10-2015

Enhanced fitness and renal function in Type 2 diabetes.

Eric S. Nylen
George Washington University

S. M. Gandhi
George Washington University

Raya E. Kheirbek
George Washington University

Peter Kokkinos
George Washington University

DOI: 10.1111/dme.12789

Short Report: Treatment

Enhanced fitness and renal function in Type 2 diabetes

E. S. Nylen[1,2], S. M. Gandhi[1,2], R. Kheirbek[3] and P. Kokkinos[4,5,6]

[1]Department of Endocrinology, Veterans Affairs Medical Center, [2]Department of Endocrinology, George Washington University School of Medicine and Health Sciences, [3]Departments of Geriatrics, [4]Cardiology, Veterans Affairs Medical Center, [5]Department of Cardiology, George Washington University School of Medicine and Health Sciences, and [6]Department of Cardiology, Georgetown University School of Medicine, Washington, DC, USA

Accepted 1 May 2015

Abstract

Aims To investigate the renal effects of fitness in people with diabetes with mild renal dysfunction.

Methods The effect of a 12-week exercise programme on estimated GFR in 128 people with diabetes was evaluated.

Results All cardiometabolic variables improved after 12 weeks of supervised exercise. Although there was a modest 3.9% increase in estimated GFR from baseline in the 128 people who completed the study, those with baseline chronic kidney disease stages 2 and 3 were found to have significant (6 and 12%, respectively; $p < 0.01$) improvements in post-exercise estimated GFR. Moreover, 42% of the people with chronic kidney disease stage 3 improved to chronic kidney disease stage 2 after the intervention.

Conclusion Short-term exercise improves renal function in those with more moderate baseline chronic kidney disease. Thus, renal function appears to be responsive to enhanced physical fitness. Being a strong and modifiable risk factor, enhanced fitness should be considered a non-pharmacological adjunct in the management of diabetic kidney disease.

Diabet. Med. 32, 1342–1345 (2015)

Introduction

Diabetes is the leading cause of chronic kidney disease and progression to end-stage renal disease, and estimated GFR (eGFR) is an independent predictor of death and cardiovascular events [1]. Approximately 40% of people with diabetes will develop chronic kidney disease. The vast majority of these people will have mild to moderate stages of chronic kidney disease based on eGFR (i.e. stages 1–3) [2], although they will also be significantly susceptible to cardiovascular disease [3]. Despite multifactorial diabetes treatment methods, the rate of chronic kidney disease is rising and end-stage renal disease rates continue to show a poor response to these treatments [4].

Cardiorespiratory fitness, as measured by exercise capacity, is a modifiable risk factor and a strong predictor of mortality in chronic illnesses, including Type 2 diabetes [5,6]. Although physical activity is the essential component for improving cardiorespiratory fitness [7], people with chronic kidney disease are known to have reduced physical function, low physical activity, increased muscle wasting and consequently have diminished exercise capacity [8]. Conflicting results, however, have been reported with regard to the role of exercise training in chronic kidney disease [9–12], which is perhaps related to the predominance of people with end-stage renal disease in interventional studies [13]. Despite the paucity of information on the milder stages of chronic kidney disease, eGFR correlates with physical activity and exercise capacity and can therefore serve as a guide to renal responsiveness [14].

The aim of the present study was to correlate exercise capacity to eGFR in response to a short-term interventional exercise programme in people with Type 2 diabetes.

Correspondence to: Eric Nylen. E-mail: enylen@gmail.com

Methods

Exercise cohort

A total of 128 people with Type 2 diabetes were enrolled in a supervised exercise programme for 12 weeks. The exclusion criteria included failure to pass an exercise tolerance test, a major illness in the last 6 months (myocardial infarction, congestive heart failure, stroke, pneumonia or acute kidney disease) or HbA_{1c} level > 9% (> 75 mmol/mol).

