Gdański Uniwersytet Medyczny

Wydział Nauk o Zdrowiu z Instytutem Medycyny Morskiej i Tropikalnej

Rozprawa doktorska na stopień doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauk o zdrowiu

Wpływ 12 tygodniowej suplementacji witaminą D_3 połączonej z aktywnością fizyczną na wybrane parametry krwi, parametry funkcjonalne i jakość życia u pacjentów z chorobą Parkinsona leczonych metodą stymulacji głębokiej mózgu

ang. The impact of 12-week vitamin D_3 supplementation and exercise on blood parameters, physical performance, and quality of life in Parkinson's Disease with deep brain stimulation

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Podziękowania

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Dziękuję!

Spis treści

Wykaz skrótów

1,25(OH)$_2$D	-	kalcytriol
10 MWT	*10 meter walk test*	10-cio metrowy test chodu
25(OH)D	-	kalcydiol
3-HANA	*3-hydroxyanthranilic acid*	kwas 3-hydroksyantranilowy
3-HK	*3-hydroksykynurenine*	kwas 3-hydroksykinureninowy
6 MWT	*6 minute walk test*	6-cio minutowy test chodu
AA	*anthralinic acid*	kwas antralinowy
AF	-	aktywność fizyczna
BMI	*Body Mass Index*	wskaźnik masy ciała
CRP	*C-reative protein*	białko C-reaktywne
DBS	*deep brain stimulation*	stymulacja głęboka mózgu
Hcy	*homocysteine*	homocysteina
IDO	*indoleamine 2,3-dioxygenase*	2,3-dioksygenaza indoloaminy
IL-6	*interleukin-6*	interluekina-6
IU	*international units*	jednostki międzynarodowe
KATs	*kynurenine aminotransferases*	aminotransferazy kinureniny
KMO	*kynurenine 3-monooxygenase*	3-monooksydaza kinureniny
KP	*kynurenine pathway*	cykl kinureninowy
KYN	*kynurenine*	kinurenina
KYNA	*kynurenine acid*	kwas kinureninowy
KYNU	*kynureninase*	kinureninaza
LC-MS/MS	*liquid chromatography combined with tandem mass spectrometry*	wysokosprawna chromatografia cieczowa sprzężona z tandemową spektrometrią mas
PA	*picolinic acid*	kwas pikolinowy

PD	*Parkinson's Disease*	Choroba Parkinsona
PL	-	grupa kontrolna
QUIN	*quinolinic acid*	kwas chinolinowy
T0	-	pierwsze spotkanie
T1	-	drugie spotkanie
T2	-	trzecie spotkanie
TNF-α	*tumor necrosis factor-alpha*	czynnik martwicy nowotworów-alfa
TUG	*Test Up and Go*	test wstań i idź
UPDRS-III	*Unified Parkinson's Disease Rating Scale-III*	Ujednolicona Skala Oceny Choroby Parkinsona część III
VitD	-	grupa suplementowana
XANA	*xanthurenic acid*	kwas ksanturenowy

Wykaz prac wchodzących w skład rozprawy doktorskiej

W skład rozprawy doktorskiej wchodzą następujące publikacje:

1. Chromiec, P. A., **Urbaś, Z. K.***, Jacko, M., & Kaczor, J. J. (2021). The Proper Diet and Regular Physical Activity Slow Down the Development of Parkinson Disease. *Aging and disease*, *12*(7), 1605–1623. https://doi.org/10.14336/AD.2021.0123
2. **Bytowska, Z. K.***, Korewo-Labelle, D., Berezka, P., Kowalski, K., Przewłócka, K., Libionka, W., Kloc, W., & Kaczor, J. J. (2023). Effect of 12-Week BMI-Based Vitamin D_3 Supplementation in Parkinson's Disease with Deep Brain Stimulation on Physical Performance, Inflammation, and Vitamin D Metabolites. *International journal of molecular sciences*, 24(12), 10200. https://doi.org/10.3390/ijms241210200
3. **Bytowska, Z.K.***; Korewo-Labelle, D.; Kowalski, K.; Libionka, W.; Przewłócka, K.; Kloc, W.; Kaczor, J.J. Impact of 12 Weeks of Vitamin D_3 Administration in Parkinson's Patients with Deep Brain Stimulation on Kynurenine Pathway and Inflammatory Status. *Nutrients* **2023**, *15*, 3839. https://doi.org/10.3390/nu15173839

Tabela 1. Biometryczne wskaźniki publikacji

Czasopismo	Rok	Typ badania	Tytuł	MEiN	IF
Aging and Disease	2021	Praca przeglądowa	The Proper Diet and Regular Physical Activity Slow Down the Development of Parkinson Disease.	140	7,4
International Journal of Molecular Sciences	2023	Praca oryginalna	Effect of 12-Week BMI-Based Vitamin D3 Supplementation in Parkinson's Disease with Deep Brain Stimulation on Physical Performance, Inflammation, and Vitamin D Metabolites.	140	5,6
Nutrients	2023	Praca oryginalna	Impact of 12 Weeks of Vitamin D3 Administration in Parkinson's Patients with Deep Brain Stimulation on Kynurenine Pathway and Inflammatory Status.	140	5,9
Razem				420	18,9

