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Effect of combined aerobic and resistance training on kidney health in adults with type 2 diabetes: A randomized controlled trial

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ABSTRACT

Aims: Evidence on the effects of combined aerobic and resistance training on kidney function in type 2 diabetes (T2D) remains limited. We evaluated the effect of a 9-month structured exercise programme on kidney function in adults with T2D.
Methods: In this randomized controlled trial conducted in four primary care centres in Catalunya, 136 adults with T2D without kidney disease (aged 41–87 years) were randomized to an intervention group (IG, $n = 52$) or control group (CG, $n = 84$). The IG completed two supervised 60-min sessions/week of moderate-to-vigorous aerobic and resistance exercise; the CG received standard care. The outcomes included changes in estimated glomerular filtration rate (eGFR) and urinary albumin.
Results: After 9 months, eGFR increased by 1.8 mL/min/1.73 m^2 in the IG and decreased by 3.4 mL/min/1.73 m^2 in the CG (between-group difference: 5.2 mL/min/1.73 m^2 (95%CI: 0.9–9.5, $p = 0.019$)). Improvements in eGFR were significantly greater in the IG, particularly among women, those <65, and participants with uncontrolled diabetes (all $p < 0.05$). Urinary albumin changes did not differ between groups.
Conclusions: A structured aerobic and resistance exercise programme improves eGFR in adults with T2D in primary care.

What is known about this research topic?

Exercise is recommended for type 2 diabetes management.
Research conducted at the primary care level regarding combined exercise approaches is limited.

What this study adds and its future implications?

Combined aerobic and resistance training improved kidney filtration rate.
Benefits were greater in women, younger adults, and those with poor glycaemic control.
Structured combined aerobic and resistance exercise may help prevent kidney function decline.

1. Introduction

Type 2 diabetes (T2D) represents a global public health crisis, with its prevalence steadily rising and resulting in over 1 million deaths annually worldwide, ranking as the ninth leading cause of death [1]. T2D is a multifactorial and complicated condition characterized by persistent hyperglycaemia, primarily due to insulin resistance [2]. Among its various deleterious effects, diabetes is considered the principal leading cause of kidney disease [3]. According to the literature, around 30-40% of people living with diabetes develop chronic kidney disease (CKD), with a worse prognosis in the presence of other comorbidities like obesity, hypertension, and dyslipidaemia, which are

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increasingly common among our society [4]. Moreover, its coexistence not only further increases the risk of CKD onset and progression [5], but also of cardiovascular disease (CVD) [6], the main cause of morbi-mortality among this vulnerable population. The mechanisms by which chronic hyperglycaemia in diabetes leads to the progression of kidney disease remain incomplete, but it has been suggested that sustained glomerular hyperfiltration and hypertrophy can progressively damage the tubules and glomeruli, resulting in renal failure, often exacerbated by oxidation stress and inflammation [7]. As diabetic renal disease is rapidly increasing [1], effective prevention strategies based on solid evidence to maintain kidney health in diabetes are urgently needed before it is too late.

Physical activity (PA)/exercise is typically one of the first lifestyle strategies advised for T2D management, as well as for its complications [8]. In fact, the American Diabetes Association (ADA) guidelines state that a combination of moderate-to-vigorous intensity aerobic exercise (≥150 min/week) and resistance training (≥2 days/week) is a tried-and-true exercise modality for preventing and managing T2D, as well as promoting renal health [2], a view supported by the KDIGO 2024 CKD guidelines [4]. Of note, relevant evidence from RCT-based meta--analyses indicates that exercise can also be used to treat CKD [9]. It was found that aerobic exercise (e.g. walking and running modalities), even at relatively low intensities, can have a significant positive effect on eGFR and kidney disease progression in adult CKD patients, particularly when at least 30 min/session are undertaken [9].

Experimental studies have also shown that moderate aerobic exercise preserves kidney structure and function, attenuates albuminuria/proteinuria, and delays the progression of diabetic renal disease in animal models [10–12]. In individuals with diabetes, evidence indicates that the immediate renal response to exercise may involve transient increases in microalbuminuria after short bouts of exercise, particularly at higher intensities [13]. Nonetheless, these acute effects do not appear to counteract the long-term benefits, as the overall evidence supports exercise as a kidney-protective strategy. In this context, resistance training exerts renoprotective effects, partly by modulating the renin-angiotensin-aldosterone system (RAAS) towards a more favourable angiotensin converting enzyme 2 (ACE2)/angiotensin (Ang)1–7 axis and by reducing kidney inflammation in diabetic models [12]. Notably, a key aspect of diabetic kidney disease management is RAAS inhibition, which reduces glomerular hyperfiltration and slows disease progression [14].

Based on all this evidence, it is tempting to speculate that combined training could present as a reasonable strategy to prevent or delay kidney function loss in T2D patients. In this context, a diminished estimated glomerular filtration rate (eGFR) may serve as a valuable indicator of kidney function, widely used in epidemiology and clinical practice, for predicting kidney disease [15]. A recent 4.5-year observational study in T2D individuals at high cardiovascular risk reported that moderate PA (at least 2 times/week) was associated with slower eGFR decline over time and lower incidence of renal outcomes (composite of doubling of serum creatinine or end-stage kidney disease) compared to lower exercise levels (≤once/week) [16]. Similarly, other prospective cohort studies in diabetics have consistently demonstrated a reduced decline in eGFR and a lower risk of CKD in more physically active groups compared with the non-exercise group [17,18]. Furthermore, some reports revealed that higher levels of PA contributed to a reduction in kidney damage by a quantitative assessment of proteinuria, particularly by urinary albumin excretion among diabetic/prediabetic patients [16,19,20]. Although prior studies are promising, their observational design and limited characterization of exercise exposure prevent definitive conclusions. To our knowledge, only two short-term clinical trials have focused on exercise isolated interventions in people living with diabetes: one assessing combined aerobic-resistance exercise in individuals with mild kidney dysfunction [21], and another focusing on moderate aerobic exercise in individuals with albuminuria [19], both conducted outside of Mediterranean countries.

