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ARTICLE

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Influence of Pro^{12}Ala peroxisome proliferator-activated receptor γ2 polymorphism on glucose response to exercise training in type 2 diabetes

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Abstract *Aims/hypothesis:* Exercise training improves glycaemic control in some but not all individuals and little research has been done regarding genetic impact on the exercise training response in type 2 diabetes. The purpose of this study was to investigate the influence of the Pro^{12}Ala variant of the peroxisome proliferator-activated receptor (PPAR) γ2 gene on changes in fasting plasma glucose in response to exercise training. *Methods:* The study population comprised 139 sedentary type 2 diabetic patients (age: 54.4±7.2; HbA_1c: 7.7±0.9%) who completed 3 months of supervised exercise training. The primary outcome variable in our analysis was the post-intervention change in blood glucose. Other assessments included measures of body composition, insulin sensitivity indices and maximal oxygen uptake (VO_{2max}). *Results:* The frequency of the Ala allele was 8.3% and the genotypes were in Hardy–Weinberg equilibrium. At baseline, neither body composition variables (weight, BMI, waist circumference), glucose homeostasis variables (glucose, insulin, HbA_1c, homeostasis model assessment method) nor VO_{2max} were different between genotypes (wild-type: Pro^{12}Pro n=117, Ala carriers: X^{12}Ala n=22). The exercise-training intervention led to similar improvements in body composition and glucose homeostasis variables in both genotype groups ($p<0.05$). The change in fasting plasma glucose was significantly different between PPARγ2 genotypes (−1.66 mmol/l vs −0.54 mmol/l, Ala carriers and wild-type, respectively) (p=0.034 unadjusted and p=0.089 including baseline glucose) and the significant association between genotype and glucose response remained after adjusting for statistically significant predictors (age, changes in insulin and BMI [p=0.015]) and including baseline glucose, insulin and BMI (p= 0.031). *Conclusions/interpretation:* These data suggest that the Pro^{12}Ala polymorphism may influence the glycaemic response to exercise in type 2 diabetes.

Keywords Exercise training · Gene–environment interaction · Glucose · Peroxisome proliferator-activated receptor γ · Type 2 diabetes

Abbreviations DARE: Diabetes Aerobic & Resistance Exercise (study) · HOMA: homeostasis model assessment · PPAR: peroxisome proliferator-activated receptor · SNP: single nucleotide polymorphism · VO_{2max}: maximal oxygen uptake

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Introduction

Type 2 diabetes is a multi-factorial disease with strong genetic–environmental interactions, and lifestyle-related factors such as physical activity and diet are important determinants of the risk of complications [1]. Achievement of optimal glycaemic control is the focus of traditional treatment. Regular exercise, both aerobic and resistance

training [2–4], results in increased glucose uptake and insulin sensitivity [5, 6] and is a primary modality used in the treatment of type 2 diabetic patients [7–9]. As with pharmaceutical treatment, large inter-individual responses are observed in exercise training, and are hypothesised to be dependent on genetic background [10]. In other words, genetic factors could regulate the sensitivity of glucose to environmental stimuli.

The peroxisome proliferator-activated receptor (PPAR)γ is a nuclear transcription factor located at 3p25, a region showing evidence for linkage with diabetes and obesity [11]. In addition, the instrumental role PPARγ plays in adipocyte differentiation and the discovery that the insulin-sensitising thiazolidinedione drugs are potent ligands for the PPARγ gene [12, 13] have made it a popular candidate gene for obesity and diabetes [14, 15]. There are four isoforms of the PPARγ gene, differing by their transcription start site and splicing. The PPARγ2 isoform, containing a unique N-terminus domain encoded by exon B, is suggested to be the most important regulator of adipocyte differentiation and energy storage [16].

The most frequent and well-documented single nucleotide polymorphism (SNP) in the PPARγ gene is a proline to alanine ($Pro^{12}Ala$) substitution in exon B. This $Pro^{12}Ala$ SNP has been associated with reduced transcriptional activity in vitro [17]. Discordant results have been reported in the literature [17–23]; however, a recent meta-analyses of 16 studies, which included over 3,000 individuals, demonstrated that the Ala allele confers protection from diabetes (21% risk reduction) [24, 25]. It is possible that the environment, particularly diet or exercise habits, could modify the genotype effect and may account for a portion of the disparity found between separate studies. It has been proposed that PPARγ2 is one of the mediators of gene–environment interactions and several groups have shown interactions between the $Pro^{12}Ala$ genotype and dietary fat intake [26, 27] or exercise-related phenotypes [28–31]. None of these studies addressed the possible PPARγ2 $Pro^{12}Ala$ genotype–glucose response interaction prospectively, using a closely monitored exercise intervention in a population of type 2 diabetic patients, as presented here.