*Urbaś przed ślubem, Bytowska po zawarciu związku małżeńskiego

Streszczenie

Choroba Parkinsona (PD) związana jest ze starzeniem organizmu i jest drugą co do częstości występowania chorobą neurodegeneracyjną. Według danych Światowej Organizacji Zdrowia ilość pacjentów w 2019 roku przekraczała 8,5 miliona. Ze względu na starzenie się społeczeństwa zakłada się, że liczba ta będzie rosnąć w przeciągu najbliższych lat. Objawy pojawiające się w trakcie trwania choroby możemy podzielić na motoryczne i pozaruchowe. Na ten moment wszelkie sposoby leczenia skupiają się na zmniejszeniu dokuczliwości objawów. U pacjentów z PD występuje zwiększone ryzyko upadków, co w konsekwencji prowadzi do złamań wymagających często unieruchomienia czy też hospitalizacji. Jedną z przyczyn może być pogłębiający się niedobór witaminy D w trakcie rozwoju choroby. W przypadku gdy postęp choroby jest zbyt szybki, a zastosowana farmakologia powoduje zbyt wiele skutków ubocznych i nie wystarcza do zmniejszania intensywności objawów motorycznych, do leczenia włączana jest stymulacja głęboka mózgu (DBS), która jest jedną z dostępnych możliwości.

Celem rozprawy było sprawdzenie czy suplementacja witaminą D_3 dawką dostosowaną do wskaźnika masy ciała (BMI) pacjentów z PD leczonych DBS, może wpływać na spowolnienie postępu choroby poprzez: doprowadzenie do optymalnych stężeń witaminy D i jej metabolitów, zmniejszanie stanu zapalnego, regulację przebiegu cyklu kinureninowego, czy też poprawę parametrów funkcjonalnych.

W pracy przeglądowej, w której jestem współautorką przedstawiliśmy wiedzę dotyczącą aktywności fizycznej i prawidłowo dobranych suplementów w PD. Potwierdziliśmy, że regularna aktywność fizyczna może przyczyniać się do spowolnienia postępu choroby, jak i wpływać pozytywnie na jakość życia pacjentów zmniejszając dolegliwości pozaruchowe. Liczba hospitalizacji, która pojawiała się w wyniku złamań powstających na skutek upadków, będzie zmniejszać się w wyniku poprawy wydolności i sprawności pacjentów. Mniejsza ilość pobytów szpitalnych wpłynie na zmniejszenie kosztów, które powstawały w ich wyniku. Skupienie uwagi na odpowiednim dobraniu suplementacji, zawierającej między innymi witaminę D_3, może wpływać korzystnie na spowalnianie postępu choroby.

Badanie opisane w pierwszej pracy eksperymentalnej wykazuje, że połączenie DBS z 12 tygodniową suplementacją witaminą D_3 dawką dostosowaną do BMI pacjentów w PD, może mieć wpływ na zmniejszenie ryzyka upadków w tej grupie. Wnioski te wysnute są na podstawie wyników testów funkcjonalnych – przede wszystkim testu wstań i idź, które w

wyniku suplementacji poprawiają się znacząco statystycznie. Dodatkowo odpowiednio dobrana dawka witaminy D_3 wpływa na unormowanie stężeń witaminy D i jej metabolitów na poziomach optymalnych.

W drugiej pracy skupiliśmy się na tym, jak suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów, połączona z DBS, wpływa na stan zapalny oraz cykl kinureninowy w PD. Zaobserwowaliśmy istotny spadek markera stanu zapalnego – TNF-α w grupie zażywającej witaminę D_3. Dodatkowo wykazaliśmy, że metabolizm cyklu kinureninowego przesuwa się w stronę neuroprotekcyjną – w grupie suplementowanej zaobserwowano trend wzrostowy w stężeniu kwasu kinureninowego po 12 tygodniach badania, a w grupie z placebo znaczący wzrost stężenia kwasu 3-hydroksykinureninowego i istotny spadek stężenia kwasu pikolinowego.

Wyniki wykazane w cyklu prac wchodzących w skład rozprawy doktorskiej wskazują, że regularna aktywność fizyczna może spowalniać postęp PD. Odpowiednia dawka witaminy D_3, dostosowana do BMI pacjentów z PD leczonych DBS, doprowadza do optymalnego stężenia witaminy D i jej metabolitów we krwi. W konsekwencji może przyczyniać się do poprawy jakości życia tych pacjentów – zmniejszając ryzyko upadków. Dodatkowo pomaga w obniżeniu poziomu markerów stanu zapalnego i reguluje cykl kinureninowy w kierunku neuroprotekcyjnych metabolitów. To pozwala sugerować, że witamina D_3 prezentuje neuroprotekcyjne właściwości, a dawka dobrana do BMI może być stosowana jako wspomaganie leczenia DBS u pacjentów z PD. Kolejnym pozytywnym aspektem jest fakt, że proponowana przez nas suplementacja jest niedroga, co może być bardzo pozytywnie odebrane przez chorych. Badanie to jest pierwszym, w którym wzięto pod uwagę dostosowanie dawki suplementacyjnej do BMI w PD i pierwszym, w którym uwzględniono pacjentów z PD leczonych DBS.

słowa kluczowe: choroba Parkinsona, witamina D, stymulacja głęboka mózgu, BMI, stan zapalny, cykl kinureninowy, parametry funkcjonalne, dieta, aktywność fizyczna

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease. PD is associated with age and the risk of developing this disease is growing with aging. According to World Health Organization, over 8.5 million people suffered from this disease in 2019. Due to the aging population, it is assumed that this number will increase over the coming years. The symptoms in patients with PD may be categorized into motor and non-motor symptoms. At this point, all treatments focus on reducing the annoyance of symptoms. PD patients have an increased risk of falls, resulting in fractures that often require immobilization or hospitalization. One contributing factor to this risk may be a worsening vitamin D deficiency during the progression of the disease. When the progression of the disease is too rapid and conventional pharmacology used causes too many side effects and is insufficient to reduce the intensity of motor symptoms, thus deep brain stimulation (DBS) is, one of the options, incorporated into the treatment.