Importantly, early prevention of diabetic renal disease is essential due to its irreversibility and alarming burden on patients and society. Investigating the long-term impact of combined training, following the ADA [2] and KDIGO guidelines [4], on kidney health in people living with diabetes that are not affected by kidney disease is imperative from the perspective of preventive medicine. This present study is, to our knowledge, the first long-term RCT conducted in a Mediterranean primary care setting to evaluate the effects of a structured combined aerobic and resistance training programme on kidney function in adults with T2D without pre-existing kidney disease. We hypothesized that a 9-month supervised combined training intervention would improve estimated glomerular filtration rate (eGFR) and reduce urinary albumin levels compared with standard care.

2. Materials and methods

2.1. Study design

This study was a community-based, randomized controlled intervention trial, named “Pas a Pas”, consisting of a combined aerobic and resistance exercise programme. The intervention lasted for 9 months. Between 2016 and 2019, individuals with T2D were recruited from 4 primary care centres (PCC) in Reus (Catalonia, Spain). Ethic approval was obtained from the Institut d’Investigació en Atenció Primària (IDIAP), Jordi Gol. All participants provided written informed consent. This work was conducted in accordance with the principles outlined in the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Clinicaltrials.gov ID NCT02767739.

2.2. Participants and randomization

To recruit participants for the study, 6 months prior to the start of the intervention, health care professionals from the PCCs were asked to invite adult users to participate. Interested individuals underwent initial screening to assess their eligibility criteria. Eligible participants were adult PCC users, aged 18 to 87 years, diagnosed with T2D, who provided signed informed consent. Exclusion criteria consisted of an episode of ischemic heart disease within the past six months, an acute episode of arthritis that would limit the individual's ability to walk, or lung or heart disease with dyspnoea (mild to moderate effort dyspnoea) that would limit the individual's ability to undertake the proposed exercise regimen. Participants who met the eligibility criteria were randomly assigned, in a 1:1.5 ratio, to the intervention group (IG) or control group (CG) using a random number-generating computer programme. Randomization of 1 to 1.5 in favour of the control group was implemented to enhance the statistical power of the analysis.

2.3. Intervention

The 9-month supervised PA intervention consisted of a combined moderate-to-vigorous intensity aerobic and resistance exercise programme, according to international PA recommendations [22]. Individuals engaged in two supervised brisk walking group sessions per week (each lasting 60 min, totalling 120 min per week, equating to 396 METs/min/week). These brisk walking sessions, with a prior warm-up period, followed 5 km circuits around Reus, with group sizes ranging from 15 to 30 participants. In addition, individuals performed supervised resistance exercises during these sessions. Exercises targeted both upper and lower body muscle groups, including bench press, seated row, shoulder press, pull down, leg press, extensions, curls, as well as core exercises such as abdominal crunches and back extensions. These exercises were performed outdoors, utilizing publicly available fitness equipment provided by local councils in public parks.

To ensure adherence and consistently, a PA specialist supervised the standardization of procedures and training for primary care nurses,

while a healthcare professional monitored the sessions. Participants in the CG received standard clinical care from health care professionals and no specific guidance on increasing PA. All participants were advised to maintain their usual dietary habits during the study period.

2.4. Physical activity assessment

Baseline and 9-month post-intervention evaluations were conducted by trained nurses through face-to-face visits, during which individuals completed standardized questionnaires. PA levels were evaluated using the short version of the International Physical Activity Questionnaire (IPAQ-S), a validated questionnaire for the Catalan population [23]. While the IPAQ-S relies on self-reported physical activity and is inherently subject to recall and social desirability bias, it is a validated and widely used tool that reliably estimates habitual activity in clinical and population studies. Factors such as intensity (low, moderate, vigorous), frequency, and duration of PA were collected using the IPAQ-S. Total PA was quantified in metabolic equivalent task minutes per week (METs/-min/week) by multiplying the frequency, and duration (minutes per week) of each PA intensity level by its corresponding MET value (low: 3.3 MET, moderate: 4.0 MET, vigorous: 8.0 MET). These calculations provided an overall measure of PA engagement [24]. Additional, PA levels were categorized into vigorous, moderate, and walking—in accordance with widely PA guidelines [2,22].

2.5. Outcomes assessment

The primary end point of this analysis was the change in kidney function from baseline to 9 months, assessed as changes in serum creatinine-based eGFR (mL/min/1.73 m^2) calculated using the CKD-EPI equation [25], and changes in urinary albumin levels (mg/L). At baseline and 9 months, blood and spot morning urine samples were collected after an overnight fast, and serum creatinine and urinary albumin concentrations were determined, respectively, using routine biochemical analyses.

