Long-term intake of Mucuna pruriens in drug-naïve Parkinson’s disease in sub-Saharan Africa: a multicentre, non-inferiority, randomised, controlled clinical trial.

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Bjectives

(1) To describe a 52-week multicenter trial (still ongoing) comparing the long-term efficacy and tolerability of Mucuna pruriens (MP) powder vs. Levodopa+DDCI in patients with Parkinson’s disease (PD) never treated with Levodopa. (2) To describe MP-induced improvement of symptoms usually considered non-levodopa-responsive (postural instability, dysphagia) in a few cases with longstanding disease. (3) To provide insights on the feasibility of cultivating MP plants in patients’ own garden and in hospital backyards.

Background

In low-income countries, the access to levodopa is limited and patients with PD are often undertreated/untreated with great limitations in their quality of life and survival.

Methods

In this phase-2 prospective study (started in February 2018) involving 3 Ghanaian hospitals, we aim to recruit 90 patients diagnosed with idiopathic PD to be randomized to receive either MP powder or LD+DDCI in a parallel-group, non-inferiority study design. Individual daily dose was calculated considering that (i) the Levodopa content in Ghanaian MP powder was 6.3% (calculated a priori in Milan), (ii) a 5-fold conversion factor is needed due to the lack of a DDCI in MP, and (iii) body weight. Hence, 100mg of LD+DDCI corresponds to 8 g of MP powder. The primary endpoint is the non-inferior change in quality of life (measured by the PDQ-39) induced by MP as compared to LD+DDCI.

In addition, patients are assessed using the UPDRS parts I-to-IV, the Hoehn & Yahr stage, adverse events forms. Informed consent and Local Ethical Committee approvals have been obtained from the centers involved. This trial is registered at the Pan African Clinical Trial Registry, ID: PACTR201611001882367.

Results

After the first 3 months, 26 patients have been randomized (mean age 61.3±8.3 ys; PD duration 5.7 years, range 1-14). Mean daily dose of MP powder is 43.0±6.00 g/daily vs. 620±205 mg/day of Levodopa + DDCI.

Concerning safety, MP has an overall good tolerability. A few patients reported a progressive shortening of the ON-time after a few weeks of MP therapy. Notably, nobody dropped out due to adverse events.

MP powder is delivered every month and it is easy to use by patients. Some patients with longstanding and untreated disease showed a remarkable improvement in severe postural instability induced by MP (Video).

Two PD patients are successfully cultivating Mucuna plant in their own garden (Fig. 1A and 1B).

MP seeds were planted in a hospital’s garden (Fig. 2).

Conclusions

If proven effective and tolerable, MP powder may be used as an alternative source of levodopa in the long-term for indigent PD patients worldwide who cannot afford levodopa-based medications.

This work was supported by “Fondazione Grigioni per il Morbo di Parkinson” www.parkinson.it and “Brain and Malnutrition in Chronic Diseases Association Onlus” www.bm-association.it
PROtein, LEucine And vitamin D Enhancing Rehabilitation (PRO-LEADER) in patients with Parkinson’s disease or parkinsonism: a RCT

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OBJECTIVES

Physical rehabilitation is an important strategy for treating motor disability in patients with Parkinson’s disease (PD) or parkinsonism. Studies in old adults have shown that muscle-targeted nutritional support can positively influence muscle mass and physical performance but no evidence is available in Parkinsonian syndrome which are characterized by high rates of muscle dysfunction, particularly muscle weakness. We evaluated the efficacy of a muscle-targeted nutritional support on the functional outcomes of a multidisciplinary intensive rehabilitation treatment (MIRT) in patients with PD or parkinsonism.

METHODS

We conducted a randomized (1:1), controlled trial (NCT03124277) in patients suffering from PD or parkinsonism and undergoing a MIRT. Patients (n=150) (Figure 1) received a standard hospital diet with or without a vitamin D and leucine-enriched whey protein-based nutritional supplement twice daily for 30 days. The primary efficacy end point was the increase in the distance walked during a 6-minute walking test (6MWT). Secondary outcome variables were changes in: gait speed, timed up and go test (TUG), Berg balance scale, handgrip strength, Self-assessment Parkinson’s Disease Disability Scale, body weight and skeletal muscle mass (SMM).

RESULTS

Nutritional support resulted in a greater increase in the distance walked during a 6MWT (mean, 69.6 meters [95%CI, 60.7-78.6]) than no support (51.8 meters [95%CI, 37.0-66.7]): center-adjusted mean difference, 18.1 meters [95%CI, 0.9-35.3] (P=0.039). Further adjustment for changes in dopaminergic therapy and SMM yielded consistent results: mean difference, 18.0 meters (95%CI, 0.7-35.2) (P=0.043). A significant effect was also found for the following secondary end points: 4-meter walking speed (0.07 m/s [95%CI, 0.01-0.13], P=0.032), TUG test (-1.1 s [95%CI, -2.2-0.0], P=0.046), SMM (0.5 kg [95%CI, 0.0-1.0], P=0.029) (Table 1 - Figure 2).