The primary aim of the dissertation was to investigate whether vitamin D_3 supplementation with a dose adjusted to the body mass index (BMI) of PD patients treated with DBS may influence the slowing of disease progression. This influence was assessed through various mechanisms, including, achieving optimal vitamin D and its metabolites concentrations, reducing inflammation, regulating the kynurenine cycle, and enhancing functional parameters.

In a review paper in which I am a co-author, we presented findings on the positive impact of regular physical activity and selected supplements in PD. We confirmed that regular physical activity can contribute to slowing down the progression of the disease as well as have a positive impact on the quality of life of patients by reducing postural complaints. The number of hospitalizations that occurred as a result of fractures resulting from falls will decrease as a result of improved fitness and performance of patients. Fewer hospital stays will reduce the costs that arise as a result of them. Paying attention to properly selected supplementation containing vitamin D_3, among other things, may have a beneficial effect on slowing the progression of the disease.

The study described in the first experimental paper demonstrates that combining DBS with vitamin D_3 supplementation tailored to the BMI of PD patients may reduce the risk of falls within this population. These conclusions are based on the results of functional tests, particularly the Up and Go test, which exhibited significant improvement following

supplementation. Furthermore, an appropriately selected dose of vitamin D_3 normalizes concentrations of vitamin D and its metabolites at optimal levels.

In the second study, we focused on how vitamin D_3 supplementation adjusted to patients' BMI combined with DBS affects inflammation and the kynurenine cycle in PD. We found a significant decrease in the inflammatory marker TNF-α as a result of supplementation. In addition, we showed that the metabolism of the kynurenine cycle shifts toward the neuroprotective side – in the supplemented group, we observed an upward trend in kynurenic acid levels after 12 weeks of supplementation, and in the non-supplemented group a significant increase in 3-hydroxykinurenic acid levels and a significant decrease in picolinic acid levels.

The results presented in the series of papers included in the dissertation indicate that regular physical activity can indeed slow the progression of PD. Adequate vitamin D_3 supplementation adjusted to the patients' BMI leads to optimal concentrations of vitamin D and its metabolites in the blood. Consequently, it can contribute to improving the quality of life of these patients – reducing the risk of falls. In addition, it lowers inflammatory markers and regulates the kynurenine cycle toward neuroprotective metabolites. These findings support the notion that vitamin D_3 possesses neuroprotective properties, and when dosed appropriately based on BMI, it may be considered as an adjunct to DBS treatment in PD patients. An additional positive aspect is that our proposed supplementation is inexpensive which may be positively received by patients. These results are the first to consider adjusting the supplementation dose to the BMI in PD and the first to consider PD patients treated with DBS.

keywords: Parkinson's disease, vitamin D, deep brain stimulation, BMI, inflammation, kynurenine pathway, functional parameters, diet, physical activity

1. Wprowadzenie

1.1 Choroba Parkinsona

Choroba Parkinsona (*Parkinson's Disease,* PD) związana jest ze starzeniem organizmu i jest drugą co do częstości występowania chorobą neurodegeneracyjną. Według danych Światowej Organizacji zdrowia liczba pacjentów w 2019 przekraczała 8,5 miliona. Ze względu na proces starzenia się społeczeństwa zakłada się, że liczba ta będzie wzrastać w przeciągu najbliższych lat [1]. Objawy pojawiające się w trakcie trwania choroby możemy podzielić na motoryczne takie jak: bradykinezja, sztywność mięśniowa, drżenie spoczynkowe oraz zaburzenia odruchów podstawnych i pozaruchowe, gdzie możemy wyszczególnić: zaburzenia mowy, depresję, zawroty głowy, zaburzenia osobowości i inne. U pacjentów z PD występuje zwiększone ryzyko upadków, co w konsekwencji prowadzi do złamań często wymagających unieruchomienia, czy też hospitalizacji [2, 3].