2.6. Measurement of covariates

At baseline, a general questionnaire was administered to collect data on sociodemographic characteristics (age, sex, employment status and social class), medical conditions [hypertension, dyslipidaemia, controlled diabetes (defined as HbA1c <7.0 %)], REGICOR cardiovascular risk score, and smoking status. Social class was calculated using an adaptation of the British Registrar General Classification System, comprising three categories: high (class I-II), middle (class IIIN-IIIM), and lower (class IV-V) [26]. At baseline and 9-month follow-up visits, measurements of weight (kg) and height (cm) were obtained using a calibrated balance, and BMI (kg/m^2) was calculated and classified as follows: normal weight (<25 kg/m^2), overweight (25–<27 kg/m^2), and obesity (≥25 kg/m^2).

2.7. Statistical analysis

For the present analysis, a sample size of 136 participants (IG: $n = 52$, CG: $n = 84$) assessed at 9 months provided >80% power at a 5% significance level (two-sided test) to detect a 9-month mean difference of 4 mL/min/1.73 m^2 in the eGFR between study groups. This assumed a common standard deviation (SD) (of the difference in mean changes) of 7.8 mL/min/1.73 m^2, as shown in previous research [21,27]. The analysis for the primary (eGFR) and secondary (urinary albumin levels) continuous endpoints were conducted on completers-only (i.e., individuals who had both baseline and 9-month measurements) and a modified intention-to-treat population (mITT) was utilized as a complementary analysis, following a multiple imputation method. The mITT analyses included all participants randomly assigned with a baseline measure of eGFR and/or urinary albumin levels, regardless of whether they had measurements at the 9-month follow-up visit or not. Descriptive data were expressed as mean ± SD for quantitative variables or frequency (%) for categorical variables. Student t-tests and χ^2 tests were used, as appropriate, to test differences in baseline characteristics between IG and CG subjects. Continuous outcomes were assessed for normality using both Shapiro-Wilk test and visual inspection (normal plots [histogram] and Q-Q plot [quantile-quantile plot]). Differences between groups for the mean changes from baseline to 9 months of the primary outcomes (i.e., eGFR and urinary albumin levels) were assessed using both unadjusted and multivariable-adjusted linear regression analyses. Models were adjusted for confounding variables which included corresponding baseline outcome values (eGFR for albumin analyses and urinary albumin levels for eGFR analyses), age (years), sex, baseline BMI (kg/m^2), smoking status (no (ref.), yes), hypertension (no (ref.), yes), and controlled diabetes (no (ref.), yes). We analysed both the full cohort and subgroups stratified (considered as a post hoc analysis) according to baseline eGFR (<60, and ≥60 mL/min/1.73 m^2) and urinary albumin (<30 and ≥ 30 mg/L) values. In addition, stratified analyses by sex, age category (<65, ≥65 years), BMI category (<30, ≥30 kg/m^2), hypertension (no, yes), and controlled diabetes (no, yes) were also performed. Interactions were tested with the likelihood ratio tests, which involved comparing models with and without cross-product terms. Statistical significance was set to a p value < 0.05. The statistical software used was SPSS for Windows Version 27.0 (SPSS Statistics 27.0).

3. Results

A cohort of 186 participants were initially recruited from 4 PCCs. Of these, a total of 158 participants were randomized to the IG ($n = 64$) or CG ($n = 94$). During the study, 22 participants were lost to follow-up (IG: $n = 12$, CG: $n = 10$), reducing the final sample size to 136 participants −52 in the IG and 84 in the CG (Fig. 1).

The baseline characteristics of study participants by study group (IG and CG) are shown in Table 1. Both study groups exhibited similar sociodemographic characteristics and clinical conditions, with only sex and employment status presenting significant differences ($p < 0.05$) (Table 1).

Table 2 presents compliance with the intervention, assessed through changes from baseline to 9 months in total PA and by subcategories, including vigorous, moderate, and walking PA levels. After the 9-month intervention, significant differences emerged between the groups with the IG showing a substantial increase in both walking and total PA levels compared to the CG (between-group difference: 1840 METs/min/week, $p = 0.015$) (Table 2).

Table 3 presents the 9-month intervention effects on eGFR and urinary albumin levels for both the completers-only and modified intention-to-treat (mITT) analyses, as well as for renal subgroups based on baseline values of eGFR (<60 and ≥ 60 mL/min/1.73 m^2) and urinary albumin (<30 and ≥ 30 mg/L). Mean baseline eGFR values were comparable between groups. After 9 months, the completers-only adjusted analysis showed that eGFR increased by 1.8 mL/min/1.73 m^2 in the intervention group (IG) and declined by −3.4 mL/min/1.73 m^2 in the control group (CG), resulting in a significant mean between-group difference of 5.2 mL/min/1.73 m^2 (95% CI: 0.9 to 9.5; p = 0.019) after adjusting for potential confounders. These findings were consistent in the mITT analysis, with an adjusted between-group difference of 5.7 mL/min/1.73 m^2 (95% CI: 1.3 to 10.0; p = 0.011). The beneficial effect on eGFR was primarily observed among participants with baseline eGFR ≥60 mL/min/1.73 m^2, where significant between-group differences were detected in both completers-only (4.7 mL/min/1.73 m^2; 95% CI: 0.1 to 9.3; p = 0.047) and mITT analyses (5.2 mL/min/1.73 m^2; 95% CI: 0.6 to 9.8; p = 0.028). No significant changes in urinary albumin levels were observed in the overall population or after stratification by baseline albumin status in either analytical approach (Table 3).

