RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2022, Volume 56, no. 5, pages: 441–450
DOI: 10.5603/PJNNS.a2022.0060

ISSN: 0028-3843, e-ISSN: 1897-4260

This Research Paper is accompanied by Invited Editorial, see page 385

Carbohydrate metabolism and lipid profile in patients with Parkinson's disease with subthalamic deep brain stimulation

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ABSTRACT

Aim of the study. Assessment of potential effect of subthalamic nucleus deep brain stimulation (STN-DBS) on glucose metabolism in patients with Parkinson's disease (PD).

Clinical rationale for the study. Although a valuable alternative to pharmacotherapy in advanced PD, STN-DBS is thought to negatively affect the cardiometabolic profile of patients (including body mass, lipid profile). Exacerbation of glucose metabolism dysregulation after DBS could therefore be assumed.

Material and methods. Two groups of patients with Parkinson's disease were included: 20 treated pharmacologically (PHT) and 20 newly qualified for STN-DBS (DBS) — with the first assessment prior to surgery, and the second 11 months after surgery on average. Body mass index (BMI), plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glucose levels during a three-point oral glucose tolerance test were measured three times (median intervals between visits 12 and 14 months respectively).

Results. Significant differences between the two groups were noted with respect to changes in BMI, and serum concentration of TG and HDL-C over the course of the study. In the DBS group, a significant increase in BMI (26.42 *vs.* 27.24 kg/m^2, $p = 0.03$) and TG level (103.8 *vs.* 142.8 mg/dL, $p < 0.001$) with a simultaneous decrease in HDL-C level (54.4 *vs.* 46 mg/dL, $p < 0.01$) was observed. Mean glucose level after oral glucose administration was lower in the DBS than in the PHT group (147.4 *vs.* 120.2 mg/dL, $p = 0.03$ after one hour and 109.9 *vs.* 82.3 mg/dL, $p < 0.01$ after two hours) during the second visit. Also inter-visit changes in fasting glucose levels (8.4 mg/dL in the PHT group and –5.8 mg/dL in the DBS group, $p = 0.02$) differed over the study duration.

Conclusions. Our observations are similar to previous ones indicating less favourable changes in BMI and some lipid fractions in patients treated surgically. Interestingly, such a trend was not observed for glucose metabolism parameters, suggesting that mechanisms other than simple body mass changes are involved in early biochemical changes after STN-DBS in PD patients.

Clinical implications. The metabolic consequences of DBS require further investigation as an additional factor potentially affecting the outcome of therapy, and routine patient follow-up should not be limited to neurological and psychological assessments.

Key words: Parkinson's disease, deep brain stimulation, glycaemia, carbohydrates, lipid profile

(*Neurol Neurochir Pol 2022; 56 (5): 441–450*)

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Received: 12.04.2022 Accepted: 25.07.2022 Early publication date: 14.09.2022

Introduction

Recent decades have witnessed a debate regarding the relationship between Parkinson's disease (PD) and diabetes mellitus (DM). Although some case-control and cross-sectional studies have found no positive correlation between PD and DM, most cohort and observational studies have reported a greater prevalence of PD in diabetic patients [1].

Various authors have postulated the involvement of convergent molecular and biochemical mechanisms in the development of DM and PD [2–6]. Commonly proposed pathomechanisms include shared genes such as the amyloid precursor protein, genes involved in lipid metabolism, or genes associated with autoimmunity [7]. Also, genes responsible for the most common monogenic forms of PD, such as SNCA, PINK1 or DJ-1 [8], are now considered to play a role in systemic glucose metabolism and the development of DM [9–11].

One possible link between diabetes mellitus type 2 (DMT2) and PD is protein misfolding. Although the dominant protein forming toxic deposits is different in each disease (α-synuclein in PD and islet amyloid polypeptide in DMT2), the co-occurrence of misfolded proteins has been found in both the pancreas and the brain of patients with neurodegenerative disorders [12]. *In vitro* cross-reactivity between various amyloidogenic proteins has been proven, which results in faster co-aggregation of mixed monomers than observed for each protein alone [13]. Outside the brain, α-synuclein is present e.g. in pancreatic β-cells and its accumulation may promote islet amyloid polypeptide fibrils formation [14]. Meanwhile, islet amyloid polypeptide has been found in brain cells, where it also may co-aggregate with α-synuclein, enhancing the neurodegenerative process [2].

Chronic or recurrent hyperglycaemia and insulin resistance, which are key features in DMT2, lead to numerous detrimental changes on a cellular level [1], for example persistent inflammation and impaired mitochondrial respiration resulting in overproduction of reactive oxygen species, which is particularly detrimental to cells with high energy requirements such as dopaminergic neurons [15–17].

The role of inflammation in neurodegenerative disorders has been raised by various researchers [18]. In animal models, metabolic inflammation has been shown to actually exacerbate dopaminergic neurons degeneration [19].