Subjects and methods

Subjects Type 2 diabetic subjects included in the present genetic study provided informed written consent to the protocols, which were approved by the Ottawa Hospital Research Ethics Board, and completed 3 months of supervised exercise-training intervention as part of the Diabetes Aerobic & Resistance Exercise (DARE) study (Sigal et al., study in progress). The study cohort includes previously sedentary Caucasian patients aged 40–70 years with type 2 diabetes as defined by the 1997 Expert Committee [32], treated with or without oral agents, but not with insulin, and with HbA_1c between 6.6 and 9.9%. To be included in the present analysis, subjects had to specifically consent to genetic analyses and patients were ineligible if they were being treated with insulin, had participated in regular physical activity more than twice per week in the past 6 months, had significant renal disease (serum creatinine >20 μmol/l), proteinuria (>1 g/24 h), uncontrolled hypertension (BP>160/100 mmHg), unstable cardiovascular disease or other illnesses precluding exercise participation. The average duration of diabetes for participants in this study was 7.6±4.3 years.

Exercise training Prior to randomisation, subjects underwent a run-in period lasting 4 weeks designed to familiarise them with the aerobic and resistance exercise programmes and assess exercise compliance. Only subjects attending at least ten of the 12 supervised exercise sessions in this phase were allowed to continue in the study. A total of 16 individuals dropped out of the exercise study. Participants randomised to the exercise arms of the trial trained 3 days/week at YMCA health clubs in the Ottawa region under the supervision of personal trainers. All exercise-training sessions began and concluded with 5–10 min of stretching/warm-up and cool-down exercises. Subjects randomised to aerobic exercise progressed in their training regime to reach the optimal goal of 45 min of treadmill or stationary bicycle exercise at 75% of their predetermined maximum heart rate. Those randomised to resistance exercise progressed to two or three sets of eight repetitions of eight weight machine exercises, at the maximum weight that could be lifted eight times. Those randomised to aerobic and resistance exercise combined performed both the aerobic exercise and the resistance exercise regimens as described above. Although aerobic training is the traditionally recommended type of exercise, resistance training has also been shown to improve insulin sensitivity [2, 3] and to increase non-oxidative glucose disposal [4], hence for this genetic study the three exercise groups were pooled.

Baseline measurements Anthropometric measurements of height, weight and waist circumference as well as maximal oxygen uptake (VO_{2max}) (maximal cardiopulmonary stress test on a treadmill) were measured at baseline and at subsequent follow-up visits. Waist circumference was measured at the midpoint between the lower-most rib and the top of the iliac crest. Blood was drawn for complete blood count, HbA_1c, fasting plasma glucose and insulin. Insulin sensitivity was estimated using the homeostasis model assessment (HOMA) formula, fasting plasma glucose (mmol/l) × insulin (μU/l)/22.5 [33], which estimates insulin resistance using fasting serum glucose and serum insulin concentrations. Although not a direct measure of insulin-dependent glucose utilisation, it has been validated against the euglycaemic–hyperinsulinaemic clamp [34].

Genotyping Genomic DNA was extracted from blood leucocytes (Qiagen FlexiGene; Qiagen Canada, Mississauga, ON, Canada). The $Pro^{12}Ala$ variant was detected by restriction fragment length polymorphism with *Bst*U-1 using primers designed by Yen et al. [35]. The PCR conditions for this experiment were optimised as follows: initial denaturation at 95°C for 5 min, followed by 30

cycles of denaturation at 95°C for 1 min, annealing at 59°C for 1 min and extension at 72°C for 1 min, with a final extension of 10 min at 72°C. The products were digested with *Bst*U-1 at 60°C for 1 h and then electrophoresed on a 3% agarose gel stained with ethidium bromide. This digestion produces fragments of 270 bp for the Pro^{12}Pro wild-type, 270, 227 and 43 bp for the Pro^{12}Ala heterozygote and 227 and 43 bp for the Ala^{12}Ala homozygous mutant.