Exercise programme

After providing signed consent, the patients were given comprehensive nutritional and physical activity guidance. The biweekly exercise sessions were supervised by a trained exercise physiologist and consisted of a 1-h session that

included warm-up and cool-down and 30 min of combined aerobic and resistance training at an exercise intensity of 50–80% of heart rate reserve. The patients were also encouraged to be physically active during the rest of the week. Baseline and post-exercise data included BMI, systolic and diastolic blood pressure (mmHg), HbA_{1c} (mmol/mol and %), creatinine (μmol/l) and urinary albuminuria (mg/g creatinine). Capillary glucose was obtained before and immediately after each exercise session. Diabetes and other medication adjustments were unchanged during the 12-week period, unless clinically indicated.

Statistical analysis

The pre- and post-exercise responses were analysed using the paired *t*-statistic. All 128 patients participated in a minimum of 15 supervised sessions for 12 consecutive weeks. All hypotheses were two-sided and *P* values < 0.05 were taken to indicate statistical significance. All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc.).

Results

A total of 128 people with Type 2 diabetes were recruited and completed the exercise programme. The majority were black (79%) and male (95%), and their mean ± SD age was 62 ± 2.1 years. The change in eGFR from baseline using the 'CKD-EPI' formula [15] in the entire cohort was 3.9% (mean ± sd eGFR at baseline: 76.1 ± 21.9 ml/min/1.73 m^2; after exercise programme: 79.1 ± 19.7 ml/min/1.73 m^2). The patients were then classified into three groups based on baseline eGFR: group 1 included patients with eGFR > 89 ml/min/1.73 m^2 (n = 38), group 2 included patients with eGFR 60–89 ml/min/1.73 m^2 (n = 53) and group 3 included patients with chronic kidney disease stage 3 with eGFR 30–59 ml/min/1.73 m^2 (n = 37). Those with chronic kidney disease stage 3 were slightly older (age 63.8 ± 7.2 years compared with 62.0 ± 2.1 and 62.5 ± 7.4 years in the groups with chronic kidney disease stages 1 and 2, respectively) and had a longer duration of diabetes (8.9 ± 9.2 years compared with 7.5 ± 2.8 and 5.9 ± 6.8 years in the groups with chronic kidney disease 1 and 2, respectively). Exercise for 12 weeks resulted in improved trends in all cardiometabolic variables as shown in Table 1. Notably, there was a significant improvement in metabolic equivalents in all three groups ($P < 0.001$); HbA_{1c} levels were significantly lower in those with chronic kidney disease stages 1 and 3 ($P < 0.001$); and plasma glucose levels were significantly improved in the chronic kidney disease stage 1 group ($P = 0.001$). After the exercise programme, there was no significant change in eGFR in those with chronic kidney disease stage 1. By contrast, for patients in the chronic kidney disease stages 2 and 3 groups, there was a significant and gradual improvement in eGFR (improvements of 6 and 12%, respectively; $P = 0.003$ and $P = 0.0007$). Interestingly, 42% of the people with chronic kidney disease stage 3 improved to chronic kidney disease 1 or 2 (n = 16) after the intervention.

Discussion

The present study shows that renal function is responsive to the level of fitness as measured by exercise capacity. As kidney function plays a central role in diabetes morbidity and mortality, these results may be of clinical significance.

The present study showed that supervised physical activity for 12 weeks had a positive impact on all cardiometabolic variables including renal function. More specifically, a significant improvement in eGFR was seen in those patients with a compromised baseline renal function, i.e. those with chronic kidney disease stages 2 and 3; 42% of the latter group reverted to chronic kidney disease stage 1 or 2. Exercise had less of an impact, therefore, in those with a normal baseline eGFR, which could reflect the inaccuracy of