As a consequence of hyperglycaemia, the level of glycation agents, especially highly reactive methylglyoxal (MGO), is increased. MGO reacts with various proteins including α-synuclein. Glycation facilitates the formation of cross-links between α-synuclein monomers, thus promoting aggregation of its oligomers which are supposed to be even more toxic than larger conglomerates. Ubiquitin-dependent proteolysis of α-synuclein aggregates is inhibited by MGO due to both increased resistance of glycated proteins to proteasomal degradation and glycation of ubiquitin itself [1, 3, 20]. Moreover, the presence of advanced glycation end products is thought to contribute to neuronal death [21].

Apart from the epidemical association between DM and PD, the presence of DM, like other cardiovascular risk factors, undoubtedly negatively affects the clinical course of PD, contributing to faster progression of motor symptoms, prominent gait disturbances, and cognitive impairment [22, 23]. The underlying mechanisms are complex and still not fully understood. Animal studies have revealed for example a correlation between insulin resistance and more pronounced dopaminergic dysfunction [24]. Pagano et al. [22] found increased tau protein in cerebrospinal fluid and greater striatal dopaminergic deficits in patients with DM. As previously discussed, hyperglycaemia-induced protein glycation and cellular insulin resistance modulating aggregation of α-synuclein, β-amyloid and tau can accelerate the neurodegeneration process [20, 25]. Disrupted insulin signalling in the brain, apart from the loss of its physiological neuroprotective action, is supposed to decrease synaptic plasticity and affect cognition [1, 26]. Since orthostatic hypotension is one of the factors thought to contribute to cognitive decline in PD [27], a possible deleterious effect of DM is easy to predict: autonomic dysfunction, resulting from α-synuclein pathology in both peripheral and central autonomic nervous system in the course of PD, may be further aggravated by autonomic neuropathy, a common but underdiagnosed complication of DM [28].

As far as more pronounced gait disturbances are concerned, an overlap between exaggerated dopaminergic motor symptoms, cognitive impairment and peripheral diabetic neuropathy resulting in imbalance may be presumed [29].

Additionally, impaired glucose regulation has been reported in non-diabetic patients with PD, with higher glycaemia after glucose loading than in healthy controls [22, 30]. This could be attributed to non-sufficient function of pancreas β-cells secondary to dysautonomia progressing throughout the natural course of the disease [30], or to direct damage of β-cells by the deposition of pathological proteins as described above. As deposits of α-synuclein are early found in vagal nerve and its motor nucleus [31], and dorsal vagal complex is involved in glucoregulatory insulin action [32], the neurodegeneration in this area may be responsible for dysregulation of postabsorptive glucose metabolism.

Antiparkinsonian pharmacotherapy may also have an impact on glucose regulation, but the effect differs between different groups of drugs. Levodopa is considered to induce both hyperinsulinaemia and hyperglycaemia, whereas dopamine agonists are suspected to improve insulin sensitivity [6].

Clinical rationale for the study

Mutual interaction between hyperglycaemia, insulin resistance and neurodegeneration in the natural course of the disease may be further influenced by therapy for PD.

In our study, we tried to investigate whether subthalamic nucleus deep brain stimulation (STN-DBS) affects glucose variability in PD. Previous studies, including one conducted

by our group, implied an unfavourable influence of DBS on body mass index (BMI) and the lipid profile [33, 34]. Therefore, it could theoretically be assumed that increases in body mass and triglycerides (TG) levels should be accompanied by impaired glucose tolerance.

Material and methods

Participants and methods

Data was collected from 40 patients of the Department of Neurology, Medical University of Warsaw, Poland (20 male, 20 female) who met the UK Parkinson's disease Society Brain Bank criteria for the diagnosis of Parkinson's disease. The mean age of participants was 56.1 ± 10.03 years, with an average disease duration of 9.2 ± 3.93 years.

The main exclusion criteria were: additional neurological disorders, other advanced antiparkinsonian therapy (such as duodopa, apomorphine, or former neurosurgical treatment), and a previous diagnosis of diabetes mellitus.

Data was collected during three consecutive visits with median intervals between visits of 12 months (V1–V2) and 14 months (V2–V3) respectively.

At the moment of inclusion (V1), all patients were receiving optimal pharmacological treatment, i.e. levodopa/ /dopamine agonist in monotherapy or co-administered, and/ /or combined with selegiline or amantadine.

Twenty of those individuals (12 males, eight females) were recruited from patients newly qualified to STN-DBS according to the CAPSIT-PD criteria (we called this the DBS group). In this group, the first assessment (V1) was prior to surgery and the second (V2) 11 months after the implantation of electrodes, on average.

The remainder (the PHT group; eight males, 12 females) only had pharmacological treatment, continued with appropriate adjustment for the whole study duration.

Patients reported no significant changes in dietary habits after inclusion.

During each visit, body mass to the nearest 0.1 kg was measured and BMI was calculated. Plasma concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and TG were determined using Abbott's Alinity CI system. Each time a three-point oral glucose tolerance test (OGTT) was conducted — glucose levels after fasting for at least eight hours and at both 60 and 120 minutes after oral administration of 75 g glucose were measured. All analytical procedures were conducted at the Clinical Laboratory of Masovian Brodnowski Hospital.

