

**Leisure-Time Physical Activity Is Associated With the Metabolic Syndrome in Type 1 Diabetes; Effect of the *PPAR* $\gamma$  Pro12Ala Polymorphism (The FinnDiane Study).**

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The metabolic syndrome (MetS) varies in prevalence among different populations. A common feature, however, is a steep increase in the prevalence along with a decrease in glucose tolerance (1-2).

We have shown that 39% of adult type 1 diabetic patients have the MetS (3), and similar data was recently reported from Italy (4). However, whether the MetS observed in type 1 diabetes is the same as in non-diabetic and type 2 diabetic patients, is unclear.

Both lifestyle (5-8) and hereditary factors (9) seem to be involved in the development of the MetS in non-diabetic and type 2 diabetic subjects. The *PPAR* $\gamma$  (peroxisome proliferator-activated receptor gamma) Pro12Ala polymorphism has been associated with type 2 diabetes, the Ala-allele being associated with a lower risk (10); and with the MetS in some (11-12), but not all (13) studies. However, whether lifestyle or genetic factors play a role in the development and treatment of the MetS also in patients with type 1 diabetes is unknown.

Therefore, to further study the MetS in type 1 diabetes, we investigated whether physical activity and/or the *PPAR* $\gamma$  Pro12Ala polymorphism are associated with MetS in patients with type 1 diabetes in the Finnish Diabetic Nephropathy (FinnDiane) Study.

### Research Design and Methods

Using a cross-sectional study design, 1028 type 1 diabetic patients from the FinnDiane Study (3, 14) with data on leisure-time physical activity (LTPA) and MetS were studied. Patients with end-stage renal disease and/or cardiovascular events were excluded.

MetS was defined according to the NCEP ATP III criteria (15). LTPA (as

MET\*h/week) was assessed by a validated 12-month questionnaire (16), and patients were grouped as sedentary, moderately active and active as previously described (14). The *PPAR* $\gamma$  Pro12Ala (rs1801282) polymorphism was studied from 840 of the 1028 patients using an ABI Prism® 7900 Sequence Detection System (Applied Biosystems, Foster City, CA).

### Results

The mean ( $\pm$ SD) age was 36.4 $\pm$ 11.5 years, duration of diabetes 21.3 $\pm$ 11.7 years, HbA<sub>1c</sub> 8.4 $\pm$ 1.4%, BMI 25.0 $\pm$ 3.3 kg/m<sup>2</sup> and 47% were men. Median (interquartile range) LTPA was 19.7 (10.0-34.1) MET\*h/week. The prevalence of MetS was 29.5% (men:women 27.8%:31.0%, P=0.269). 31.8% had the Ala-allele for *PPAR* $\gamma$  Pro12Ala (2.6% were homozygous). According to genotype, there were no differences in BMI, waist-to-hip ratio, lipid profile or HbA<sub>1c</sub> (data not shown).

The prevalence of MetS did not differ by genotype (Pro12Pro 30.4%, Pro12Ala 30.6%, Ala12Ala 36.4%; P=0.836). LTPA in the presence vs. absence of MetS was 17.0 (8.6-31.6) vs. 20.8 (10.8-34.7) MET\*h/week (age-adjusted P=0.038). Table 1 shows prevalences of the MetS and its individual components according to LTPA and *PPAR* $\gamma$  genotype.

Among patients reporting LTPA of low vs. moderate vs. high intensity; 39.0% vs. 28.3% vs. 23.2% (age-adjusted P=0.008) had MetS. Regarding frequency of LTPA, corresponding prevalences for <1 vs. 1-2 vs.  $\geq$ 3 sessions/week were 33.0% vs. 29.9% vs. 27.7% (age-adjusted P=0.325), respectively.

In a multiple logistic regression model, LTPA as a log-transformed continuous variable (OR, 95%CI: 0.73, 0.58-0.92) and laser-treated retinopathy (1.97, 1.19-3.27) were independently associated with the MetS. The model also included *PPAR* $\gamma$  Pro12Pro genotype (0.99, 0.62-1.58), weekly doses (12g/dose) of alcohol (1.26, 0.98-1.60), male gender (0.98, 0.62-1.56), age (1.01, 0.99-1.03), low social class (1.09, 0.69-1.72), smoking (0.76, 0.45-1.30), and diabetic nephropathy (1.84, 0.92-3.68).

