (23·7%)	-	0.562
Post transplantation diabetes		5 (7·6%)	10 (15·6%)	-	0·123
Any anti-glycaemic medication		1 (1.5%)	3 (4.7%)	-	0.298
Major adverse cardiac event		0 (0·0%)	0 (0·0%)	-	1·000
Allograft rejection[1]		1 (1·5%)	0 (0·0%)	-	0·539
Death		0 (0·0%)	0 (0·0%)	-	1·000
Death-censored graft loss		0 (0·0%)	0 (0·0%)	-	1·000

[1]Borderline cellular rejection according to Banff criteria

Δ change among paired samples only (n=103)

Figure 1. CONSORT flow diagram