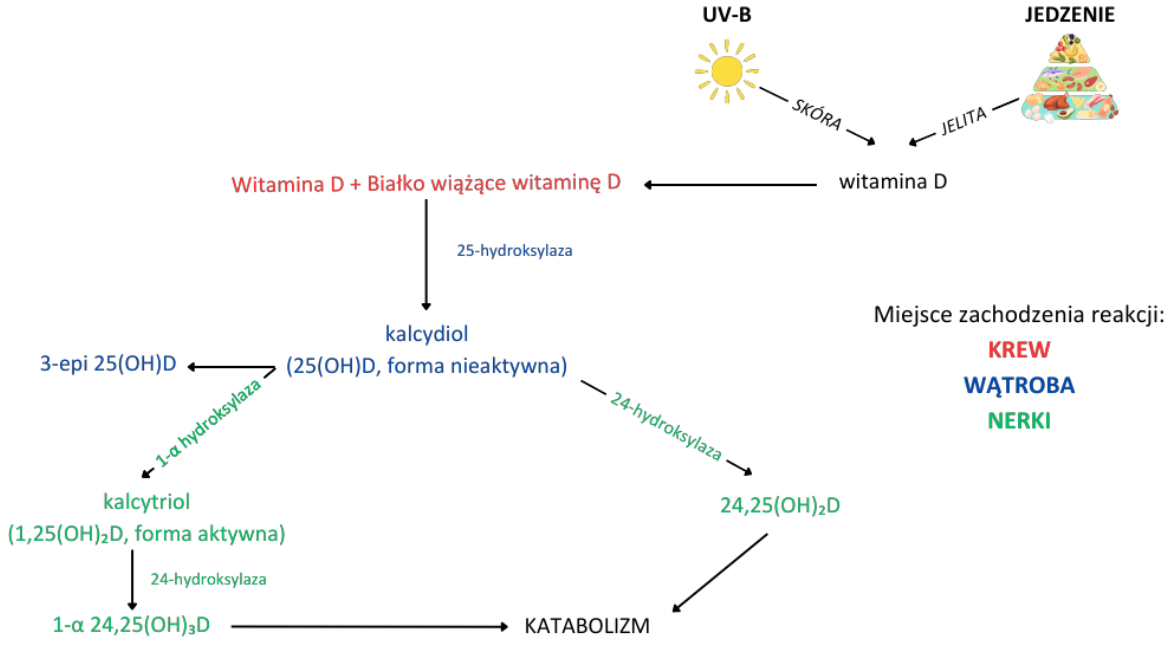
W trakcie postępowania choroby obserwuje się zanikanie produkcji dopaminy w związku z degeneracją istoty czarnej w mózgu. W badaniach pośmiertnych w mózgach chorych na PD można zauważyć powtarzające się zaburzenia takie jak: agregacja i nieprawidłowe zwijanie α-synukleiny, uszkodzenia mitochondriów, podwyższony stan zapalny i zwiększone stężenie markerów stresu oksydacyjnego. Patologia związana z białkiem jakim jest α-synukleina jest często opisywana jako toksyczna dla neuronów dopaminergicznych, co prowadzi do ich degeneracji [3]. Prekursory dopaminy są najczęściej stosowaną farmakoterapią używaną w celu łagodzenia objawów choroby. Choroba na ten moment jest nieuleczalna, wobec czego stosowane leczenie skupia się na zmniejszaniu dolegliwości. Jednym z najczęściej stosowanych leków jest lewodopa, której długotrwałe stosowanie wiąże się z szeregiem skutków ubocznych. Zaliczamy do nich: generację reaktywnych form tlenu, które w konsekwencji będą prowadzić do zwiększonej autofagii i apoptozy czy uszkodzeń mitochondriów. Ponadto, obserwuje się zwiększoną odpowiedź zapalną oraz wzrost stężenia homocysteiny (*homocysteine,* Hcy), co dodatkowo zwiększa ryzyko wystąpienia chorób naczyniowych, upośledzeń poznawczych czy demencji [4, 5]. Za podwyższanie stężenia Hcy w wyniku przyjmowania lewodopy odpowiedzialna jest jej O-metylacja syntetyzowana przez O-metylotransferazę katecholową. W wyniku tej reakcji produkowana jest S-adenozylohomocysteina, która w krótkim czasie hydrolizowana jest do Hcy [6]. Podwyższone stężenie Hcy może natomiast wpływać na zmniejszoną gęstość kości i w konsekwencji zwiększać ryzyko złamań [7].

1.2 Stymulacja głęboka mózgu

Początkowo lewodopa pomaga w redukowaniu objawów motorycznych – ten okres nazywany jest „miesiącem miodowym" i dotyczy wczesnego stadium choroby. Wraz z progresem choroby „okno terapeutyczne" lewodopy zawęża się i mogą wystąpić dokuczliwe objawy uboczne. W miarę postępującego rozwoju choroby, maleje wrażliwość receptorów dopaminowych, co prowadzi do zwiększonej utraty komórek dopaminergicznych. Efektem tego jest brak trwałej reakcji na lewodopę. Skutkuje to trudnymi do przewidzenia zaburzeniami motorycznymi i wydłużonymi okresami braku działania leku. Wśród zaburzeń możemy wyróżnić sztywność mięśniową, drżenie i zastyganie przed wykonaniem ruchu, które poprzedzają kolejną dawkę leku [8]. W takim przypadku jednym z rozwiązań jest zastosowanie stymulacji głębokiej mózgu (*deep brain stimulation,* DBS), w celu zmniejszenia dolegliwości ze strony objawów motorycznych oraz zmniejszenia dawki farmaceutyków. U pacjentów z PD najczęstszym miejscem wszczepiania elektrod stymulatora są jądra niskowzgórzowe [9, 10].

1.3 Witamina D

Witamina D jest jedną z najważniejszych witamin w naszym organizmie. Jej głównym zdaniem jest między innymi utrzymywanie równowagi wapniowo-fosforowej [11]. Metabolizm witaminy D przedstawiony został na Ryc. 1. Witamina D może być syntetyzowana przezskórnie pod wpływem promieniowania UV-B lub możemy przyjmować ją z pożywieniem. Po ekspozycji na słońce w skórze zachodzi przemiana 7-dehydrocholesterolu w cholekalcyferol. Następnie jest on hydroksylowany przy udziale 25-hydroksylazy do kalcydiolu (25(OH)D), czyli nieaktywnej formy witaminy D. Jednak to właśnie ten metabolit jest najczęściej używany do oznaczania stężenia witaminy D w organizmie ludzkim ze względu na swój długi czas półtrwania we krwi, w przeciwieństwie do aktywnej formy jaką jest kalcytriol ($1,25(OH)_2D$), który syntetyzowany jest przy udziale 1α-hydroksylazy. W celu zapobieganiu toksycznemu akumulowaniu 25(OH)D organizm jest zaopatrzony w system obronny, który przy udziale 24-hydroksylazy przekształca 25(OH)D w $24,25(OH)_2D$, który później ulega rozpadowi i wydaleniu z organizmu (Ryc. 1).



Rycina 1. Metabolizm witaminy D. Opracowanie własne.