### Conclusions

Low LTPA was associated with a higher prevalence of the MetS, supporting our previous findings on LTPA and insulin sensitivity in type 1 diabetes (14). Due to the cross-sectional study design, LTPA could have been reduced by exercise-limiting factors associated with the MetS. However, the likelihood of complication-derived physical activity bias was reduced by controlling for diabetic complications.

The *PPAR* $\gamma$  Pro12Ala polymorphism was not associated with the MetS. Patients with the Ala-allele, however, had 2.4-fold higher prevalence of the MetS when sedentary patients were compared with physically active, while in patients with the Pro12Pro genotype, LTPA did not affect the prevalence of the MetS. Of individual criteria, waist circumference seemed important for this genotype-dependent association, favoring a pivotal role of insulin sensitivity, the key factor in the MetS (17).

Interestingly, the Ala-allele has been associated with greater exercise-

induced improvement of insulin sensitivity measures (18-19) in healthy individuals and reduction in fasting plasma glucose in type 2 diabetic patients (20). In the Finnish Diabetes Prevention (DPS) Study, a paradoxical diabetogenic effect of the Ala-allele in subjects with impaired glucose tolerance was eliminated by lifestyle intervention (21).

Based on the DPS and our study, the Ala-allele might be viewed upon as not being exclusively beneficial for insulin sensitivity and glucose homeostasis, because the Ala-allele, when combined with low physical activity, may on the contrary be detrimental. In our study, sedentary Ala-carriers had more frequently MetS than sedentary patients with Pro12Pro genotype. Thus, *PPAR* $\gamma$  Pro12Ala may be a true exercise-response gene variant working in both directions, promoting insulin sensitivity in physically active while impeding sensitivity in sedentary subjects.

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**Table 1.**

Proportion of type 1 diabetic patients (%) with the metabolic syndrome and its individual components (NCEP ATPIII) according to level of LTPA and genotype for *PPAR $\gamma$*  Pro12Ala. Ala-carriers: Pro12Ala or Ala12Ala genotype. Number of patients: all 1028, Pro12Pro 573, Ala-carriers 267. \* $\chi^2$  test, † $\chi^2$  test for trend.

		<b>Sedentary (N=254)</b>	<b>Moderately active (N=588)</b>	<b>Active (N=186)</b>	<b>P *</b>	<b>P †</b>
<b>Metabolic syndrome:</b>	All	35.0	28.4	25.3	0.058	0.021
	Pro12Pro	33.6	29.4	28.6	0.600	0.358
	Ala-carr.	43.8	29.6	18.2	0.015	0.004
<b>Individual components:</b>						
Waist	All	21.7	14.6	11.8	0.009	0.004
	Pro12Pro	19.1	14.2	12.4	0.266	0.121
	Ala-carr.	29.7	15.1	6.8	0.004	0.001
Triglycerides	All	16.1	12.6	11.3	0.259	0.120
	Pro12Pro	15.1	13.0	13.3	0.813	-
	Ala-carr.	15.6	9.4	2.3	0.070	0.021
HDL-cholesterol	All	26.8	25.0	25.3	0.861	-
	Pro12Pro	28.9	27.2	27.6	0.926	-
	Ala-carr.	31.3	24.5	27.3	0.586	-
Hypertension	All	66.5	60.2	60.8	0.209	-
	Pro12Pro	66.4	61.1	57.1	0.297	0.122
	Ala-carr.	73.4	59.1	65.9	0.125	-

NCEP ATPIII criteria: waist circumference >102 cm (men), >88 cm (women), triglycerides  $\geq$ 1.70 mmol/l, HDL-cholesterol <1.00 mmol/l (men), <1.30 mmol/l (women), and blood pressure  $\geq$ 130/85 mmHg or antihypertensive medication. All patients fulfilled the criteria for fasting blood glucose  $\geq$ 6.11 mmol/l. A minimum of three criteria were requested for diagnosis of the metabolic syndrome.