Overall, the analyses stratified by sex, age, BMI, hypertension, and controlled diabetes consistently showed improvement in eGFR after 9

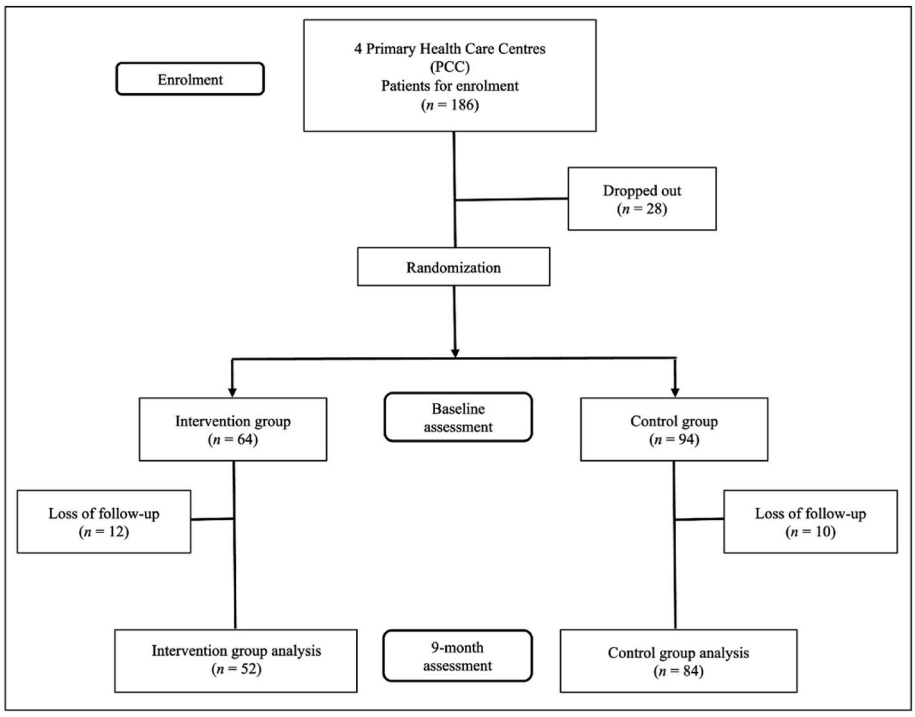


Fig. 1. Study flow diagram of participants.

months in favour of the IG (Fig. 2). Significant between-group differences in eGFR levels were observed particularly among women, participants under 65 years of age, and those with uncontrolled diabetes (all $p < 0.05$).

Data are means (95% CI). Abbreviations: eGFR, estimated glomerular filtration rate; IG, intervention group; CG, control group. *Linear regression models adjusted for corresponding baseline outcome values (eGFR or urinary albumin), age (years), sex, baseline BMI (kg/m^2), smoking status (no (ref.), yes), hypertension (no (ref.), yes), and controlled diabetes (no (ref.), yes). The diamonds represent means, and the whisker plots represent 95% CIs. The significance of the numbers in bold as p value < 0.05.

4. Discussion

This trial found that T2D individuals without a prior diagnosis of kidney disease who followed a 9-month combined moderate-to-vigorous intensity aerobic and resistance exercise programme experienced a significant improvement in eGFR compared to the control receiving usual care. Beyond statistical significance, this improvement is clinically relevant because even modest increases in eGFR in individuals with normal-to-mildly impaired kidney function may slow the decline in renal function, delay the onset of advanced CKD, and lower cardiovascular risk, which is highly prevalent in this population [4]. Despite these benefits in kidney function, urinary albumin levels remained unchanged between groups over the study period. From a public health perspective, these findings underscore the potential of structured exercise programmes as effective non-pharmacological strategy for kidney health preservation. Their integration into clinical guidelines and health policies could contribute to improved disease management and a reduction in the burden of kidney-related and cardiovascular complications in individuals with T2D.

Despite the predominance of observational studies suggesting the renal benefits of regular exercise [16,17], to our knowledge, only two short-term clinical trials have focused on exercise isolated interventions in people living with diabetes [19,21]. Although methodologically different from our study, their findings are consistent with ours. Focusing on eGFR, a quasi-experimental study by Nylen et al. [21], which had no control group, investigated the effects of a 12-week combined aerobic-resistance exercise program (60-min biweekly sessions) in people living with diabetes with CKD stages 1-3. The authors found significant improvements in eGFR, particularly among those with compromised baseline renal function—CKD stage 2 (eGFR 60-89 mL/min/1.73 m^2) and stage 3 (eGFR 30-59 mL/min/1.73 m^2)—with increases of 6% and 12%, respectively (both $p < 0.01$). Notably, 42% of CKD stage 3 participants reverted to stages 1 or 2 after the intervention. However, no significant association was found among those with normal-high renal function at baseline (eGFR $\geq$90 mL/min/1.73 m^2). While these findings are promising, the study's design limits the ability to establish causality.

In our study, we confirmed a beneficial effect of combining aerobic exercise with resistance training on kidney function for the full cohort, but to elucidate the effects of renal subgroups on such relation, we performed stratified analyses by eGFR at baseline. Interestingly, we found that our exercise programme protected against declines in kidney function, specifically for those with normal-mildly impaired eGFR (eGFR $\geq$60 mL/min/1.73 m^2), with a mean between-group difference in eGFR of 4.7 mL/min/1.73 m^2. Nonetheless, intervention benefits for eGFR were more pronounced in participants with moderately/severely impaired eGFR (eGFR $<$60 mL/min/1.73 m^2); however, the small sample size for this subgroup likely reduced the statistical power, limiting our ability to observe statistically significant results. Even so, this finding suggests that a combined exercise approach may help delay or prevent the progression to end-stage kidney disease in this high-risk population.