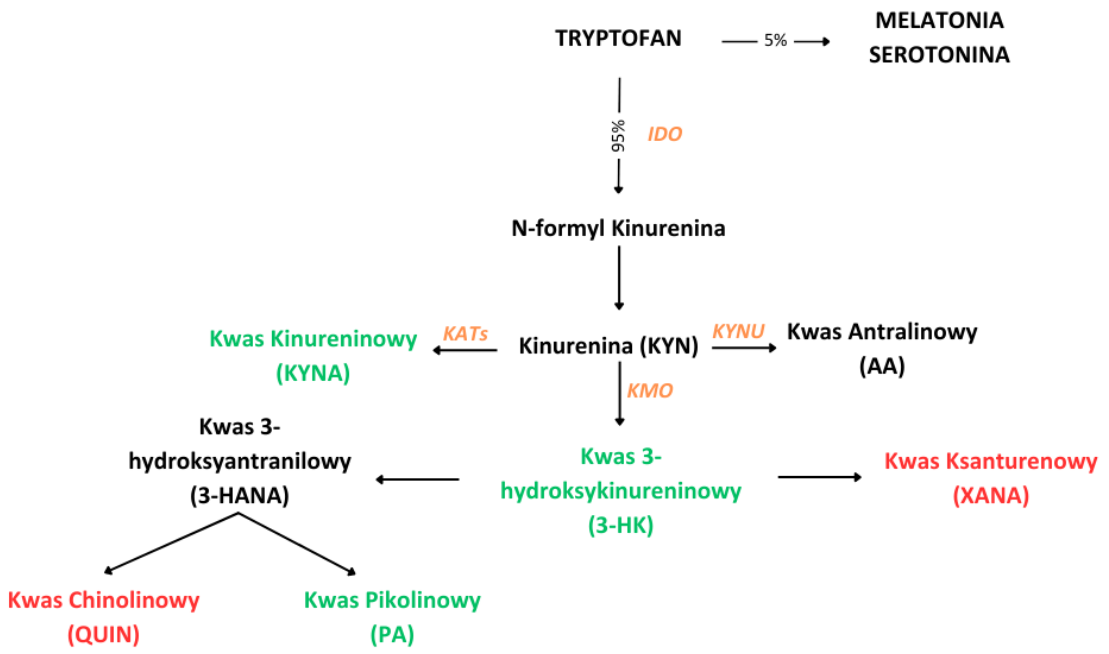
W szerokości geograficznej Polski występuje stosunkowo niewiele słonecznych dni w roku kalendarzowym, co prowadzi do częstych niedoborów witaminy D w naszym regionie. Dostarczenie odpowiednich ilości witaminy D w pożywieniu jest stosunkowo trudne, dlatego też zaleca się jej całoroczną suplementację [12–14]. Niedobory witaminy D w trakcie przebiegu PD są potwierdzone wieloma badaniami. Konsekwencje te mają nie tylko wpływ na pogorszenie przebiegu choroby, lecz także zwiększone ryzyko wystąpienia depresji, podniesienie stężenia markerów prozapalnych, osłabienie siły mięśniowej oraz większe ryzyko upadków. Te z kolei mogą prowadzić do złamań, spowodowanych obniżoną (zmniejszoną) gęstością kości [15–18].

W dalszym ciągu suplementacja witaminą D_3 u pacjentów z PD nie jest tak powszechna jak powinna być. W badaniach wykazano, że pacjenci z PD mają mniejsze stężenia $25(OH)D_3$ we krwi w porównaniu do zdrowych osób w tym samym wieku i są to wartości poniżej optymalnych (<30 ng/ml). Dlatego też dawkowanie witaminy D_3 w tej jednostce chorobowej powinno być wyższe. W badaniu sugerujemy dawkę opartą o wskaźnik masy ciała (*Body Mass Index*, BMI) – im wyższe BMI tym wyższa dawka. Wyższe BMI w tej grupie chorych jest skorelowane z większą zawartością tkanki tłuszczowej, co może wpływać na rozprowadzanie witaminy D w organizmie – badania pokazują, że u osób z nadwagą czy otyłością powinno się stosować większe dawki niż u osób z prawidłową masą ciała [19, 20]. Na ten moment niewiele badań, które biorą pod uwagę wpływ suplementacji

witaminą D_3 na przebieg PD, nie wspominając o chorych na PD z DBS, a jeśli są to w ustalaniu dawki nie biorą pod uwagę BMI pacjentów [21, 22].

1.4 Cykl kinureninowy i stan zapalny w chorobie Parkinsona

Głównym szlakiem metabolizmu tryptofanu (95%) jest szlak kinureninowy (*Kynurenine Pathway*, KP). Pozostałe 5% jest przekształcane w serotoninę, syntetyzowaną następnie do melatoniny. Metabolizm KP został przedstawiony na Ryc. 2. KP aktywowany jest przez 2,3-dioksygenazę indoloaminową (*Indoleamine 2,3-Dioxygenase*, IDO). Tryptofan w pierwszej kolejności przekształca się w N-formylokinureninę, która ze względu na brak stabilności jest bardzo szybko metabolizowana do kinureniny (*Kynurenine*, KYN). Następnie KYN może być katabolizowana w trzech różnych kierunkach: do 3-hydroksykynureniny (*3-hydroksykynurenine*, 3-HK), kwasu kinureninowego (*Kynurenic Acid*, KYNA) lub kwasu antranilowego (*Anthranilic Acid*, AA). KYNA ma właściwości neuroprotekcyjne. 3-HK, który jest neurotoksyczny, jest przekształcany w kwas 3-hydroksyantranilowy (*3-hydroxyantrhranilic Acid*, 3-HANA), a następnie katabolizowany do kwasu chinolinowego (*Quinolinic Acid*, QUIN) lub kwasu pikolinowego (*Picolonic Acid*, PA), z których pierwszy jest neurotoksyczny zaś drugi może działać neuroprotekcyjnie. 3-HK może być również przekształcany do kwasu ksanturenowego (*Xanthurenic Acid*, XANA), który również ma właściwości neurotoksyczne (Ryc. 2). KP jest często zaburzony w PD, nasilona zostaje produkcja metabolitów o właściwościach neurotoksycznych, a stężenie metabolitów o właściwościach neuroprotekcyjnych obniża się [23–25].