An assessment of the severity of symptoms against the Unified Parkinson's Disease Rating Scale (UPDRS) was performed during each visit as well.

The study was approved by the Ethics Committee of the Medical University of Warsaw. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki. All participants gave informed consent prior to their inclusion.

Statistical analysis

All calculations were performed with Statistica software (version 13.1 Dell Inc., Statsoft). In the case of some parameters with non-Gaussian distribution, logistic transformation of the data was performed and normal distribution proved for all variables with W Shapiro-Wilk Test. The data delivered represented parameters gathered on three consecutive visits. For analysis, we used ANOVA for repeated measurements. The variances homogeneity was assessed with Cochran's C test and Bartlett's test. The data sphericity (equality of variance differences between all experimental pairs) was assessed with Mauchley test with its "W" statistic. The smaller the "W" value, the greater the deviation from sphericity. If the assumption of sphericity was met, one-dimensional tests could be performed. Otherwise, the Greenhouse-Geisser and Huynh-Feldt corrections were applied and finally multivariate tests (MANOVA). In post-hoc analysis, the NIR Fisher test was used. In order to compare inter-visit changes in the assessed parameters (expressed as Δ equal to the value of the variable on the later visit minus the value of the variable on the earlier visit) between groups, the t-student test and the Mann–Whitney U-test (for normally and the non-normally distributed data respectively) were carried out.

In all calculations, $p < 0.05$ was considered to be significant. Appropriate plots of statistically significant results are presented.

Results

At the moment of inclusion, the groups were similarly distributed in terms of age (56.8 ± 11.41 years in the PHT group and 55.4 ± 8.60 years in the DBS group, $p = 0.6637$), disease duration (9.0 ± 3.99 in the PHT group and 9.3 ± 3.96 in the DBS group, $p = 0.9254$), disease stage assessed against Hoen-Yahr Scale (2.45 ± 0.51 in the PHT group and 2.85 ± 0.587 in the DBS group, $p = 0.634$), and motor symptom severity expressed as UPDRS part III score in "on" (patients receiving their standard pharmacotherapy) and "off" (after at least 12 h withdrawal of levodopa and 24-h without other antiparkinsonian drugs) condition (8.4 ± 5.21 "on" and 33.9 ± 9.67 "off" in the PHT group, 6.9 ± 3.45 "on" and 37.7 ± 7.87 "off" in the DBS group, $p > 0.05$ for both). The main data acquired is set out in Table 1.

In terms of neurological examination and symptom severity against UPDRS, there was significant inter-visit amelioration in motor subscale score assessed in "on" condition ($p < 0.001$). "On" condition was understood as normal pharmacotherapy in the PHT group and normal pharmacotherapy with the stimulation switched on in the DBS group. For both PHT and DBS patients, there was a reduction in the UPDRS part III "on" score in the later phase of the study (for V2-V3 interval – PHT