In addition, our other subgroup analysis stratified by sex, age, BMI, hypertension, and controlled diabetes revealed key insights regarding kidney function. A significant between-group difference for eGFR resulting from the combined training programme was found in women, but not in men. These sex disparities could potentially be attributed to exercise-induced hormonal differences, as higher PA levels increase testosterone in men while elevating oestradiol, the primary form of oestrogen, in women [28]. In fact, kidney pathophysiology seems to be influenced by sex hormones [29], with experimental studies indicating

Table 1
Baseline characteristics of study participants by study group.

	All (n = 136)	IG (n = 52)	CG (n = 84)	p value
Age (years), mean ± SD	66.9 ± 8.2	67.1 ± 6.7	66.8 ± 9.1	0.824
Age categories (years), n (%)				0.626
<65	54 (39.7)	22 (42.3)	32 (38.1)	
≥65	82 (60.3)	30 (57.7)	52 (61.9)	
Women, n (%)	74 (54.4)	35 (67.3)	39 (46.4)	0.018
Weight (kg), mean ± SD	81.5 ± 14.4	82.4 ± 14.7	80.9 ± 14.3	0.545
BMI (kg/m^2), mean ± SD	30.9 ± 5.0	31.4 ± 4.8	30.6 ± 5.1	0.321
BMI categories, n (%)				0.529
Normal weight	13 (9.6)	3 (5.8)	10 (11.9)	
Overweight	43 (31.6)	17 (32.7)	26 (31.0)	
Obesity	80 (58.8)	32 (61.5)	48 (57.1)	
Employment status, n (%)				0.007
Worker	17 (12.5)	1 (1.9)	16 (19.0)	
Unemployed/retired	101 (74.3)	41 (78.8)	60 (71.5)	
Incapacitated/permanently disabled/other	18 (13.3)	10 (19.2)	8 (9.6)	
Social class, n (%)				0.826
High class I-II	6 (4.4)	2 (3.8)	4 (4.8)	
Middle class IIIN-IIIM	63 (46.3)	16 (30.8)	47 (56.0)	
Lower class IV-V	25 (18.4)	6 (11.5)	19 (22.6)	
Missing	42 (30.9)	28 (53.8)	14 (16.7)	
Hypertension, n (%)				0.291
No	35 (25.7)	16 (30.8)	19 (22.6)	
Yes	101 (74.3)	36 (69.2)	65 (77.4)	
Dyslipidaemia, n (%)				0.614
No	44 (32.4)	16 (32.0)	28 (36.4)	
Yes	92 (67.6)	34 (68.0)	49 (63.6)	
Smoking, n (%)				0.246
No	120 (88.2)	48 (92.3)	72 (85.7)	
Yes	16 (11.8)	4 (7.7)	12 (14.3)	
Controlled diabetes, n (%)				0.553
No	82 (60.3)	33 (63.5)	49 (58.3)	
Yes	54 (39.7)	19 (36.5)	35 (41.7)	
REGICOR Cardiovascular risk score (point), mean ± SD	7.1 ± 3.3	6.9 ± 3.3	7.2 ± 3.4	0.713
Missing, n (%)	27 (20)	7 (13)	20 (24)	

Values are expressed in means ± SD (standard deviation) or number (%, percentage). Abbreviations: BMI, body mass index; REGICOR, cardiovascular risk calculator; IG, intervention group; CG, control group. P values for between-groups differences from Student's t-test or Chi-square test, as appropriate. The significance of the numbers in bold as p value < 0.05.

more severe kidney damage in males, as testosterone accelerates disease progression through glomerulosclerosis formation, whereas oestrogen provides protective effects in females [30]. Together, this could explain why the women in our study experienced greater improvements in eGFR in response to PA, suggesting that exercise may differentially reveal early kidney dysfunction between sexes. However, in diabetes, sex-related differences regarding kidney outcomes are complex, with some observational evidence suggesting higher kidney damage risk to men [31], while other studies indicate greater risk to women [32]. More interventional research is obviously needed with a strong focus on sexual dimorphisms in exercise-related kidney function decline responses, considering the influence of sex hormones.

In our study, age appears to influence kidney function, with younger participants (<65 years) showing greater benefits, contrary to previous studies suggesting greater improvements in older individuals. The lack of immediate eGFR improvements in this group could be attributed to age-related physiological changes, such as declining cardiovascular response and progressive muscle loss [33], potentially affecting renal metabolic activity. Further research is needed to clarify these effects and determine the most effective exercise modality across different age groups.

It is well established that poorly controlled diabetes, marked by persistent or frequent hyperglycaemia along with other metabolic imbalances, can lead to high filtration states in the glomerulus, causing not only glomerular injury but also tubulointerstitial damage, progressively contributing to renal failure in people living with diabetes [34]. Notably in our study, we observed greater eGFR improvements in the IG, particularly among patients with uncontrolled diabetes, possibly reflecting the benefits of improved glycaemic control.