Table 1 Cardiometabolic response to exercise

	Chronic kidney disease stage 1 (n = 38)		Chronic kidney disease stage 2 (n = 53)		Chronic kidney disease stage 3 (n = 37)	
	Before exercise	After exercise	Before exercise	After exercise	Before exercise	After exercise
METs	8.7 ± 2	10.2 ± 2.4*	8.4 ± 0.3	10.0 ± 2.4*	6.9 ± 1.6	8.4 ± 2.3*
Weight, kg	101.3 ± 16.7	99.6 ± 14.0	101.7 ± 16.5	99.4 ± 14.5	102.7 ± 17.2	101.7 ± 17.0
Systolic blood pressure	121.4 ± 14.6	116.1 ± 13.8	124.4 ± 15.4	121.2 ± 14.4	128 ± 15	124 ± 14
Diastolic blood pressure	71.4 ± 9.6	68.1 ± 9.7	72.9 ± 9.8	70.8 ± 11.4	71 ± 8	69 ± 8
HbA_{1c}, mmol/mol	61 ± 16	52 ± 10*	62 ± 19	57 ± 14	66 ± 21	56 ± 13*
HbA_{1c}, %	7.7 ± 1.5	6.9 ± 0.9*	7.8 ± 1.7	7.4 ± 1.3	8.2 ± 1.9	7.3 ± 1.2*
Glucose, mmol/l	7.65 ± 2.7	6.43 ± 1.7*	8.05 ± 2.9	7.10 ± 2.1	8.05 ± 3.1	7.49 ± 3.8
Creatinine, μmol/l	70.9 ± 15.3	67.9 ± 9.2	86.2 ± 16.0	86.9 ± 19.1	114.4 ± 25.9	106.8 ± 28.2
UAE†, mg/g	40.5 ± 87	32.9 ± 81	22.6 ± 36	16.7 ± 21	46.8 ± 35	31.8 ± 22
eGFR, ml/min/1.73 m^2	103.6 ± 11.2	100.6 ± 13.1	73.5 ± 6.9	78.3 ± 13.1	51.6 ± 8.7	58 ± 13.2

METs, metabolic equivalents; UAE, urinary albumin excretion.
*$P < 0.05$.
†Median and interquartile range (quartile 1 to 3).

Published 2015.

the formula for eGFR in those with closer to normal renal function, and/or the fact that these patients need a higher exercise dose to show a change.

We believe these results to be clinically relevant because exercise is a non-invasive and non-pharmaceutical treatment method that can be performed and adapted at an individual level. Indeed, the cumulative exercise dose in the present interventional study was less than the recommended 150 min/week [16]. Potentially, a similar amount of exercise could help those patients with progressive kidney disease not only to improve their kidney function but also to possibly prevent or delay the need for dialysis in the long term. As fitness is a modifiable risk factor in most patients, an appropriate exercise programme could be implemented for people at high risk of developing chronic kidney disease to prevent or at least attenuate the rate of progression. Indeed, a recent meta-analysis supports a multitude of benefits from physical activity of > 30 min/session for 3 days per week in patients with chronic kidney disease [11] although the majority of studies have been in those with more advanced stages of chronic kidney disease, including those receiving dialysis or who have undergone transplants [11–13]. To date, little research has been conducted in the majority of patients who have the pre-dialysis range of chronic kidney disease stages and who have significant cardiovascular disease risk [3] and the highest potential for comorbidity modulation. Moreover, there is a lack of exercise promotion in these patients [17]. Aerobic exercise in patients at the pre-dialysis stage has been shown to increase exercise capacity significantly, as measured by peak oxygen consumption ($VO_{2\ max}$) [9], exercise tolerance [9] and anaerobic threshold [9]. Moreover, in one study, there was a significant improvement in eGFR after 12 weeks of aerobic exercise in overweight patients with chronic kidney disease stages 3 and 4 [18].

The response of increased exercise capacity supports the likelihood that causal mechanism(s) may exist. The salutary response to exercise may be related to several factors. People with diabetes are known to exercise significantly less than the general population, and this is most likely compounded in those with diabetes and chronic kidney disease. Patients with chronic kidney disease have a 50–80% reduction in exercise capacity [19], a high degree of inactivity, muscle wasting, reduced muscle function and muscle weakness [10,11]. Other causal factors could be related to the kidney disease itself, such as endothelial dysfunction, oxidative stress, inflammation and dyslipidaemia [20]; for example, regular exercise affects structural and functional adaptations of the endothelial response to vasoconstrictors and vasodilators and exercise also has anti-inflammatory effects.

Strengths of the present study include its supervised exercise approach, which enhances individual guidance and compliance. Its limitations include not knowing the precise cause of chronic kidney disease and limitations inherent to the eGFR calculation; we used the CKD-EPI formula, considered by many to be the optimum method [15].