Rycina 2. Szlak Kinureninowy. Opracowanie własne. Na zielono zaznaczono związki o charakterze neuroprotekcyjnym, na czerwono zaznaczono związku o charakterze neurotoksycznym. Skróty użyte na rycinie: IDO – 2,3-dioksygenaza indoloaminy, KATs – aminotransferazy kinureniny, KYNU – kinureninaza, KMO – 3-monooksydaza kinureniny.

W porównaniu do zdrowych osób w tym samym wieku, w PD stan zapalny często jest podwyższony [26]. Wykazano, że podwyższone stężenie białka C-reaktywnego (*C-reactive protein*, CRP) we krwi może prognozować zwiększone prawdopodobieństwo wystąpienia choroby Parkinsona [27]. W badaniu z 2019 roku autorzy wykazali, że stężenie czynnika martwicy nowotworów-alfa (*tumor necrosis factor-alpha*, TNF-α) było wyższe u pacjentów z PD niż u zdrowych osób w tym samym wieku [28]. W innym badaniu wykazano, że stężenie cytokin prozapalnych, w tym interleukiny-6 (*interleukin-6*, IL-6) było wyższe u pacjentów z PD w porównaniu do grupy kontrolnej [29]. Stan zapalny jest często połączony ze starzeniem organizmu, co może przyczyniać się do stymulacji KP. Pierwszy enzym w KP, IDO może być regulowany przez obecność TNF-α czy też IL-6, co w konsekwencji może powodować zwiększone ryzyko wystąpienia chorób neurodegeneracyjnych [30, 31].

Biorąc pod uwagę wszystkie aspekty i chęć zgłębienia tematu suplementacji witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS, wyszczególniłam cele rozprawy doktorskiej.

2. Cele rozprawy doktorskiej

Cele pracy przedstawiono poniżej:

1. Ocena wpływu aktywności fizycznej i stosowania suplementów diety na przebieg PD.
2. Zbadanie efektywności suplementacji witaminą D_3 dawką dobraną do BMI pacjentów z PD z DBS na stężenie metabolitów witaminy D w surowicy.
3. Sprawdzenie czy suplementacja witaminą D_3 dawką dobraną do BMI pacjentów może wpływać na parametry funkcjonalne u pacjentów z PD leczonych przy użyciu DBS.
4. Określenie czy suplementacja witaminą D_3 dawką dobraną do BMI pacjentów może wpływać korzystnie na stężenie markerów stanu zapalnego i metabolitów cyklu kinureninowego w surowicy u pacjentów z PD leczonych przy użyciu DBS.
5. Identyfikacja roli suplementacji witaminą D_3 jako wspomagania leczenia w PD u pacjentów z DBS.

Wyżej wymienione cele zostały zrealizowane w cyklu opublikowanych prac naukowych ujętych w niniejszej rozprawie doktorskiej.

3. Omówienie publikacji wchodzących w skład rozprawy doktorskiej.

Pracę doktorską tworzy cykl trzech artykułów opublikowanych w indeksowanych czasopismach naukowych (1 praca przeglądowa, 2 prace oryginalne).

3.1 Pierwsza publikacja

Praca przeglądowa *Chromiec, P. A., **Urbaś, Z. K.**, Jacko, M., & Kaczor, J. J. (2021). The Proper Diet and Regular Physical Activity Slow Down the Development of Parkinson Disease. Aging and disease, 12(7), 1605–1623. https://doi.org/10.14336/AD.2021.0123* miała na celu przedstawienie wpływu aktywności fizycznej (AF) i stosowania suplementów diety na przebieg PD.

W wyniku przeglądu literatury ustalono, że regularna AF jest jednym z fundamentalnych aspektów procesu „zdrowego starzenia" [32]. Fakt, że PD dotyka starsze osoby, stanowi potwierdzenie, iż tę grupę pacjentów powinno zachęcać się do uprawiania systematycznej aktywności ruchowej. W pracy opisano wybrane formy stosowania AF, które w wyniku badań na ludziach wykazały pozytywny wpływ na przebieg PD.

1. Ćwiczenia aerobowe – wykazano, że stosowanie ćwiczeń na bieżni, na której jest możliwość dostosowania tempa oraz nachylenia, jest korzystne do wspomagania terapii w PD. W trakcie rozwoju choroby chód pacjentów pogarsza się, dlatego też chodzenie przez nich na bieżni może spowalniać ten proces. Dodatkowo może wpływać na zmniejszanie ilości upadków, które w tej grupie są częstym zjawiskiem, powodować zwiększanie siły mięśniowej oraz wzmacniać wydolność krążeniowo-oddechową [33–36].
2. Nordic walking – jest uważany za udoskonaloną formę spacerowania, ponieważ dzięki używanym kijkom angażuje całe ciało do pracy. W badaniach wykazano, że już 6 tygodniowy trening poprawia tempo chodu i jakość życia u chorych na PD oraz w ich rodzinach [37].
3. Trening siłowy/oporowy – potwierdzono badaniami, że trening siłowy w PD poprawia siłę mięśniową, jakość życia, ruchomość oraz zwiększa beztłuszczową masę ciała [38, 39].
4. Choreoterapia – wykazano, że taniec pozytywnie wpływa na mobilność, tempo chodu oraz równowagę w PD. Ponadto, umożliwia ćwiczenie rozpoczynania ruchu oraz jego dokładności, planowania i pamięci, a także wielozadaniowości.