Supporting our findings, multiple trials have demonstrated significant improvements in eGFR-based kidney function through intensive lifestyle interventions combining exercise (e.g. aerobic, resistance, or a combination of both) and diet [35,36]. For instance, the ReverseDiabetes2 programme reported significant increases in eGFR after just 6 months of a multicomponent lifestyle intervention in patients with T2D [36]. Similarly, a post hoc analysis of the Look AHEAD trial in overweight and obese adults with T2D reported improved eGFR-based kidney function following an 8-year intensive lifestyle intervention, compared to standard diabetes support and education (usual care) [35]. Our group has also contributed high-level evidence in this field [37,38]. In the large-scale PREvención con DIeta MEDiterránea-Plus (PREDIMED-Plus) multicentric trial, involving older obese adults with metabolic syndrome, we found that a 1-year intensive lifestyle intervention—combining an energy-restricted Mediterranean diet with physical exercise—significantly reduced the risk of eGFR-based CKD incidence and reversed existing CKD [37]. Furthermore, a recent analysis of the same cohort confirmed that these beneficial effects on kidney function were sustained after 3 years of intervention [38]. However, although prior research aligns with our study's findings, its multicomponent design, unlike our intervention, does not allow for discerning the renal benefits of exercise alone without diet modifications in diabetes.

Regarding proteinuria, we did not observe beneficial impacts of the PA intervention on reducing urinary albumin excretion, whether analysed as a full cohort or stratified by baseline levels of <30 mg/L and ≥30 mg/L. This aligns with findings by Nylen et al. [21] who reported no significant effect on albuminuria after a 12-week combined aerobic-resistance exercise programme [21]. However, a small (n = 30) 6-month trial of brisk walking-based moderate aerobic exercise (3-5 sessions/week, 45–60 min) reported that the prevalence of microalbuminuria tended to decrease during the follow-up period among overweight and obese men with T2D and microalbuminuria at baseline, compared to a healthy control group [19]. Nevertheless, the authors did not observe significant between-group or within-group differences in urinary albumin excretion.

It is noteworthy that some short-term studies in individuals with diabetes have reported immediate renal responses to exercise, with transient increases in microalbuminuria, particularly at higher intensities [13]. In line with this, a large cross-sectional study in adults without baseline microalbuminuria reported that exercise-induced albuminuria, assessed after a standardized acute exercise test (Bruce protocol), was more common among individuals with metabolic syndrome [39]. Extending these findings, Koh et al. (50) observed that

Table 2
Baseline and 9-month changes in physical activity by study group.

	Baseline		9-month change		Between-group difference (95% CI)*	p value
	IG (n = 52)	CG (n = 84)	IG (n = 52)	CG (n = 84)		
Physical activity level (METs/min/week), mean ± SD						
Vigorous	306 ± 1215	537 ± 2717	76 ± 2340	2 ± 2155	74 (−746 to 895)	0.857
Moderate	808 ± 938	1075 ± 2369	703 ± 1836†	257 ± 2066	445 (−283 to 1175)	0.229
Walking	2156 ± 2593	2571 ± 3003	1100 ± 1693†	−220 ± 2526	1320 (493 to 2146)	**0.002**
Total	3271 ± 3043	4184 ± 5652	1879 ± 3851†	39 ± 4101	1840 (364 to 3316)	**0.015**

Values are expressed in means ± SD (standard deviation) or number (%, percentage). *Data are means (95% CI). Abbreviations: METs, metabolic equivalents; IG, intervention group; CG, control group. *P* values for between-group differences from Student's t-test. The significance of the numbers in bold as p value < 0.05. †p value < 0.01 for within-group 9-month changes.

Table 3
Baseline and 1-year change in kidney function markers by group: completers-only and modified intention-to-treat (mITT).