CONCLUSIONS

In patients with PD or parkinsonism, the consumption of a whey protein-based nutritional formula enriched with essential amino acids and vitamin D improved the efficacy of a MIRT, particularly lower body physical function.

This work was supported by “Fondazione Grigioni per il Morbo di Parkinson” www.parkinson.it and “Brain and Malnutrition in Chronic Diseases Association Onlus” www.bm-association.it

<table>
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<tr>
<th>ENDPOINTS</th>
<th>SUPPLEMENTED CHANGE* (N=75)</th>
<th>STANDARD CARE CHANGE* (N=75)</th>
<th>TREATMENT EFFECT DIFFERENCE*</th>
<th>P-VALUE</th>
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</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>69.6 (60.7, 78.6)</td>
<td>51.8 (37.0, 66.7)</td>
<td>18.1 (0.9, 35.3)</td>
<td>0.039</td>
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<tr>
<td>Secondary endpoints</td>
<td></td>
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<tr>
<td>4-meter gait speed course [m/s]</td>
<td>0.12 (0.09, 0.16)</td>
<td>0.06 (0.01, 0.11)</td>
<td>0.07 (0.01, 0.13)</td>
<td>0.032</td>
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<tr>
<td>Timed up and go test (s)</td>
<td>-3.8 (-4.8, -2.8)</td>
<td>-2.7 (-3.2, -2.1)</td>
<td>-1.1 (-2.2, 0.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Berg balance scale (score)</td>
<td>6.4 (5.4, 7.4)</td>
<td>6.8 (5.7, 7.8)</td>
<td>-0.3 (-1.6, 1.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Handgrip strength (kg)</td>
<td>1.2 (0.3, 2.2)</td>
<td>0.1 (-1.2, 1.1)</td>
<td>1.3 (0.1, 2.7)</td>
<td>0.068</td>
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<tr>
<td>SPDDS (score)</td>
<td>-11.6 (2.5, -10.6)</td>
<td>-12.1 (-13.5, -10.6)</td>
<td>0.5 (-1.0, 2.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>-1.3 (-1.9, -0.8)</td>
<td>-1.5 (-1.6, -0.8)</td>
<td>-0.1 (0.3, 0.6)</td>
<td>0.78</td>
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<tr>
<td>Skeletal muscle mass (kg)</td>
<td>0.1 (0.3, 0.4)</td>
<td>-0.5 (-0.8, -0.1)</td>
<td>0.5 (0.0, 1.0)</td>
<td>0.029</td>
</tr>
<tr>
<td>Skeletal muscle mass index (kg/m²)</td>
<td>0.03 (-0.09, 0.14)</td>
<td>-0.15 (-0.27, -0.04)</td>
<td>0.18 (0.02, 0.34)</td>
<td>0.029</td>
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<tr>
<td>Post-hoc exploratory endpoints</td>
<td>UPDRS total score</td>
<td>-1.4 (-15.7, -13.3)</td>
<td>-14.8 (-16.6, -13.3)</td>
<td>0.3 (-14.2, 2.0)</td>
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<tr>
<td>UPDRS part II score</td>
<td>-1.4 (-8.6, -1.6)</td>
<td>-7.6 (-9.8, -6.4)</td>
<td>-0.2 (-12.0, 0.8)</td>
<td>0.75</td>
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<tr>
<td>Calorie intake (kcal/kg/day)</td>
<td>-1.5 (1.5, 0.7)</td>
<td>0.5 (0.4, 1.6)</td>
<td>2.0 (0.4, 3.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Protein intake (g/kg/day)</td>
<td>0.43 (0.05, 0.81)</td>
<td>0.04 (0.01, 0.08)</td>
<td>0.39 (0.30, 0.48)</td>
<td>&lt;0.001</td>
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<tr>
<td>Calf circumference (cm)</td>
<td>-0.2 (0.0, 0.3)</td>
<td>-0.1 (-0.2, 0.1)</td>
<td>0.2 (0.0, 0.4)</td>
<td>0.031</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (nmol/L)</td>
<td>6.6 (3.4, 9.8)</td>
<td>-3.2 (-4.2, -0.3)</td>
<td>9.8 (5.5, 14.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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TABLE 1. Summary of study results

FIGURE 1. Flow diagram of patients identified and included in the study

FIGURE 2. Effects of muscle-targeted nutritional support on the functional outcomes