Table 1. Descriptive statistics

Parameter	PHT (n = 20)			DBS (n = 20)		
	Visit	Mean (min–max)	SD ± 95% CI	Visit	Mean (min–max)	SD ± 95% CI
Age		56.8 (30–73)	11.4 ± 8.7–16.7		55.4 (40–70)	8.6 ± 6.5–12.6
Body weight	V1	81.3 (59–129.2)	17.3 ± 13.2–25.3	V1	77.9 (50.2–123.4) †	21 ± 16–30.7
	V2	80.9 (58–124.9)	17.6 ± 13.4–25.8	V2	80.7 (58.8–123.8) †	20.4 ± 15.5–29.8
	V3	80.4 (56–123.7)	18.8 ± 14.3–27.4	V3	80.1 (60–118.3)	17.2 ± 13.1–25.1
BMI	V1	28.5 (22.8–43.7)	5.1 ± 3.9–7.5	V1	26.4 (18.7–41.7) †§	6.4 ± 4.8–9.3
	V2	28.4 (22.3–42.2)	5.2 ± 4–7.7	V2	27.4 (21.7–41.8) †	6.2 ± 4.7–9
	V3	28.2 (21.5–41.7)	5.6 ± 4.3–8.2	V3	27.2 (22.3–40) §	5.2 ± 4–7.7
Carbohydrate parameters						
Glucose	V1	80 (62–104) †§	10.6 ± 8–15.4	V1	88.9 (64–142)	17.4 ± 13.2–25.4
	V2	87.6 (75–106) †	8.9 ± 6.7–13	V2	83.8 (64–117)	14.2 ± 10.8–20.8
	V3	88.4 (60–140) §	17.1 ± 13–25	V3	83.1 (65–96)	8.4 ± 6.4–12.2
OGTT1	V1	133.8 (67–210)	42.2 ± 32.1–61.7	V1	117.9 (67–198)	29.5 ± 22.5–43.1
	V2	147.4 (80–205)	37.9 ± 28.9–55.4	V2	120.2 (69–235)	40.3 ± 30.7–58.9
	V3	133.4 (68–278)	43.4 ± 33–63.5	V3	134.6 (55–200)	43.7 ± 33.2–63.9
OGTT2	V1	97.5 (56–185) †§	35 ± 26.6–51.1	V1	86.8 (53–122) §	20.7 ± 15.7–30.2
	V2	109.9 (46–175) †‡	35.3 ± 26.8–51.5	V2	82.3 (39–145) ‡	27.7 ± 21.1–40.5
	V3	103.6 (62–300) ‡§	50.6 ± 38.5–74	V3	87.6 (57–124) ‡§	18.8 ± 14.3–27.5
HbA1c%	V1	5.4 (4.9–6)	0.3 ± 0.2–0.4	V1	5.3 (4–6.3)	0.5 ± 0.4–0.7
	V2	5.4 (4.9–5.9)	0.3 ± 0.2–0.4	V2	5.4 (4.1–6)	0.4 ± 0.3–0.6
	V3	5.5 (5–6.5)	0.3 ± 0.3–0.5	V3	5.5 (4.9–6.3)	0.3 ± 0.3–0.5
Lipid parameters						
TC	V1	191.6 (101–281)	43.4 ± 33–63.3	V1	187.6 (130–295)	46.8 ± 35.6–68.4
	V2	191.1 (130–269)	37.3 ± 28.4–54.5	V2	199.8 (140–348)	48.6 ± 37–71
	V3	179.1 (80–244)	48.7 ± 37.1–71.2	V3	194.3 (125–307)	52.3 ± 39.8–76.4
HDL-C	V1	55.2 (37–78)	11.6 ± 8.9–17	V1	54.4 (31–89) §	17.4 ± 13.2–25.4
	V2	55.1 (36–76)	11.4 ± 8.6–16.6	V2	51.1 (34–88) ‡	14.9 ± 11.3–21.7
	V3	53.9 (31–80)	13.5 ± 10.2–19.7	V3	46 (30–72) ‡§	12.9 ± 9.8–18.8
LDL-C	V1	116.3 (39–185)	37.3 ± 28.4–54.5	V1	112.6 (51–184)	38.7 ± 29.4–56.5
	V2	120.2 (78–197)	35 ± 26.6–51.1	V2	123.9 (57–254)	44.6 ± 33.9–65.1
	V3	110.2 (31–173)	34.7 ± 26.4–50.7	V3	119.9 (53–229)	43.4 ± 33–63.4
TG	V1	101.6 (42–176) §	41.5 ± 31.6–60.7	V1	103.8 (48–217) †§	44.2 ± 33.6–64.6
	V2	103.2 (46–208) ‡	43.7 ± 33.2–63.8	V2	120.9 (67–239) †‡	45.8 ± 34.8–66.9
	V3	95.6 (43–180) ‡§	39.3 ± 29.9–57.5	V3	142.8 (60–346) ‡§	81.4 ± 61.9–118.9
Neurological examination						
UPDRS III On	V1	8.4 (2–18) §	5.2 ± 4–7.6	V1	6.9 (2–19) §	3.5 ± 2.6–5
	V2	8.1 (0–14) ‡	3.9 ± 3–5.7	V2	5.5 (3–18) ‡	3.3 ± 2.5–4.8
	V3	6.5 (3–12) ‡§	2.4 ± 1.8–3.4	V3	5.4 (2–20) ‡§	3.9 ± 3–5.7
UPDRS III Off	V1	33.9 (17–52) †§	9.7 ± 7.4–14.1	V1	37.7 (27–55) †§	7.9 ± 6–11.5
	V2	37.6 (21–56) †‡	8.4 ± 6.4–12.2	V2	41.5 (30–59) †‡	8.3 ± 6.3–12.2
	V3	39.6 (25–57) ‡§	7.8 ± 5.9–11.3	V3	43.6 (32–61) ‡§	8 ± 6.1–11.7

Statistical significance: † $p < 0.05$ for V1 *vs.* V2 comparison; ‡ $p < 0.05$ for V2 *vs.* V3 comparison; § $p < 0.05$ for V1 *vs.* V3 comparison in separate groups; min — minimal value; max — maximal value; SD — standard deviation; CI — confidence interval; OGTT1 — serum level of glucose 60 minutes after oral administration of 75 g glucose; OGTT2 — serum level of glucose 120 minutes after oral administration of 75 g glucose; TC — total cholesterol; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TG — triglycerides