Variable	Intervention group		Control group		Intervention *vs* control			
	Completers-only	mITT (MI)	Completers-only	mITT (MI)	Between-group difference (95% CI)			
					Completers-only	p value	mITT (MI)	p value
eGFR, ml/min/1.73m^2	(n = 52)	(n = 64)	(n = 84)	(n = 94)				
Baseline	80.6 (76.8 to 84.5)	80.8 (77.4 to 84.2)	80.0 (76.2 to 84.0)	80.5 (77.0 to 84.0)				
9-month change (unadjusted)	1.4 (−1.9 to 4.8)	1.9 (−1.6 to 5.4)	−3.2 (−5.8 to −0.5)	−3.3 (−5.88 to −0.6)	4.6 (0.3 to 8.9)	**0.036**	5.2 (0.8 to 9.6)	**0.020**
9-month change (adjusted)*	1.8 (−1.5 to 5.2)	2.2 (−1.3 to 5.7)	−3.4 (−6.0 to −0.8)	−3.4 (−6.0 to −0.9)	5.2 (0.9 to 9.5)	**0.019**	5.7 (1.3 to 10.0)	**0.011**
eGFR categories								
≥60 mL/min/1.73m^2	(n = 46)	(n = 57)	(n = 72)	(n = 82)				
Baseline	84.1 (81.1 to 87.1)	84.3 (81.6 to 86.9)	85.3 (82.4 to 88.3)	85.2 (82.5 to 87.9)				
9-month change (unadjusted)	0.1 (−2.5 to 2.6)	0.7 (−2.9 to 4.3)	−4.0 (−7.2 to −0.8)	−4.0 (−6.8 to −1.3)	4.0 (−0.4 to 8.5)	0.076	4.7 (−0.2 to 9.2)	**0.043**
9-month change (adjusted)*	0.4 (−3.1 to 4.0)	1.0 (−2.7 to 4.6)	−4.2 (−7.1 to −1.4)	−4.2 (−6.9 to −1.5)	4.7 (0.1 to 9.3)	**0.047**	5.2 (0.6 to 9.8)	**0.028**
<60 mL/min/1.73m^2	(n = 6)	(n = 7)	(n = 12)	(n = 12)				
Baseline	54.3 (47.5 to 61.0)	52.6 (46.7 to 58.5)	48.2 (43.9 to 52.5)	48.2 (44.1 to 52.3)				
9-month change (unadjusted)	12.1 (−5.8 to 30.0)	12.4 (2.3 to 22.4)	1.8 (−4.4 to 8.1)	1.9 (−5.3 to 9.0)	10.3 (−3.1 to 23.6)	0.123	10.5 (−2.8 to 23.8)	0.114
9-month change (adjusted)*	14.1 (−0.3 to 28.7)	14.31 (−4.03 to 24.58)	0.8 (−7.9 to 9.6)	0.7 (−5.7 to 7.0)	13.4 (−6.7 to 33.4)	0.165	13.6 (−2.6 to 29.9)	0.086
Urinary albumin, mg/L	(n = 40)	(n = 45)	(n = 66)	(n = 71)				
Baseline	15.6 (10.9 to 20.3)	17.9 (12.2 to 23.8)	23.1 (15.1 to 31.1)	22.6 (15.1 to 30.0)				
9-month change (unadjusted)	−1.2 (−10.4 to 8.0)	−2.2 (−11.8 to 7.5)	2.7 (−4.6 to 9.9)	3.5 (−3.5 to 10.5)	−3.8 (−15.5 to 7.8)	0.519	−5.7 (−17.5 to 6.1)	0.340
9-month change (adjusted)*	−1.1 (−10.0 to 7.7)	−0.8 (−10.2 to 8.5)	2.6 (−4.3 to 9.6)	2.7 (−4.0 to 9.3)	−3.7 (−15.3 to 7.8)	0.520	−3.5 (−15.2 to 8.2)	0.553
Urinary albumin categories								
<30 mg/L	(n = 33)	(n = 36)	(n = 50)	(n = 54)				
Baseline	10.0 (7.4 to 12.6)	9.9 (7.5 to 12.3)	9.4 (7.4 to 11.5)	9.2 (7.3 to 11.2)				
9-month change (unadjusted)	1.0 (−3.7 to 5.8)	0.3 (−7.9 to 8.8)	5.3 (−1.1 to 11.7)	5.9 (−0.0 to 11.9)	−4.3 (−12.9 to 4.3)	0.323	−5.7 (−15.9 to 4.5)	0.266
9-month change (adjusted)*	1.4 (−5.1 to 7.9)	1.5 (−6.5 to 9.6)	5.0 (−0.2 to 10.3)	5.2 (−0.8 to 11.1)	−3.6 (−12.2 to 5.0)	0.403	−3.6 (−13.9 to 6.7)	0.481
≥30 mg/L	(n = 7)	(n = 9)	(n = 16)	(n = 17)				
Baseline	41.9 (30.3 to 53.4)	50.3 (36.0 to 64.6)	66.0 (43.2 to 88.7)	64.9 (44.1 to 85.7)				
9-month change (unadjusted)	−10.9 (−28.8 to 7.1)	−12.1 (−44.9 to 20.7)	−5.5 (−38.2 to 27.1)	−4.3 (−27.5 to 18.8)	−5.3 (−53.5 to 42.9)	0.820	−7.8 (−49.8 to 34.2)	0.704
9-month change (adjusted)*	−7.1 (−61.2 to 47.0)	−8.2 (−48.7 to 32.4)	−7.4 (−39.6 to 25.0)	−6.5 (−32.0 to 19.0)	0.2 (−71.7 to 72.2)	0.994	−1.6 (−60.0 to 56.7)	0.952

Data are means (95% CI). Abbreviations: eGFR, estimated glomerular filtration rate; IG, intervention group; CG, control group; mITT = modified intention-to-treat; MI = multiple imputation. Linear regression models were used to calculate the β coefficient (β) and 95% confidence interval (95% CI). *Model adjusted for corresponding baseline outcome values (eGFR or urinary albumin), age (years), sex, baseline BMI (kg/m2), smoking status (no (ref.), yes), hypertension (no (ref.), yes), and controlled diabetes (no (ref.), yes). P values for between-groups differences from linear regression models. The significance of the numbers in bold as p value < 0.05.

normoalbuminuric adults with diabetes exhibited sex-specific responses: females, but not males, experienced a transient post-exercise rise in ACR into the microalbuminuric range (≈3.5 mg/mmol) 1 h after low-intensity exercise. Although values returned to baseline within 2 h and did not differ from first-morning samples, these results raise the possibility that exercise may unmask early diabetic nephropathy in a