Statistical analyses Hardy–Weinberg equilibrium was tested using chi square with 1 *df*. Between- and within-genotype differences in measured variables at baseline and after exercise intervention were analysed using regression analyses unadjusted and adjusted for the baseline values. All change variables were calculated as the post-intervention value minus the baseline value. Multiple linear regression analysis was used to evaluate whether or not the association between Pro^{12}Ala genotype and change in glucose was still present after adjusting for other variables associated with glucose change, with and without the baseline values. We considered multiple potential predictors of glycaemic response: genotype, change in plasma insulin, change in waist circumference, weight or BMI, as well as age, sex and compliance and their various interactions. The statistically significant predictors used in the final models are shown in Tables 3 and 4. Two-sided Fisher's exact tests were used to analyse differences between genotype groups with medications.

Significance levels were accepted at $p \leq 0.05$ for the univariate or $p \leq 0.1$ for the multiple regression analyses. Statistical analyses were performed using SAS version 8.0 or 8.2 (SAS Institute, Cary, NC, USA).

Results

Genotype frequency and baseline data In the 139 type 2 diabetic patients who completed 3 months of exercise training and consented to the genetic study, 16% carried at least one Ala allele. Genotypes were in Hardy–Weinberg equilibrium (wild-type, 84%; heterozygous, 15%; homozygous mutant, 0.7%, χ^2=9.6, p=0.08). The allelic frequency of the Ala allele (0.083) in our diabetic population is less than that reported for non-diabetic Caucasian populations (0.12) [17, 36], albeit not quite significantly different (p=0.064). There was only one Ala/Ala homozygote and hence this individual was included as an Ala carrier for subsequent calculations. Ala carriers and wild-type individuals had similar anthropometrics and glucose homeostasis variables at baseline (Table 1). There were no statistically significant differences between genotype groups with respect to oral hypoglycaemic medication (65 vs 78%, p=0.33), glucose-lowering sulphonylurea medication (50 vs 65%, p=0.26), alpha-glucosidase inhibitors (3 vs 0%, p=1.00), thiazolidinedione medication (24 vs 26%, p=1.00), fibrate therapy (12 vs 22%, p=0.20), ACE inhibitors (46 vs 48%, p=1.00), angiotensin II receptor antagonists (6 vs 9%, p=0.65) or β-blockers (7 vs 9%, p=0.68).

Table 1 Comparison of baseline characteristics by PPARγ2 genotype group

	Pro/Pro (n=117)	X/Ala (n=22)
Age (years)	53.7±0.7	55.4±1.5
Sex (male/female)	78/39	14/8
Weight (kg)	97.5±1.8	103.6±3.9
BMI (kg/m^2)	33.5±0.6	34.9±1.1
Waist circumference (cm)	110.2±1.5	112.5±2.4
Fasting plasma glucose (mmol/l)	9.5±0.2	10.1±0.5
Fasting plasma insulin (pmol/l)	105.2±5.73	106.1±10.4
$HOMA_{score}$	6.4±0.4	6.8±0.8
HbA_1c (%)	7.7±0.1	7.7±0.2
VO_{2max} (ml·kg^{-1}·min^{-1})	23.0±0.4	20.6±0.9

Pro^{12}Ala and Ala^{12}Ala are grouped together as X/Ala. Data are means±SE

Pro^{12}Ala polymorphism association with glucose homeostasis and body composition variables after exercise intervention Table 2 shows that after 3 months of exercise training intervention, both Pro^{12}Pro (wild-type) and X^{12}Ala (Ala carriers) groups saw significant improvement in the glucose homeostasis indices, glucose, insulin, HbA_1c and $HOMA_{score}$ (p<0.05). Similarly the body composition variables of weight, waist circumference and BMI improved over baseline in both genotype groups (p<0.05) and there were no differences in compliance to the exercise-training programme as measured by attendance at the exercise sessions (86.2±1.63 vs 87.0±3.3%, p=0.82). Although all glucose homeostasis variables (insulin, HOMA and HbA_1c) showed a trend towards greater improvement in Ala carriers, the only variable whose change significantly differed between PPARγ2 genotypes following the ex-

Table 2 Change from baseline in glucose homeostasis and body composition variables split by PPARγ2 genotype

	Pro/Pro	X/Ala
Glucose homeostasis variables		
Fasting plasma glucose (mmol/l)	−0.54±0.20*	−1.66±0.44*,†
HbA_1c (%)	−0.27±0.09*	−0.53±0.20*
Fasting plasma insulin (pmol/l)	−12.91±4.08*	−15.4±6.96*
$HOMA_{score}$	−0.86±0.32*	−2.02±0.70*
Body composition variables		
Weight (kg)	−1.65±0.32*	−1.33±0.54*
BMI (kg/m^2)	−0.56±0.11*	−0.46±0.17*
Waist circumference (cm)	−2.47±0.43*	−1.51±0.54*