FIGURE 2. Effects of muscle-targeted nutritional support on the functional outcomes
Plasma levels of vitamin D in patients with Parkinson’s disease: correlation with Mini Mental State Examination and disease duration

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OBJECTIVES

In recent years, attention has been paid to the role of vitamin D in Parkinson’s disease (PD), as it has been found that in the brain are present both the specific receptors for vitamin D and the enzyme 25(OH)-D-1α-hydroxylase, necessary for the synthesis of the active metabolite 1,25-dihydroxyvitamin D. It has been shown that PD patients have low vitamin D levels and that a greater severity of the disease is connected with a lower serum concentration of the vitamin. The aim of the study is to evaluate the plasma levels of 25(OH) D in PD, correlating these values with the cognitive function and with disease duration.

<table>
<thead>
<tr>
<th>Plasma levels (ng/ml)</th>
<th>Vitamin D (25-OH) Status</th>
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<tr>
<td>&lt;10</td>
<td>Highly deficient</td>
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<tr>
<td>10-20</td>
<td>Deficient</td>
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<tr>
<td>20-30</td>
<td>Insufficient</td>
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<tr>
<td>30-50</td>
<td>Sufficient</td>
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<td>&gt; 150</td>
<td>Toxic</td>
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</table>

METHODS

Plasma 25(OH) D levels of PD patients recruited from throughout Italy were collected and correlated with anthropometric characteristics, Mini Mental State Examination (MMSE) and disease duration.

Major exclusion criteria: age <60 yr; oral supplementation of vitamin D; disease duration < 5 yr.

RESULTS

The aim of the study was to evaluate 500 PD; preliminary data included 120 patients, 71.6% were male (28.4% female). Mean age was 71 yr (range 60-87) and mean BMI was 26.6 kg/m² (±4.65), with no statistical difference between male and female. The mean 25(OH) D level was 18.4 ng/ml (±9.88). 93.3% of patients didn’t reach optimal levels of 32 ng/ml, including 59.1% <20ng/ml and 17.5% <10ng/ml.

MMSE was ≤20 in 5 % patients; >20 and ≤ 24 in 16 %; >24 in 79%. Mean disease duration was 10.9 ± 6.3 yr. By simple linear correlation, a significant direct association between 25(OH)D and BMI (p<0.01) and between 25(OH)D and MMSE score (p=0.01) and inverse association between 25(OH)D and disease duration (p<0.01) was observed.

CONCLUSIONS

Only 6.7% of PD reach optimal plasma levels of 25(OH)D. The higher percent of men in recruitment is due to a major incidence of supplementation in women (exclusion criteria). Low 25(OH) D levels correlated with higher BMI, worse cognitive abilities, and longer disease duration. In PD population vitamin D supplementation is needed. We are collecting nutritional data from Food Frequency Questionnaire to evaluate nutritional intake, to investigate the role of vitamin D in the risk of PD.

This work was supported by “Fondazione Grigioni per il Morbo di Parkinson” www.parkinson.it and “Brain and Malnutrition in Chronic Diseases Association Onlus” www.bm-association.it
Unraveling gut microbiota in Parkinson’s disease and atypical parkinsonism

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5 Clinical Nutrition and Diets Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

¹ and ** Equal contribution

OBJECTIVES
Recent evidences support the hypothesis that dysfunction in the gut microbiota may play a critical role in the pathogenesis of Parkinson’s disease (PD). However, findings are heterogeneous probably due to the presence of several confounders. We evaluated the differences in gut microbiota among PD, atypical parkinsonism (i.e. multiple system atrophy [MSA] and progressive supranuclear palsy [PSP]) and healthy controls (HC) and whether microbiota may act as modulator of disease progression and clinical phenotype.

METHODS
We recruited patients with idiopathic PD (n=193, of whom 39 were de-novo), PSP (n=22), MSA (n=22), and HC (n=113). Several confounders were taken into account, including pharmacological therapy, dietary habits and genetic status. Information on the type of lactation were also recorded. (Table 1)

![Image](https://via.placeholder.com/150)

**FIGURE 1:** Principal coordinates analysis of weighted UniFrac distances representing the differences in patients groups (A) and in disease duration stages (B).