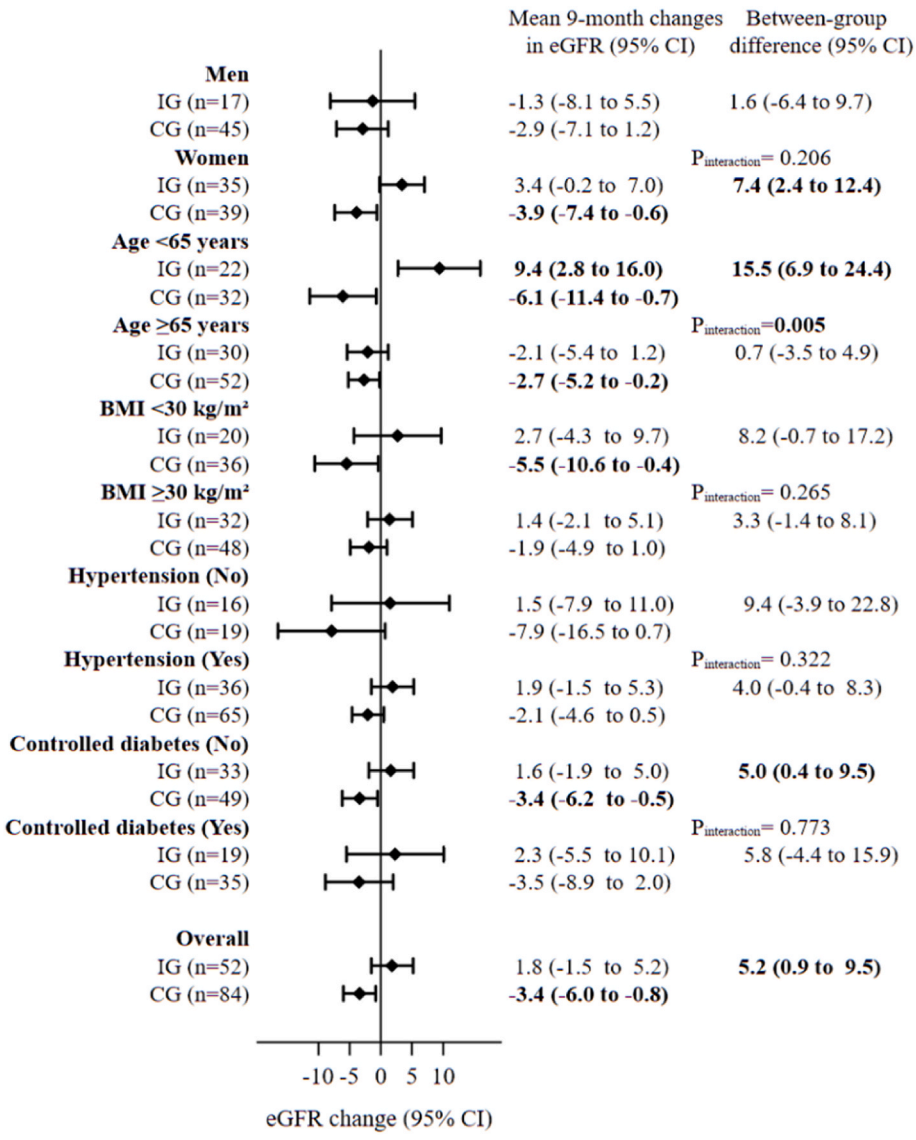


Fig. 2. Mean 9-month changes in eGFR-based kidney function (95% CI) in specific subgroups by study group.

sex-specific manner—this requires further study. Importantly, such acute elevations are likely to reflect transient hemodynamic and endothelial susceptibility rather than persistent renal injury, and therefore do not contradict our findings, which derive from fasting early-morning ACR measurements that capture chronic training adaptations. Together, these observations emphasize that urinary albumin is influenced by both exercise intensity (acute response) and intervention duration (training effects). Indeed, while acute studies demonstrate transient rises in albuminuria, evidence from longer-term research, including randomized trials [40] and prospective cohorts [16,18], indicates that meaningful reductions —and even normalization— of albuminuria often require at least 24 months of follow-up.

The preservation of eGFR observed in the intervention group is clinically meaningful, as even modest declines in eGFR are associated with increased risk of chronic kidney disease progression and cardiovascular morbidity [4,17]. In this study, the consistent between-group differences observed in both completers-only and mITT analyses suggest that structured combined aerobic and resistance training may help attenuate early renal function decline in people living with type 2 diabetes without established kidney disease. Given that participants had predominantly normal or mildly impaired kidney function at baseline, these findings support the role of exercise as an early preventive strategy rather than a treatment for advanced CKD. Integration of structured exercise programmes into primary care settings may therefore represent a feasible, non-pharmacological approach to preserving kidney function in this high-risk population, in line with current ADA and KDIGO recommendations [2,4].

In interpreting our findings, several important limitations need to be considered. Firstly, findings from a sample of Mediterranean Caucasian individuals with T2D may not be generalizable to other populations with diverse ethnic, geographic, and cultural backgrounds. In addition, our study examined changes in creatinine-based eGFR and urinary albumin levels at 9 months only and did not consider the longer-term effects. Urinary albumin analyses in participants with baseline albuminuria (≥30 mg/L) involved very small subgroups (IG: n = 7; CG: n = 16), resulting in wide confidence intervals and limited reliability, and these findings should be interpreted with caution. Furthermore, direct GFR measurement using a 'gold standard' exogenous filtration marker (e.g., inulin or iohexol) was not performed due to cost and time constraints, nor was serum cystatin C used as an alternative endogenous marker. Cystatin C may be more accurate than creatinine in estimating GFR, as it is less affected by nutritional factors and weight losses [41], which could have potentially impacted our findings. Finally, the 1:1.5 randomization ratio and modest final sample size may have limited the power to detect

differences in certain subgroups and so results involving smaller subgroups should be interpreted cautiously.

In summary, this 9-month intervention provides robust evidence of the potential benefits of combining moderate-to-vigorous intensity aerobic exercise and resistance training on kidney function in individuals with T2D. Future research should focus on larger, long-term studies to further validate and expand these findings regarding the impact of combined exercise on renal health.

Author contributions

Conceptualization, O.B., A. D-L., F.V., R.P., and V.A.; data curation, F.V., R.P., and V.A.; formal analysis, O.B., A. D-L.; writing—original draft preparation, O.B., and A. D-L.; writing—review and editing, O.B., A. D-L., and V.A.; supervision, F.V., R.P.; funding acquisition, R.P., V.A. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to subject confidentiality but are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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