TABLE 1. Pathologically proven Japanese patients with multiple system atrophy

Demographic features	MSA with mean age at onset (n = 155)	Later-onset MSA (n = 10)	*P*
Age at onset, y	59.0 (53.0, 65.0)	77.5 (75.0, 80.8)	< 0.001
Sex, female, n (%)	68 (43.9%)	6 (60.0%)	0.505
Age at death, y	67.0 (62.0, 71.0)	81.0 (79.3, 83.8)	< 0.001
Disease duration, y	7.0 (4.8, 10.0)	4.0 (2.4, 4.7)	< 0.001
OPCA dominant, n (%)	49 (31.6%)	1 (10.0%)	0.277
SND dominant, n (%)	37 (23.9%)	8 (80.0%)	< 0.001
OPCA-SND mixed, n (%)	69 (44.5%)	1 (10.0%)	0.070

OPCA, olivopontocerebellar atrophy; MSA, multiple system atrophy; SND, striatonigral degeneration.
Data of age and duration are displayed as median (25th, 75th percentiles) or number (percentage).

and the retrospective nature and lack of detailed comorbidities of clinical cohorts.

In summary, our study suggests that the second consensus criteria for diagnosis of MSA needs to be revised with respect to the range of onset age of MSA.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Insulin Sensitivity in De Novo Parkinson's Disease: A Hyperinsulinemic-Euglycemic Clamp Study

A recent clinical trial found that exenatide, an antidiabetic drug, could slow down the rate of decline in motor performance in patients with Parkinson's disease (PD).[1] A higher prevalence of diabetes mellitus (DM) has been reported in PD patients,[2] whereas an increased incidence of PD was found in patients with DM.[3–5] Although these findings suggest that peripheral insulin resistance might be involved in PD pathogenesis,[6] systemic substrate metabolism and its responsiveness to insulin stimulation have not been rigorously assessed before in de novo, medication-free PD patients. Therefore, using the hyperinsulinemic-euglycemic clamp technique, the most accurate and precise method available for quantifying insulin sensitivity, we aimed to assess whether insulin resistance is an inherent feature of PD.

We performed a hyperinsulinemic-euglycemic clamp with stable isotopes ([6,6-$^2H_2$]-glucose and [$^2H_5$]- glycerol), as

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TABLE 1. Metabolic parameters in patients with PD and matched controls during basal and hyperinsulinemic steady-state conditions

	Basal Condition			Hyperinsulinemia		
	PD Patients	Controls	*P* Value	PD Patients	Controls	*P* Value
Glucose R_d (μmol/kg_{FFM}/min)	21.9 ± 0.5	21.0 ± 0.5	0.26	57.5 ± 8.5	48.0 ± 4.9	0.35
EGP (μmol/kg_{FFM}/min)[aa]	21.9 ± 0.5	21.0 ± 0.5	0.26	14.4 ± 1.6	12.3 ± 1.0	0.30
HIR (μmol kg_{FFM}/min/pmol × L)	481 ± 23	444 ± 21	0.26	3,829 ± 227	3,020 ± 265	0.04**
Glycerol R_a (μmol/kg_{FM}/min)	7.6 ± 0.7	8.0 ± 0.8	0.66	2.5 ± 0.2	2.6 ± 0.3	0.87
Plasma insulin (mU/L)	3.1 ± 1.4	2.1 ± 0.7	0.47	40.5 ± 3.7	35.8 ± 2.7	0.32
MCR_I (mL/m^2/min)	—	—	—	1.1 ± 0.1	1.2 ± 0.1	0.26
Glucose (mmol/L)	5.5 ± 0.1	5.1 ± 0.3	0.20	5.8 ± 0. 1	5.3 ± 0.2	0.06
Glycerol (mmol/L)	68.4 ± 8.3	72.5 ± 9.5	0.75	19.3 ± 1.9	21.8 ± 3.9	0.59
HbA1c (%)	5.4 ± 0.1	5.4 ± 0.1	0.91	—	—	—
Triacylglycerol (mmol/L)	1.2 ± 0.2	1.2 ± 0.1	0.79	—	—	—
Total cholesterol (mmol/L)	5.9 ± 0.3	5.7 ± 0.3	0.68	—	—	—
TSH (mU/L)	2.2 ± 0.6	2.0 ± 0.1	0.81	—	—	—

Data are means ± SEM.
*$P < 0.05$.
[a]In basal, unstimulated conditions, the endogenous glucose production rate (EGP) equals the glucose disappearance rate (Glucose R_d).

EGP, endogenous glucose production; FFM, fat free mass; FM, fat mass; HIR, hepatic insulin resistance; MCR_I, metabolic clearance rate of insulin; R_a, rate of appearance; R_d, rate of disappearance; HbA1c, glycosylated hemoglobin; TSH, thyroid-stimulating hormone.

previously described,[7] to accurately quantify glucose and fat metabolism in 8 de novo, medication-free PD patients and 8 age-, sex-, fat-, and lean body mass–matched controls (Supporting Information Table S1). The diagnosis of PD was made by a movement disorders specialist (R.A.C.R.) according to the UK Parkinson's Disease Society Brain Bank criteria. The study was approved by the local ethics committee. Intergroup differences were assessed using the unpaired *t* test, with the significance threshold set at $P < 0.05$. Given the exploratory nature of the study, we did not apply multiple comparison adjustments. Data are presented as mean ± standard error.

During basal steady-state conditions, peripheral glucose disposal rate and endogenous glucose production rate were similar between PD patients and controls (21.9 ± 0.5 vs. 21.0 ± 0.5 μmol/$kg_{FatFreeMass(FFM)}$/min, respectively; $P = 0.26$). In PD and control subjects, insulin stimulation increased whole-body glucose disposal rate (57.5 ± 8.5 vs. 48.0 ± 4.9 μmol/kg_{FFM}/min; $P = 0.35$) and suppressed glucose production rate (14.4 ± 1.6 vs. 12.3 ± 1.0 μmol/kg_{FFM}/min; $P = 0.30$) to a similar extent, although with a slightly higher hepatic insulin resistance index in PD patients (3,829 ± 227 vs. 3,020 ± 265 μmol kg_{FFM}/min/pmol × L; $P = 0.04$; Table 1). Both plasma glycerol levels and its rate of appearance, a measure of lipolysis, were similar between the two groups, with a similar degree of suppression of lipolysis by hyperinsulinemia (Table 1).

We found that whole-body glucose disposal rate, the gold standard for quantification of peripheral insulin resistance, was remarkably similar between newly diagnosed, medication-free PD patients and age-, sex-, and body composition–matched controls. In addition, other physiological responses of systemic glucose and fat metabolism to insulin challenge were unaltered in PD patients. These findings thus indicate that PD is not associated with insulin resistance. Our results therefore also suggest that the putative neuroprotective action of antidiabetic drugs, including exenatide, may originate from their effect at the neuronal level rather than on systemic metabolism.[1] However, given the increased risk of developing PD and a more aggressive course of PD in those with DM,[3–5] it remains possible that treatment of the systemic metabolic disturbances in PD patients with hyperglycemia and insulin resistance may affect disease progression.

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Supporting Data

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