



Universiteit
Leiden
The Netherlands

Insulin sensitivity in De Novo Parkinson's disease: a hyperinsulinemic-euglycemic clamp study

Aziz, N.A.; Roos, R.A.C.; Pijl, H.

Citation

Aziz, N. A., Roos, R. A. C., & Pijl, H. (2020). Insulin sensitivity in De Novo Parkinson's disease: a hyperinsulinemic-euglycemic clamp study. *Movement Disorders*, 35(9), 1693-1694. doi:10.1002/mds.28181

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3181369>

Note: To cite this publication please use the final published version (if applicable).

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. ●

Yang Hyun Lee, MD,¹  Takashi Ando, MD,^{2,8}


Jae Jung Lee, MD,³  Min Seok Baek, MD,⁴

Chul Hyoung Lyoo, MD, PhD,⁴ Sang Jin Kim, MD, PhD,⁵

Minkyong Kim, MD,⁶ Jin Whan Cho, MD, PhD,⁶

Young H. Sohn, MD, PhD,¹ Masahisa Katsuno, MD, PhD,²

Hirohisa Watanabe, MD, PhD,⁷ Mari Yoshida, MD, PhD,^{8*}

and Phil Hyu Lee, MD, PhD^{1,9*} 

¹Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

²Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

³Department of Neurology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, South Korea

⁴Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

⁵Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea

⁶Department of Neurology, Samsung Medical Center,

Sungkyunkwan University School of Medicine, Seoul, South Korea

⁷Department of Neurology, Fujita Health University, Toyoake, Japan

⁸Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, Nagakute, Japan

⁹Severance Biomedical Science Institute, Yonsei University, Seoul, Korea

References

- Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71: 670–676.
- Obelieniene D, Bauzaite S, Kulakiene I, Keleras E, Eitmonaite I, Rastenyte D. Diagnostic challenges in multiple system atrophy. *Neuropsychiatr Dis Treat* 2018;14:179–184.
- Kim HJ, Jeon BS, Lee JY, Yun JY. Survival of Korean patients with multiple system atrophy. *Mov Disord* 2011;26:909–912.
- Ben-Shlomo Y, Wenning GK, Tison F, Quinn NP. Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. *Neurology* 1997;48:384–393.

- Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. *Brain* 2002;125:1070–1083.
- Roncevic D, Palma JA, Martinez J, Goulding N, Norcliffe-Kaufmann L, Kaufmann H. Cerebellar and parkinsonian phenotypes in multiple system atrophy: similarities, differences and survival. *J Neural Transm (Vienna)* 2014;121:507–512.

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 ([6,6-²H₂]-glucose and [²H₃]- glycerol), as

© 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

*Correspondence to: Dr. N. Ahmad Aziz, Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Venusberg-Campus 1, Building 99, 53127 Bonn, Germany; E-mail: ahmad.aziz@dzne.de

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Funding agencies: This work was supported by the Netherlands Organization for Scientific Research (# 017.003.098).

Received: 4 April 2020; **Revised:** 27 May 2020; **Accepted:** 1 June 2020

Published online 30 June 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28181

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

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

Data are means \pm SEM.

* $P < 0.05$.

^{aa}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 \pm 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 \pm 0.5 vs. 21.0 \pm 0.5 $\mu\text{mol/kg}_{\text{FatFreeMass}}/\text{min}$, respectively; $P = 0.26$). In PD and control subjects, insulin stimulation increased whole-body glucose disposal rate (57.5 \pm 8.5 vs. 48.0 \pm 4.9 $\mu\text{mol/kg}_{\text{FFM}}/\text{min}$; $P = 0.35$) and suppressed glucose production rate (14.4 \pm 1.6 vs. 12.3 \pm 1.0 $\mu\text{mol/kg}_{\text{FFM}}/\text{min}$; $P = 0.30$) to a similar extent, although with a slightly higher hepatic insulin resistance index in PD patients (3,829 \pm 227 vs. 3,020 \pm 265 $\mu\text{mol kg}_{\text{FFM}}/\text{min}/\text{pmol} \times \text{L}$; $P = 0.04$; 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. ■

N. Ahmad Aziz, MD, PhD,^{1,2*} 
 Raymund A.C. Roos, MD, PhD,³ and Hanno Pijl, MD, PhD⁴
¹Department of Neurology, Faculty of Medicine,
 University of Bonn, Bonn, Germany
²Population Health Sciences, German Centre for
 Neurodegenerative Diseases (DZNE), Bonn, Germany
³Department of Neurology and ⁴Endocrinology and Metabolic
 Diseases, Leiden University Medical Center, Leiden,
 The Netherlands

References

1. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1664–1675.
2. Pressley JC, Louis ED, Tang MX, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. *Neurology* 2003;60:87–93.
3. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: a record-linkage cohort study. *Neurology* 2018;91:e139–e142.
4. Pagano G, Polychronis S, Wilson H, et al. Diabetes mellitus and Parkinson disease. *Neurology* 2018;90:e1654–e1662.
5. Jeong SM, Han K, Kim D, Rhee SY, Jang W, Shin DW. Body mass index, diabetes, and the risk of Parkinson's disease. *Mov Disord* 2020;35:236–244.
6. Foltynie T, Athauda D. Diabetes, BMI, and Parkinson's. *Mov Disord* 2020;35:201–203.
7. Aziz NA, Pijl H, Frolich M, et al. Systemic energy homeostasis in Huntington's disease patients. *J Neurol Neurosurg Psychiatry* 2010; 81:1233–1237.

Supporting Data

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