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A Common Glu^{298}→Asp (894G→T) Mutation at Exon 7 of the Endothelial Nitric Oxide Synthase Gene and Vascular Complications in Type 2 Diabetes

Nitric oxide (NO) regulates endothelium-dependent vasodilatation and blood pressure, and reduced production has been implicated in hypertension, atherosclerosis, and diabetes (1–3). Endothelial constitutive nitric oxide synthase (ecNOS) mediates the oxidation of L-arginine to produce NO and determines basal vascular wall NO production (4). The gene encoding ecNOS is located on chromosome 7q35-36 and comprises 26 exons (5). To identify genetic markers relevant to NO-related vascular risk, we explored in 574 middle-aged Australian type 2 diabetic patients a possible role for a Glu^{298}→Asp mutation at exon 7 of the ecNOS gene; an association between the mutation and coronary risk was reported in the Cambridge Heart Anti-Oxidant Study (6). Patients recruited were those aged 62.4 ± 0.5 years (mean ± SEM), 329 men and 245 women, with and without documented macro- and microvascular complications. The genotype distribution was 7.5, 40.6, and 51.9% for TT, TG, and GG, respectively. It was in Hardy-Weinberg equilibrium ($\chi^2 = 0.088$, $P > 0.05$) and not different between men and women ($\chi^2 = 0.713$, $P = 0.700$). The ecNOS TT and TG genotypes were not associated with age, age at onset of documented diabetes, BMI, systolic and diastolic blood pressures (BPs), lipid profile, plasma creatinine and glycosylated hemoglobin (HbA_{1c}) levels, or urinary albumin index (UAI: albumin/creatinine ratio). Furthermore, as shown in Table 1, in χ^2 comparisons, the mutation was not associated with vascular events ($\chi^2 = 4.698$, $P = 0.095$ for angina pectoris; $\chi^2 = 1.100$, $P = 0.577$ for myocardial infarction; $\chi^2 = 0.181$, $P = 0.913$ for stroke; $\chi^2 = 1.414$, $P = 0.493$ for peripheral vascular disease; $\chi^2 = 2.372$, $P = 0.305$ for microalbuminuria; $\chi^2 = 1.434$, $P = 0.488$ for neuropathy; and $\chi^2 = 4.260$, $P = 0.119$ for retinopathy). In a logistic regression analysis, in which vascular events were entered as dependent variables and age, sex, BMI, current smoking status, systolic and diastolic BPs, total cholesterol, triglycerides, HDL cholesterol, HbA_{1c}, and UAI were entered as independent variables, the ecNOS TT and TG genotypes were still not predictive of the occurrence of vascular events.

In conclusion, we identified a 27.8% allele frequency of the Glu^{298}→Asp mutation at exon 7 of the ecNOS gene in type 2 diabetic patients, but in these patients the mutation was not associated with macro- or microvascular complications or with any of the traditional atherogenic risk factors.

Table 1—*Vascular complications and the ecNOS genotypes in type 2 diabetes*

	TT	TG	GG	*P* value
Angina pectoris				
Yes	11 (25.6)	40 (17.2)	40 (13.4)	0.095
No	33	192	258	
Myocardial infarction				
Yes	6 (14.0)	35 (15.1)	54 (18.1)	0.577
No	37	197	244	
Stroke				
Yes	1 (2.6)	7 (3.6)	10 (3.9)	0.913
No	38	187	245	
Peripheral vascular disease				
Yes	5 (12.8)	41 (21.1)	51 (20.0)	0.493
No	34	153	204	
Microalbuminuria				
Yes	7 (20.6)	44 (28.8)	65 (30.5)	0.305
No	27	109	148	
Retinopathy				
Yes	5 (20.8)	23 (16.8)	43 (26.7)	0.119
No	19	114	118	
Neuropathy				
Yes	8 (21.1)	46 (26.0)	49 (21.1)	0.488
No	30	131	183	

Data are *n* or *n* (%). *P* values refer to comparisons of the frequencies of the occurrence of vascular complications among the three ecNOS genotypes by χ^2 analysis.

HUA CAI, MBBS
XINGLI WANG, MBBS, PHD
STEPHEN COLAGIURI, MD, FRACP
DAVID E.L. WILCKEN, MD, FRCP, FRACP

From the Cardiovascular Genetics Laboratory (H.C., X.W., D.E.L.W.) and the Diabetes Centre (S.C.), Prince of Wales Hospital, Randwick, New South Wales, Australia.

Address correspondence to Prof. David E.L. Wilcken, Cardiovascular Genetics Laboratory, Ground Floor, South Wing, Edmund Blacket Building, Prince of Wales Hospital, Randwick, NSW, Australia, 2031. E-mail: d.wilcken@unsw.edu.au.

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Influence of a Physical Training Program on Psychological Well-Being in Elderly Type 2 Diabetes Patients

Psychological well-being, physical training, and type 2 diabetes

Physical activity is positively associated with mental health and psychological well-being, but so far only a few studies have investigated the association between physical activity and psychological factors in patients with diabetes (1,2). In a cross-sectional study in this group of patients, of whom the majority had type 2 diabetes, the level of physical activity turned out to be the only significant self-management behavior to predict quality of life (2). We were interested in the effects of a physical training program on psychological well-being in these patients. The present study was part of a prospective randomized trial to evaluate the effects of physical training on glycemic control and lipid profile in elderly obese type 2 diabetes patients (3). We hypothesized first that aerobic physical training results in an improved psychological well-being and second, that an improved psychological well-being is mediated by changes in the maximal aerobic capacity (Vo_{2max}).