Muzyka zmniejsza intensywność objawów pozaruchowych poprawiając samopoczucie pacjentów [40, 41].

5. Tai Chi – wpływa nie tylko na aspekty ruchowe, ale również psychologiczne takie jak między innymi zmniejszanie stresu [42, 43]. W jednym z badań wykazano, że Tai Chi może powodować spowolnienie postępu PD oraz zmniejszenie dziennej dawki lewodopy [44].

Badania, które potwierdzają neuroprotekcyjne działanie AF w przebiegu PD były przeprowadzane również na modelu zwierzęcym. W badaniu z 2011 roku autorzy wykazali, że trening aerobowy działa ochronnie na neurony i mitochondria, zwiększa stężenie neurotroficznego czynnika pochodzenia mózgowego [45]. Podsumowując, AF w PD pozwala na zmniejszenie upośledzeń ruchowych oraz zaburzenia równowagi, poprawia znacząco wyniki Ujednoliconej Skali Oceny Choroby Parkinsona części III (*Unified Parkinson's Disease Rating Scale-III,* UPDRS-III), wydłuża długość kroku i zwiększa prędkość chodu. Sugeruje się, że AF może spowalniać tempo rozwoju PD i zmniejszać ryzyko wystąpienia PD u zdrowych osób [46–49]. Pomimo obiecujących wyników badań na modelach zwierzęcych nie ma wielu badań na ludziach, które potwierdzałyby skuteczność jednego, konkretnego rodzaju treningu. Zaproponowanie jednego właściwego rozwiązania jest więc problematyczne, niemniej jednak regularne uprawianie AF o umiarkowanej intensywności jest korzystne w spowalnianiu rozwoju PD. Dodatkowo AF może wpływać na KP. W badaniach wykazano, że w mięśniu, który jest trenowany zwiększa się aktywność aminotransferazy kinureninowej, która pozwala na obwodowe przekształcanie KYN w kierunku KYNA, co skutkuje zapobieganiem przenikania KYN do mózgu. Dodatkowo AF zmniejsza stężenie neurotoksycznych metabolitów KP [50, 51].

Kolejnym aspektem sprawdzanym w wyżej wymienionej pracy było stosowanie suplementacji w diecie. Podobnie jak z AF, zdrowa i zbilansowana dieta jest jednym z czynników, które wspiera „zdrowe starzenie" organizmu. Suplementacja w chorobach neurodegeneracyjnych może przyczyniać się do zmniejszania intensywność dolegliwości.

W badaniach opisuje się skuteczność niektórych suplementów, które mogą wpływać na przebieg choroby czy też intensywność objawów. Podczas leczenia PD wielu pacjentów stosuje lewodopę. W wyniku jej przyjmowania, w związku ze zwiększonym zapotrzebowaniem na witaminy z grupy B, które są potrzebne do jej metabolizowania, może zwiększać się stężenie Hcy we krwi. Podwyższone stężenie Hcy może prowadzić nie tylko do zmniejszania siły mięśniowej, ale też przyczyniać się do wyższego ryzyka upadków i złamań ze względu na zmniejszenie gęstości kości. Z tego względu stosowanie

suplementacji witaminami z grupy B (kwasu foliowego i witaminy B_{12}) poleca się w tej grupie pacjentów, w celu obniżenia stężenia Hcy w procesie remetylacji przy ich udziale [52, 53].

Pacjenci z PD mają obniżone stężenie $25(OH)D_3$ w porównaniu do osób zdrowych w tym samym wieku. Głównym zadaniem witaminy D jest regulowanie równowagi wapniowo-potasowej, ale jej działanie nie skupia się jedynie na tym. Pomaga również w obniżaniu stanu zapalnego poprzez zmniejszanie syntezy cytokin prozapalnych, zmniejsza stres oksydacyjny i zwiększa biogenezę mitochondriów [54–56].

W PD polecane jest stosowanie jednej z najzdrowszych diet na świecie, jaką jest dieta śródziemnomorska (bogata w świeże warzywa i owoce, produkty zbożowe, strączki, orzechy, sery i jogurty, oliwę z oliwek, ryby i owoce morza przy jednoczesnym ograniczeniu cukrów oraz mięsa – zwłaszcza wołowiny i tłuszczy pochodzenia zwierzęcego) [57, 58]. Istotne jest spożywanie odpowiedniej ilości kwasów tłuszczowych (bogate w nie są między innymi tłuste ryby takie jak łosoś, makrela i śledź), które zwiększają pobudliwość błon nerwowych, przyspieszają tempo przewodnictwa nerwowego oraz chronią przed szkodliwym działaniem stresu oksydacyjnego [59].