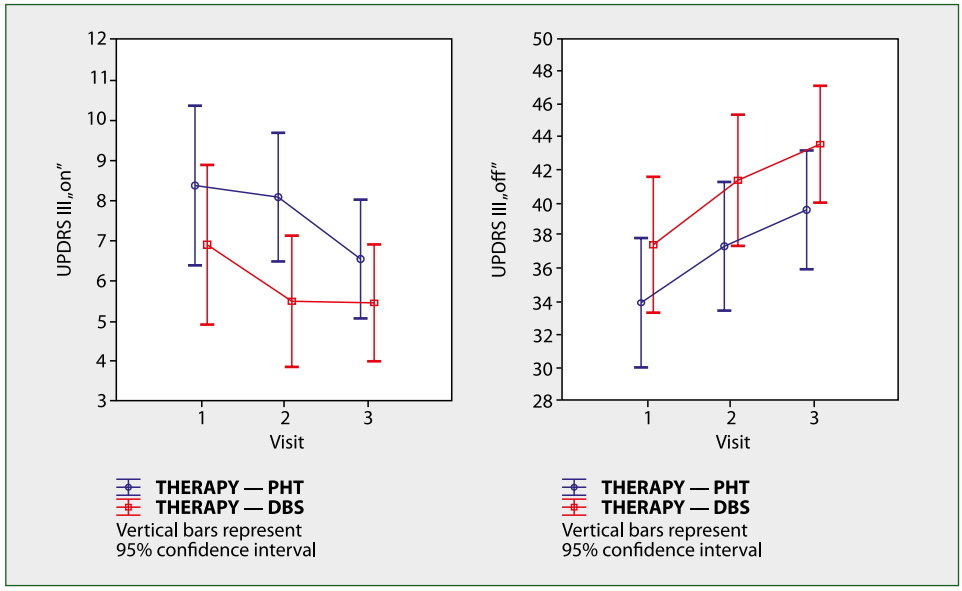

Figure 1. UPDRS part III score in "on" and "off" conditions

Table 2. Comparison of changes in assessed parameters over whole study duration (V1–V3 interval) according to method of treatment of Parkinson's disease (pharmacotherapy alone *vs.* pharmacotherapy and STN-DBS) expressed as Δ equal to value of variable on later visit minus value of variable on earlier visit

	Group		P-value
	PHT	DBS	
ΔBMI_V1–V3	**–0.32 ± 2.068**	**0.81 ± 2.245**	**0.0143**
ΔGlu_V1–V3	**8.4 ± 20.61**	**–5.8 ± 15.57**	**0.0186**
ΔOGTT1_V1–V3	–0.4 ± 48.83	16.7 ± 59.01	0.3272
ΔOGTT2_V1–V3	6.1 ± 46.83	0.8 ± 26.54	0.6592
ΔHBA1c%_V1–V3	0.03 ± 0.394	0.12 ± 0.321	0.2423
ΔTC_V1–V3	–12.5 ± 40.9	6.8 ± 25.91	0.2766
ΔHDL-C_V1–V3	**–1.3 ± 7.11**	**–8.4 ± 10.16**	**0.0146**
ΔLDL-C_V1–V3	–6.1 ± 30.32	7.4 ± 23.65	0.3547
ΔTG_V1–V3	**–6.1 ± 31.22**	**39.0 ± 46.78**	**< 0.001**

OGTT1 — serum level of glucose 60 minutes after oral administration of 75 g glucose; OGTT2 — serum level of glucose 120 minutes after oral administration of 75 g glucose; TC — total cholesterol; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TG — triglycerides

$p < 0.001$; DBS $p = 0.0048$) and over the whole study duration (for V1–V3 interval — PHT $p = 0.0023$; DBS $p = 0.0161$) (Fig. 1). Meanwhile, a statistically significant deterioration in the UPDRS part III score in the "off" phase (for the PHT group as defined previously and for the DBS group with the stimulation switched off as well) was observed in both groups for each interval (V1–V2 PHT $p < 0.001$; DBS $p < 0.001$, V2–V3 PHT $p = 0.0266$; DBS $p = 0.0172$ and V1–V3 PHT $p < 0.001$; DBS $p < 0.001$), which matches the natural course of the disease (Fig. 1).

Although average levodopa equivalent daily dose (LEDD) was higher in the DBS group at inclusion, there was no significant difference in levodopa daily dose (LDD) between groups during the first visit. As predicted, both LEDD and LDD decreased over the study duration in patients treated surgically (LEDD 1,473.3 mg, LDD 1,235.0 mg at V1 and LEDD 734.5 mg, LDD 491.3 at V3, $p < 0.01$ for both parameters). At the same time, reverse changes in both LEDD and LDD were noted in the PHT group (LEDD 1,167.5 mg at V1 and 1,465.5 mg at V3, $p < 0.01$, LDD 1,011.5 mg at V1 and 1,220.0 mg at V3, $p = 0.0257$), which is also typically observed in disease progression.

Longitudinal analysis was conducted to determine changes in all assessed parameters over time in both groups. We also compared inter-visit changes in the assessed parameters (expressed as Δ equal to the value of the variable on the later visit minus the value of the variable on the earlier visit) between the two groups of patients (Tab. 2).