There were 92 patients with type 2 diabetes who applied for the study. Of these, 58 enrolled and were randomized to either a physical training group (TG) (n = 30; aged 64.2 ± 5.4 years [mean ± SD]) or a control group (CG) (n = 28; aged 61.8 ± 5.4 years). There were 51 patients who completed the study. The training program consisted of an intensive supervised 6-week physical training period in which the patients exercised three times a week for 1 h, aiming at 60–80% of their Vo_{2max}. This period was followed by a 6-week guided home training period. The control group followed a diabetes education program during that time. In the 14-week follow-up phase, patients in the training group were advised to continue their home training, but without supervision. Psychological well-being was assessed by means of the 22-item self-administrated well-being questionnaire of Bradley and Lewis (4), which was completed at baseline, after 6 weeks of training, and at the end of the study. Items referring to physical symptoms possibly related to diabetes were excluded to obtain a pure estimate of the psychological domain of well-being. The scores of the questionnaire were determined by four subscales: depression, anxiety, energy, and positive well-being. A repeated measures analysis of variance with polynomial contrasts was used to determine differences in well-being. To test for Vo_{2max} as a mediator variable, regression analyses were performed according to Baron and Kenny (5).

At baseline, no differences between TG and CG were found with respect to age, BMI, duration of disease, sex, physical activity status, smoking habits, HbA_{1c}, Vo_{2max}, the total psychological well-being score, or the four subscales. After 6 weeks of training, a significant improvement was found in TG for total psychological well-being (baseline: 49.2 ± 11.2 [TG], 45.3 ± 14.4 [CG]; after 6 weeks: 54.8 ± 7.6 [TG], 46.9 ± 14.2 [CG]; F = 5.46, P = 0.023), anxiety (baseline: 5.0 ± 4.1 [TG], 5.3 ± 4.0 [CG]; after 6 weeks: 2.8 ± 3.2 [TG], 5.3 ± 4.3 [CG]; F = 7.80, P = 0.007), positive well-being (baseline: 13.9 ± 4.3 [TG], 11.5 ± 5.1 [CG]; after 6 weeks: 14.4 ± 3.1 [TG], 12.2 ± 4.7 [CG]; F = 6.37, P = 0.014), and energy (baseline: 8.0 ± 2.4 [TG], 7.9 ± 3.5 [CG]; after 6 weeks: 9.4 ± 2.1 [TG], 8.0 ± 3.0 [CG]; F = 4.88, P = 0.031). For depression, no significant difference was found. After 6 weeks of training, a significant difference in Vo_{2max} levels emerged between TG and CG ($P < 0.01$) and remained significant until the end of the study, although the scores of TG decreased (TG: 21.0 [prestudy], 22.0 [after 6 weeks], and 21.0 ml · kg^{-1} · min^{-1} [after 26 weeks]; CG: 20.8 [prestudy], 19.6 [after 6 weeks], and 18.2 ml · kg^{-1} · min^{-1} [after 26 weeks]). The Vo_{2max} difference score was used in the analysis as a mediator variable for total psychological well-being, but no mediation could be observed.

It is important to note that after the supervised period of 6 weeks, well-being scores returned to baseline levels. It is possible that changes in compliance with the training program caused the declining scores of Vo_{2max} and well-being at the follow-up measurements. Several factors can influence compliance with training programs, e.g., group participation, spouse support, and periodic testing. It is imaginable that the decreased support and attention for the training group during the unsupervised period caused the declining well-being scores. Another explanation may be that physical training benefits the physiological response to stress (6). The initial improvements in aerobic capacity coupled with the psychological well-being scores and the subsequent return to baseline values of both parameters seems to support this view. However, no statistical proof of direct influence of Vo_{2max} on improvement of quality of life could be obtained. Finally, a cognitive explanation for the stress-reducing effects of physical training can be given (7). Training may affect feelings of self-esteem, as a result of the mastering and the increased performance of challenging physical activities, and subsequently improve well-being. When the initially positive excitement and actual performance decline, the positive psychological effects may subside as well. Based on the results of the present study, it seems that feelings of well-being, presumably related to self-efficacy or self-esteem, are only positively affected by a training program when the participant's actual performance of the training activities is continued.

P. CHRISTINE LIGTENBERG, MD
GUIDO L.R. GODAERT, PHD
ED F. HILLENAAR, MSC
JOOST B.L. HOEKSTRA, MD, PHD

From the Department of Internal Medicine (P.C.L.), University Hospital Utrecht; the Department of Clinical and Health Psychology (G.L.R.G., E.F.H.), University of Utrecht; and the Department of Internal Medicine (J.B.L.H.), Diakonessen Hospital, Utrecht, the Netherlands.

Address correspondence to Christine P. Ligtenberg, University Hospital Utrecht, Dept. of Internal Medicine, Room G02.228, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: pligtenb@digd.azu.nl.