In summary, we show that a short-term interventional exercise programme improved eGFR in those with mild to moderate chronic kidney disease (stages 2 and 3). Because a moderate intensity exercise programme was effective in improving fitness, we suggest that exercise interventions for individuals at risk of chronic kidney disease and those with pre-clinical chronic kidney disease merit scrutiny in a randomized trial.

Acknowledgements

We thank the LIVe team: Monica Aiken, Katie Himmerick, Lauren Korshak, Irue Namata-Elangwe, Joseph Powell and Helen Sheriff of the Veterans Affairs Medical Center, Washington, DC, for their essential role in performing the exercise stress tests, nutritional and exercise counselling and assistance with data collection.

Competing interests

None declared.

References

1 Go AS, Glenn M, Fan D, McCulloch CE, Hsu CY. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
2 De Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011; **305**: 2532–2539.
3 Papademetriou V, Lovato L, Doumas M, Nylen E, Mottl A, Cohen RM *et al.* Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* 2015; **87**: 649–659.
4 Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D *et al.* Changes in Diabetes-Related Complications in the United States, 1990–2010. *N Engl J Med* 2014; **370**: 1514–1523.
5 Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; **346**: 793–801.
6 Kokkinos P, Myers J, Nylen E, Panagiotakos DB, Manolis A, Pittaras A *et al.* Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. *Diabetes Care* 2009; **32**: 623–628.
7 Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J *et al.* Familial aggregation of VO2 max response to exercise training: Results from the HERITAGE family study. *J Appl Physiol* 1999; **87**: 1003–1008.
8 Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010; **91**: 1128S–1132S.
9 Boyce ML, Robergs RA, Avasthi PS, Roldan C, Foster A, Montner P *et al.* Exercise training by individuals with predialysis renal failure: Cardiorespiratory endurance, hypertension, and renal function. *Am J Kidney Dis* 1997; **30**: 180–192.
10 Eidemak I, Haaber AB, Feldt-Rasmussen B, Kanstrup IL, Strandgaard S. Exercise training and the progression of chronic renal failure. *Nephron* 1997; **75**: 36–40.

11 Heiwe S, Jacobson SH. Exercise Training in Adults With CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis* 2014; **3**: 383–393.
12 Robinson-Cohen C, Littman AJ, Duncan GE. Physical activity and change in estimated GFR among persons with CKD. *J Am Soc Nephrol* 2014; **25**: 399–406.
13 Gould DW, Graham-Brown MPM, Watson EL, Viana JL, Smith AC. Physiological benefits of exercise in pre-dialysis chronic kidney disease. *Nephrology* 2014; **9**: 519–527.
14 Hawkins MS, Sevick MA, Richardson CR, Fried LF, Arena VC, Kriska AM. Association between physical activity and kidney function: National Health and Nutrition Examination Survey. *Med Sci Sport Exerc* 2011; **43**: 1457–1464.
15 Levey AS, Stevens LA. The CKD-Epidemiological Collaboration (CKD-EPI) creatinine equation; estimating GFR using more accurate GFR estimates, lower CKD prevalence, and better risk predictions. *Am J Kid Dis* 2010; **55**: 622–627.
16 Kidney Disease: Improving Global outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kid Int* 2013; **3** (Suppl.): 1–150.
17 Delgado C, Johansen KL. Deficient counseling on physical activity among nephrologists. *Nephron Clin Pract* 2010; **116**: c330–c336.
18 Baria F, Kamimura MA, Aoike DT, Ammirati A, Rocha ML, de Mello MT *et al*. Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients. *Nephrol Dial Transplant* 2014; **29**: 857–864.
19 Johansen KL, Painter P. Exercise in individuals with CKD. *Am J Kid Dis* 2012; **59**: 126–134.
20 Van Craenenbroeck AH, Van Craenenbroeck EM, Kouidi E, Vrints CJ, Couttenye MM, Conraads VM. Vascular Effects of Exercise Training in CKD: Current Evidence and Pathophysiological Mechanisms. *Clin J Am Soc Nephrol* 2014; **9**: 1305–1318.

Published 2015.