We observed an increase in body weight in surgically treated patients between consecutive visits ($p = 0.0074$). A significant increase in body mass was noted between the

first and the second visit (77.9 kg at V1 *vs.* 80.7 kg at V2, p = 0.0141). Consequently, BMI in this group of patients also increased significantly (p < 0.001), with the most pronounced change during the first year after implantation of electrodes and a later stabilisation (26.42 ± 6.36 kg/m^2 upon V1, 27.41 ± 6.15 kg/m^2 upon V2 and 27.24 ± 5.24 kg/m^2 upon V3, for V1–V2 interval p = 0.0113 and V1–V3 p = 0.0338) (Fig 2). A statistically significant difference was noted for BMI changes over time depending on the therapy (ΔBMI V1–V2 –0.15 ± 1.360 kg/m^2 in the PHT and 0.98 ± 1.020 kg/m^2 in the DBS group, and ΔBMI V1–V3 -0.32 ± 2.068 kg/m^2 in the PHT and 0.81 ± 2.245 kg/m^2 in the DBS group, p < 0.001 and p = 0.0143 respectively).

Analysis concerning the lipid profile showed inter-visit variation of HDL-C and TG plasma concentration in patients from the DBS group. A significant decrease in HDL-C serum level was observed for the V2–V3 interval (p = 0.0038) and over the whole study duration (p < 0.001) (Fig. 2). A gradual increase in TG plasma concentration was noted during each consecutive visit (p < 0.001 for V1–V3 interval and p = 0.0366 and 0.0081 for V1–V2 and V2–V3 intervals respectively), whereas the reverse tendency for serum level of TG was observed in the PHT group (p < 0.001 for V1–V3 interval) with a more pronounced decrease between visits V2 and V3 (p < 0.001) (Fig. 2). Moreover, significant differences in ΔHDL-C and ΔTG over the whole study duration (ΔHDL-C –1.3 ± 7.11 mg/dL in the PHT *vs.* –8.4 ± 10.15 mg/dL in the DBS group, p = 0.0146 And ΔTG –6.1 ± 31.22 mg/dL in the PHT *vs.* 39.0 ± 46.78 mg/dL in the DBS group, p = 0.001), with a major alteration of the latter during the second phase of the study (ΔTG V2–V3 –7.7 ± 28.56 mg/dL in the PHT group *vs.* 21.9 ± 49.55 mg/dL in the DBS group, p = 0.0013), were noted for inter-group comparison.

The carbohydrate metabolism parameters were of particular interest to us. As far as assessed parameter variation over time in separate groups is concerned, significant changes were observed for fasting glucose level in the PHT group only (p < 0.001) and glucose concentration 120 minutes after oral administration of 75 g glucose in both groups (p = 0.0108 for the PHT group and p < 0.001 for the DBS group).

Further analysis revealed an increase in fasting glucose level within V1–V2 (p = 0.0356) and V1–V3 (p = 0.0206) intervals in the PHT group (Fig. 2). Also, inter-group comparison of fasting glucose changes between visits exposed significant differences depending on the method of treatment over the course of the study (Δglu V1–V3 8.4 ± 20.61 mg/dL in the PHT group and –5.8 ± 15.57 mg/dL in the DBS group, p = 0.0186) with major changes during the first phase of the study (Δglu V1–V2 7.6 ± 12.29 mg/dL in the PHT group and –5.1 ± 16.81 mg/dL in the DBS group, p = 0.0096).

In the Oral Glucose Tolerance Test (OGTT), the serum glucose concentration after 120 minutes in the PHT group increased significantly between the first and the second visit (p = 0.0007), with a slight reduction during further observation (p = 0.0000), but still with a significant increase over the study duration (p = 0.0066). In DBS patients, there was a minor increase in serum glucose concentration at the final point of OGTT during the V2–V3 interval (p = 0.004) and over the whole study duration (p = 0.0142). However, the mean plasma glucose levels in OGTT during the first assessment after DBS were significantly lower than in the PHT group (147.4 ± 37.94 *vs.* 120.2 ± 40.32 mg/dL, p = 0.0339 after one hour and 109.9 ± 35.29 *vs.* 82.3 ± 27.71 mg/dL, p < 0.0092 after two hours) with no such observation for other time points (Fig. 2). Results of inter-visit comparisons with *post-hoc* analysis are set out in Supplementary Table 3.

Discussion

Metabolic side effects of STN-DBS have been reported previously [33, 35]. The aim of this current study was to evaluate the possible impact of the method of treatment on glucose variability as another factor contributing to overall cardiovascular risk.

Our results concerning an increase in BMI in patients after the implantation of DBS with a later minor non-significant fall and stabilisation at higher than preoperative values are in good agreement with previous reports. As the majority of our patients were not underweight, the post-surgical weight gain could not be interpreted as normalisation of body mass after previous excessive loss, and therefore should be regarded rather as an adverse side-effect.

Similarly, the deterioration in the lipid profile, including a progressive increase in TG level and lowering of HDL-C plasma concentration during the first years after surgery, observed in our study population, concurs with previous findings [33, 34]. The exact underlying mechanism has not yet been established.