The change values were calculated as post-intervention minus baseline values. Pro^{12}Ala and Ala^{12}Ala grouped together as X/Ala. Data are means±SE

*p<0.05, significant from baseline within genotype, †p=0.034, R^2=3.5%, n=131 unadjusted and p=0.089, R^2=27.9%, n=131 adjusted for baseline glucose, statistically significant difference across genotype group

Table 3 Adjusted effect of Pro^{12}Ala on glucose change

Effect	Coefficient ± SE	*p*
Pro^{12}Ala	−1.21±0.49	0.015
Age	0.06±0.02	0.027
Δ insulin	0.01±0.004	0.008
Δ BMI	0.30±0.16	0.072

R^2=15.7%, n=127

ercise training was fasting plasma glucose. Ala carriers showed a greater improvement in glycaemia (Ala carriers −1.66 vs wild-type −0.54 mmol/l, p=0.034 unadjusted and p=0.089 including baseline glucose) even though their change in body composition was consistently less favourable than in the wild-type (Table 2). Although Ala carriers showed a greater improvement in glucose in all three exercise-training groups, the numbers were too small for appropriate comparison. This significant association between genotype and glucose response remained after adjusting for the other significant predictors (age, changes in insulin and BMI [p=0.015]) and including the baseline glucose, insulin and BMI (p=0.031). Hence, the unadjusted and adjusted effects of genotype on fasting plasma glucose response were significant (Tables 2, 3 and 4).

Discussion

The control of blood glucose is a cornerstone in the treatment of type 2 diabetic patients. Physical activity, considered to be an integral component of diabetes management [7, 8], has been shown to be associated with improved glucose control and a reduction in long-term complications [37–39]. Similarly to others who have found the Ala to be less frequent in individuals with type 2 diabetes than controls [17, 24, 40], 16% of our type 2 diabetic population carried at least one Ala allele (vs 21% in non-diabetic cohorts [21, 26]), a frequency comparable with previous reports from diabetic populations [21]. In line with the meta-analysis published in 2003 [41], we did not find an association between the Ala allele and lower BMI. Probably due to the superseding lack of insulin sensitivity in the type 2 diabetic population, we did not find the Ala allele to be associated with improved insulin sensitivity at baseline as reported for a non-diabetic population [17, 31]. While we did observe that type 2 diabetic carriers of the PPARγ2 Ala allele demonstrated an improved glucose homeostasis profile over the wild-type, only fasting glucose exhibited a significantly greater reduction after the 3-month exercise-training intervention. Our data are strengthened by two other recent independent studies, albeit in healthy male populations, that have demonstrated that the Ala allele correlated with positive changes in insulin sensitivity following exercise training. Kahara et al. [42] reported decreased insulin resistance after 3 months of exercise training, at an intensity of 50% of maximal heart rate for 20–60 min, 2–3 days per week, in a population of 123 healthy (21–69 years), normal-glucose-tolerant Japanese men. However, the frequency of the Ala allele in this study population was very low, almost four times less than was found in our type 2 diabetic population and only six carriers were included in their analyses [42]. A second study looking at 73 sedentary, healthy individuals (50–75 years) who underwent 6 months of supervised aerobic training, 3 days/week for 40 min at 65–75% found that only male carriers (n=32) of the Ala allele were particularly responsive to the insulin-sensitising effect of endurance exercise training [31]. A few other studies have considered interactions between the Pro^{12}Ala genotype and exercise-related phenotypes. The Finnish Diabetes Prevention study, which included obese subjects (40–68 years) with impaired glucose tolerance given advice on physical activity [30], showed that the Ala allele may predispose to the development of type 2 diabetes. However, making beneficial changes to diet and physical activity may reverse this effect [30]. Franks et al. [29] suggested that the beneficial additive effects of physical activity and dietary polyunsaturated fatty acids on insulin sensitivity were restricted to the wild-type individuals. Although this study measured physical activity energy expenditure and looked for associations between the Pro^{12}Ala polymorphism, diet and physical activity, it was a cross-sectional study in non-diabetic individuals from the MRC Ely Study, which did not include an exercise intervention [29]. The only other study we are aware of on the association between PPARγ2 Pro^{12}Ala polymorphism and exercise response showed that the Ala allele is associated with a lower BMI in lean army recruits undergoing 10 weeks of training [28]. None of the above-mentioned studies examining Pro^{12}Ala genotype–exercise interaction focused on a population of type 2 diabetic patients whose response may differ due to their appreciable insensitivity to insulin.