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<thead>
<tr>
<th>FEATURE</th>
<th>TAXONOMIC LEVEL</th>
<th>RELATIVE TAXA ABUNDANCE</th>
<th>EFFECT A</th>
<th>P-value</th>
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<tr>
<td></td>
<td>PHYLUM</td>
<td>NAME</td>
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**TABLE 1.** Significant associations between relative taxa abundance and clinical features in Parkinson’s disease patients

![Image](https://via.placeholder.com/150)

**FIGURE 2.** Network plots describing co-abundance of bacterial genera in the gut microbiota.

RESULTS
Despite simple non-parametric comparison of PD patients and HC showed several differences in relative taxa abundances, the number of significant comparisons was reduced after adjusting for multiple confounders. We observed a constant effect of age on almost all abundances. The use of COMT inhibitors appeared to influence the level of several taxa. Overall, PD patients had increased Verrucomicrobia, Christensenellaceae, Lactobacillaceae, and decreased Lachnospiraceae and Ruminococcaceae than HC. Reduced level of Lachnospiraceae was significant in all PD duration strata, while many of these differences were associated with disease progression. De-novo PD differed from HC only by lower abundance in Lachnospiraceae. Compared to PD, Lachnospiraceae and Ruminococcaceae were not significantly lower in MSA, while in PSP cases other genera of Ruminococcaceae and Lactobacillaceae were higher and comparable, respectively. Increased Lactobacillaceae, Christensenellaceae, Verrucomicrobia and decreased Lachnospiraceae were associated with worse disease severity, including intellectual impairment, axial features (gait disturbances and postural instability) and other non-motor symptoms. (Figure 1-2)

CONCLUSIONS
Gut microbiota may play a role in the pathogenesis of PD and act as modulator of individual differences in disease severity, especially non-dopaminergic features (cognition and axial symptoms).

This work was supported by “Fondazione Grigioni per il Morbo di Parkinson” [www.parkinson.it] and “Brain and Malnutrition in Chronic Diseases Association Onlus” [www.bm-association.it]
Long-Duration Response to Levodopa in advanced Parkinson’s Disease: Relevance for RCT on Disease-Modifying therapies.

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**BACKGROUND**

In sub-Saharan Africa, the access to levodopa is limited and therapy is often initiated several years after the onset.

**OBJECTIVE**

To investigate the natural history of Parkinson’s disease (PD) in a cohort of newly diagnosed patients and the response to acute levodopa challenge; to compare baseline OFF to the overnight-OFF state after the initiation of levodopa therapy.

**METHODS**

This is a prospective multicenter study in sub-Saharan Africa (Ghana and Zambia), where levodopa is usually initiated several years after the onset (if ever). Acute levodopa challenge was performed in 30 patients with PD never treated with any anti-PD medication (age at onset 57.6±13.7 y, mean disease duration 7.0±3.9 y). Data were collected at the baseline (first-ever levodopa intake), at 1-year and 2-year follow-up.

**Paradigmatic case**

Baseline OFF. 42-year-old patient had a PD duration of about 22 years, never treated. He presented with diffuse resting tremor, severe muscle rigidity with painful dystonic postures, he was unable to stand unassisted. Notably, he had dysphagia. UPDRS III 80.

**ON.** The initiation of Levodopa (400mg/day) greatly improved motor symptoms after a few days: he could walk unassisted. UPDRS III 49

At 6-m follow-up, tremor was absent, he walked unassisted and recovered at pull-test. He had 3-h wearing-off and mild dyskinesias. UPDRS III 28

**OFF.** After overnight withdrawal, he was able to stand up and walk unassisted, though limb tremor was moderate and did not recover at pull-test. UPDRS III 52

**RESULTS**

First-ever Levodopa challenge: baseline OFF-state UPDRS-III vs. ON-state were 41.9 vs. 25.5, respectively (p<0.001). At 1-y follow-up, UPDRS-III after overnight withdrawal of levodopa (overnight-OFF) was significantly better than baseline-OFF (p<0.001). This effect remained significant (no interaction observed) even in those with PD duration ≥7 y (n=13, mean duration 10.3 y), all of whom had fluctuations and dyskinesias. Levodopa induced a similar OFF-to-ON change in UPDRS-III at baseline and at 1-y follow-up (39.5% and 42.1%, respectively). Compared to the natural progression of PD, levodopa treatment resulted in a 30% lower annual decline of motor symptoms (3.3 vs. 2.3 UPDRS-III points/y) with lower variance in UPDRS-III scores explained by disease duration (67% vs. 36%; Fig.1). At 2-y follow-up, overnight-OFF (mean UPDRS-III 28.0) was still 30% better than baseline-OFF (p=0.001; Fig.2). Surprisingly, the improvement of the overnight-OFF was already evident after 24 hours of Levodopa (Fig. 3)

**DISCUSSION & CONCLUSIONS**

Although patients in advanced PD stages experienced early motor fluctuations and dyskinesias, their motor performance in the OFF-state is invariably less severe than the baseline, independently of disease duration. Concerning RCT on disease-modifying therapies, our data suggest that overnight OFF-state is not a reliable marker of disease progression even in advanced stages of PD. Further research is needed to identify the neuronal structures able to store dopamine in advanced stages, when the majority of nigral neurons are degenerated.