As previously discussed in other papers, these changes may potentially be attributed inter alia to the normalisation of energy expenditure due to reductions of muscle rigidity, tremor and levodopa-induced dyskinesia, as well as to the influence of the electric current on brain structures in proximity to the implanted electrodes [36–39]. The possible influence of levodopa dose reduction should also be taken into account. Some authors have reported that TG and TC serum levels are significantly lower in patients on levodopa than in untreated ones. These findings have been attributed to the peripheral inhibitory effect of levodopa-derived dopamine on the autonomic nervous system, resulting in improved insulin sensitivity with increased glucose uptake and reduced lipolysis [40].

There have been far fewer studies concerning the influence of DBS on glucose metabolism, and the results are inconsistent. Lammers et al. [41] reported no influence of DBS on endogenous glucose production, hepatic or peripheral insulin sensitivity, or basal plasma concentrations of glucose, insulin, or other glucoregulatory hormones. Conversely, Batisse-Lignier et al. [42] found that DBS regulates post-absorptive glucose metabolism.

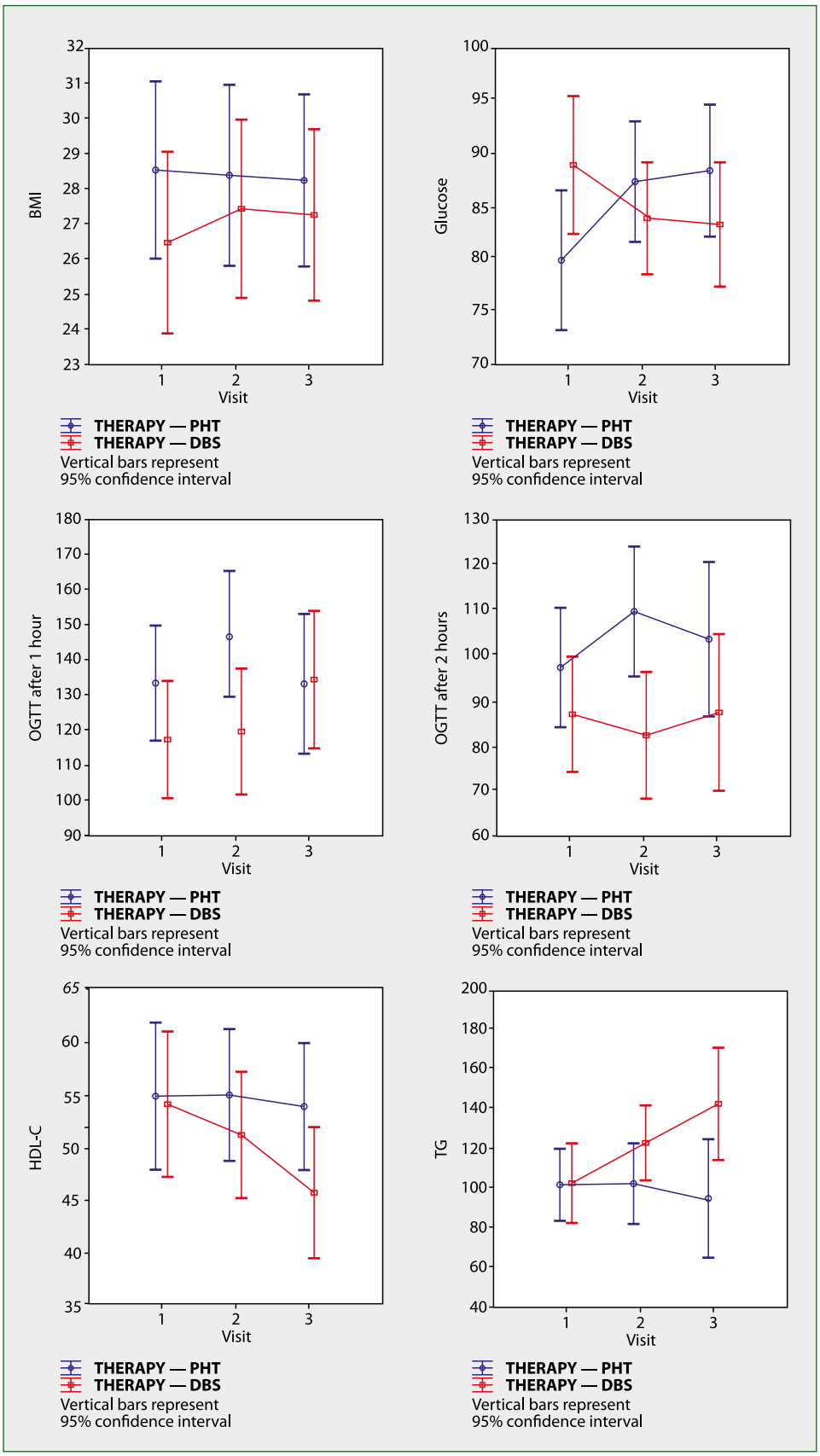

Figure 2. Body mass index, serum glucose (fasting and 60 and 120 minutes after oral administration of 75 g glucose), high-density lipoprotein cholesterol, and triglycerides levels in both groups of patients during subsequent visits

In our study, a comparison of inter-visit changes in fasting glucose levels between groups (with an upward trend in the PHT group and a downward trend in the DBS group) indicates the possible influence of DBS on basal glucose metabolism.