In vitro, transfection studies have illustrated that the Ala variant is associated with reduced binding affinity to PPARγ response elements [17, 43] and reduced transcription of certain PPARγ-regulated genes (i.e. lipoprotein lipase, acyl-CoA oxidase) has been shown in cells overexpressing the Ala variant [43]. These studies suggest that individuals carrying the Ala allele have a constitutively reduced PPARγ transcriptional activity. A significant number of genes regulated by PPARγ2 are involved in NEFA metabolism [44–48] and it has been demonstrated that the Ala allele is associated with lower NEFA release during

Table 4 Adjusted effect of Pro^{12}Ala on glucose change including baseline variables

Effect	Coefficient ± SE	*p*
Baseline glucose	0.56±0.06	<0.001
Pro^{12}Ala	−0.91±0.42	0.031
Age	0.03±0.02	0.141
Δ insulin	0.01±0.004	<0.001
Baseline insulin	0.002±0.003	0.435
Δ BMI	0.36±0.14	0.014
Baseline BMI	0.04±0.03	0.138

R^2=47.3%, n=127

insulin stimulation in lean subjects [49, 50]. On a small subset of the type 2 diabetic population studied we observed the same trend: although non-significant, the mean NEFA concentration in the Ala carriers (n=6) was lower at baseline and after exercise intervention compared with wild-type (n=52). We therefore hypothesised that the reduced transcriptional activity for the Ala variant enhances the ability of insulin to suppress lipolysis in adipocytes, resulting in lower plasma NEFA concentrations. This reduced availability of NEFA allowed for glucose to be preferentially oxidised as a fuel source, which contributed to the greater glucose tolerance after exercise training. The lower lipolysis rates resulted in a smaller loss of body fat. Indeed, we observed a dramatic improvement in fasting glucose in Ala carriers in the absence of a significantly greater reduction in body weight. Accordingly, a group who compared lipid and carbohydrate oxidation in Ala carriers and Pro homozygotes has suggested that the mechanism by which the Ala allele improves insulin sensitivity might involve enhanced suppression of lipid oxidation permitting more efficient (predominantly non-oxidative) glucose disposal [51]. Furthermore, it was demonstrated that following a 6-month dietary intervention, post-menopausal women carrying the Ala allele were more insulin sensitive and had a greater increase in fasting carbohydrate oxidation and a greater decrease in fasting lipid oxidation than the wild-type with similar weight loss [52].

Exercise training and the Ala allele must act either independently or in unison to modify glucose homeostasis through increasing glucose uptake or by decreasing hepatic glucose output. At the whole-body level, exercise training has been shown to increase insulin sensitivity [53–55] and has also been shown to decrease basal hepatic glucose production in patients with type 2 diabetes [56]. At baseline, the association of the Ala allele with lower fasting glucose or insulin is inconsistent [31, 42, 49, 57, 58]. However, the Ala allele has been associated with more efficient insulin suppression of glucose production [57] as well as greater insulin clearance [59]. It has been proposed that carriers of the Ala allele have greater insulin sensitivity after embarking upon a physical activity regime [31, 42]. The findings in our population of type 2 diabetic patients support this hypothesis, as Ala carriers showed an improvement in fasting plasma glucose despite similar changes in fasting insulin.

The present study did not include a specific dietary intervention; all patients were given the same dietary advice by a dietician based on the Canadian Diabetes Association recommendations [60]. It has been suggested that dietary changes that correlate with exercise training [29] may be partly responsible for the better glucose tolerance observed in the Ala carriers. However, we would expect such dietary changes, possibly correlating with exercise training, to also result in a favourable change in body composition. Here, we have shown that Ala carriers displayed a less favourable change in body composition than the wild-type, suggesting that dietary fat modification does not predominantly account for the observed interaction.

In summary, the present study, conducted using a well-controlled, individualised exercise intervention, suggests that the PPARγ2 $Pro^{12}Ala$ SNP influences the fasting glucose response to exercise training in previously sedentary type 2 diabetic patients. These results, which need to be confirmed by other independent studies, suggest a possible benefit for tailored genotype-specific treatment interventions. More intensive treatment strategies may be required for type 2 diabetic patients who are wild-type (Pro/Pro) for the PPARγ2 locus.

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