The results of short-term glucose variability analysis during OGTT are ambiguous. The glucose level two hours after oral glucose loading tended to increase over the study duration in patients after STN-DBS. In considering the peripheral dopaminergic action described above for lipid metabolism and the reverse correlation between glucose level and LEDD described by some authors [30], this last observation could be attributed to rapid reduction in LEDD during the initial period after surgery, with subsequent stabilisation of metabolism at a new level. However, due to the opposite effects of levodopa and dopamine agonists on glucose metabolism reported in former studies [6], the role of modification of dopaminergic treatment in metabolic alteration after STN-DBS remains unclear.

On the other hand, although HbA1c%, which reflects average glycaemia over the preceding three months, did not differ significantly between groups or in particular groups over time, mean glycaemia levels after glucose loading during the first year after surgery seem to be significantly lower than in pharmacologically treated patients.

These results suggest that unfavourable changes in the lipid profile and body mass do not result in analogical alterations in glucose metabolism, implying a potential positive effect of DBS. Several mechanisms in which STN-DBS could affect glucose metabolism may be hypothesised.

The role of the hypothalamus as a metabolism regulatory centre is well established [32]. Additionally, some studies have suggested the involvement of the dorsal thalamus in glucose metabolism [43] and the subthalamic region was proven to be the anatomical localisation of the hypoglycaemia sensor [44].

Therefore, the spread of electric current outside the STN is likely to affect adjacent pathways involved in the regulation of glucose homeostasis, consequently altering peripheral glucose metabolism. As no changes in insulin levels after DBS have been found in previous studies [41, 42], the effect of local electric current on the hypothalamus-dorsal vagal complex axis, responsible among other things for the central regulation of hepatic glucose production [32], should be taken into account. The direct modulation of the STN-thalamus circuits also could not be excluded.

Although the results of recent studies are inconclusive, there is some evidence of the influence of DBS on dysautonomia in PD. As autonomic dysfunction is one of the proposed mechanisms of the impaired insulin secretion after glucose loading in PD [30], potential/possible normalisation of autonomic function after surgery could also contribute to improved glucose tolerance [45]. As autonomic dysfunction is one of the proposed mechanisms of the impaired insulin secretion after glucose loading in PD [30], the normalisation of autonomic function after surgery could also contribute to improved glucose tolerance.

An association between lower levels of brain-derived neurotrophic factor (BDNF) and insulin resistance has been described, implying its role in glucose metabolism and a potential pathogenic role in DMT2 [46]. Recent animal studies on a potential neuroprotective role of STN-DBS demonstrated that STN-DBS significantly increases striatal BDNF level and partially restores the normal corticostriatal BDNF relationship in the α-syn preformed fibril model in rats [47]. This last observation, if reproduced in human studies, could also indicate a regulatory effect of STN-DBS on postabsorptive glucose metabolism.

While taking into account the suggested role of hyperglycaemia and insulin signalling dysregulation in the neurodegenerative process [5, 17, 26], a neutral or even favourable effect of DBS on glucose variability is a comforting finding, considering its supposed negative influence on some other cardiovascular factors.

The main limitations of our study were the small number of enrolled patients and the possible effect of additional variables that were hard to control, such as lifestyle or the dietary habits of patients. The actual effect of STN-DBS on carbohydrate metabolism may have been partially disguised by the influence of dopaminergic drugs. For ethical reasons, pharmacotherapy had to be adjusted after surgery and continued over the course of the study. Moreover, our intention was to assess the metabolic status of patients in real life situations, not in theoretical conditions.

The study population was relatively young, and glucose metabolism changes with age, which could potentially influence the results. However, DBS is the therapeutic option most often proposed to younger patients (due to exclusion criteria including cognitive dysfunction or presence of pronounced vascular changes in electrode placement trajectory) and average age at disease onset, as well as its duration, was similar in both groups (47.8 and 9.0 years respectively in the PHT group and 46.1 and 9.3 years in the DBS group) to avoid age-related differences in metabolism between groups. Also, longer life expectancy among such patients makes them more susceptible to the long-term consequences of metabolic disorders, additionally justifying efforts to identify potential metabolic side effects of the applied therapy.

Clinical implications/future directions

Our data is insufficient to conclude whether DBS normalises carbohydrate metabolism disturbed in the course of PD or accompanying levodopa treatment. However, it indicates that in this group of patients, unfavourable changes in BMI and the serum lipid profile are not necessarily accompanied by impaired glucose metabolism.

In the light of numerous reports of a deleterious effect of hyperglycaemia, insulin dysregulation and other cardiovascular risk factors on the clinical course of PD itself, the influence of DBS on global metabolism and autonomic function is an important issue potentially affecting the outcome of therapy.

An assessment of the actual impact of DBS on various metabolic processes requires larger population studies with longer follow-ups. Closer investigation of possible mechanisms underlying biochemical changes after DBS are necessary to identify predictors of metabolic alteration following surgery.

Conflicts of interests: *None.*
Funding: *None.*

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