W pracy zostały opisane niektóre z nutriceutyków takie jak kurkumina (obecna w przyprawie curry) – wykazano jej działanie antyoksydacyjne, przeciwzapalne, a dodatkowo toksyczność α-synukeliny zmniejsza się po jej stosowaniu [60]. Luteolin (można go znaleźć w brokułach, zielonym pieprzu i tymianku) – wykazuje silne działanie neuroprotekcyjne [61], genisteina (obecna w soi) – wykazuje działanie neuroprotekcyjne chroniąc komórki nerwowe przed stresem oksydacyjnym [62]. Kwercetyna – ma działanie antyoksydacyjne i przeciwzapalne [63], resweratrol (można go znaleźć w czerwonym winie i gorzkiej czekoladzie) – efektywny antyoksydant i antydepresant [64], antocyjany (do spożycia razem z wieloma warzywami i owocami) – badania pokazują, że przyjmowanie autocyjanów z dietą może zmniejszać ryzyko wystąpienia PD [65], Ginkgo Biloba – poprawia pamięć i koncentrację [66], żeń-szeń – w przypadku jego spożycia można obserwować działanie przeciwzapalne i antyoksydacyjne [67], kofeina – może zmniejszać ryzyko wystąpienia PD gdy przyjmowana jest w dawce 3-5 mg/kg masy ciała [68], kapsaicyna (odpowiedzialna za ostry smak w papryczkach) – w połączeniu z resweratrolem wykazuje działanie neuroprotekcyjne [69] czy też sulforafan (obecny głównie w brokułach) – jest antyoksydantem [70].

W opublikowanym artykule pojawia się wiele przesłanek na temat stosowania suplementów i odpowiedniej diety, a duża część z nich oparta jest na badaniach na

zwierzętach. Nie ma wielu zarejestrowanych eksperymentów medycznych w tym temacie. Dostępna literatura sugeruje jednak, że suplementy, które zostały wymienione wyżej, mogą wpływać na wyniki testów funkcjonalnych i niektóre zmiany biochemiczne u pacjentów z PD. Należy pamiętać, że głównym aspektem będzie regularność ich stosowania, co w dużej mierze zależy od samych pacjentów. Wielu z nich poza PD jest dotkniętych otyłością oraz depresją i brak im chęci do rozpoczęcia AF, co skutkuje pogłębianiem stanu zapalnego.

Podsumowując, to badanie pozwoliło mi na realizację pierwszego celu rozprawy doktorskiej. Istnieje wiele poszlak, które sugerują, że AF i stosowanie odpowiednio dobranych suplementów diety mogą spowalniać postęp PD. Właściwe byłoby więc znalezienie terapii, która połączy te dwa elementy. Jednakże trudno jest zaproponować jedno właściwe rozwiązanie dla wszystkich chorych, ze względu na dużą zmienność osobniczą. Można założyć, że regularna AF połączona z odpowiednią suplementacją może wspomagać leczenie PD przy niskich kosztach. Reasumując, na podstawie zebranych i opublikowanych danych naukowych, zdecydowaliśmy się na przeprowadzenie badań eksperymentalnych, w których sprawdziliśmy jak suplementacja witaminą D_3 dawką dostosowaną do BMI wpływa na markery stanu zapalnego, cykl kinureninowy i parametry funkcjonalne u pacjentów z PD leczonych przy pomocy DBS.

3.2 Druga publikacja

Pierwsza opublikowana praca eksperymentalna ***Bytowska, Z. K.,*** *Korewo-Labelle, D., Berezka, P., Kowalski, K., Przewłócka, K., Libionka, W., Kloc, W., & Kaczor, J. J. (2023). Effect of 12-Week BMI-Based Vitamin D3 Supplementation in Parkinson's Disease with Deep Brain Stimulation on Physical Performance, Inflammation, and Vitamin D Metabolites. International journal of molecular sciences, 24(12), 10200. https://doi.org/10.3390/ijms241210200* miała na celu sprawdzenie czy suplementacja witaminą D_3, dawką dobraną do BMI pacjentów, wpływa na stężenie metabolitów witaminy D, markerów stanu zapalnego oraz parametry funkcjonalne u pacjentów z PD leczonych DBS.

Badanie zostało zarejestrowane na stronie ClinicalTrials.gov (NCT04768023), a na jego przeprowadzenie uzyskano zgodę Niezależnej Komisji Bioetycznej do spraw Badań Naukowych Gdańskiego Uniwersytetu Medycznego (NKBBN/522-648/2019). Badanie zostało przeprowadzone metodą podwójnie ślepej próby z placebo w grupie kontrolnej. Pacjenci zostali przydzieleni do grup w sposób losowy. Rekrutacja pacjentów odbywała się na Oddziale Neurochirurgii w Szpitalu im. Mikołaja Kopernika w Gdańsku. Trwała od Listopada 2019 do Lutego 2022, w sezonach jesienno – zimowych, aby uniknąć wpływu ekspozycji na słońce. Rekrutacja miała miejsce w samym centrum pandemii COVID-19, w związku z tym nie udało się zrekrutować zakładanej liczby pacjentów. Z tego względu, postanowiliśmy zmienić układ grup (w porównaniu ze złożoną kartą tematyczną), aby liczebność w grupach była jak największa i pozwoliła na uzyskanie wyników istotnych statystycznie. Kryteria włączenia do badania obejmowały: zgodę na udział w badaniu, DBS jąder niskowzgórzowych, brak suplementacji witaminą D_3 przed rozpoczęciem badania, brak poważnych chorób towarzyszących i deklarację zaangażowania. Zrekrutowano 50 pacjentów, w trakcie trwania badania kilkunastu pacjentów zostało z niego wykluczonych ze względu na różnorodne czynniki, które zostały opisane w pracy. W analizie uwzględniono 13 pacjentów z grupy suplementowanej (VitD), którzy otrzymywali suplementację witaminą D_3 dawką dostosowaną do ich BMI oraz 16 pacjentów w grupie kontrolnej (PL), którzy otrzymywali placebo w postaci oleju roślinnego.

Suplementacja trwała 12 tygodni, a dawka dostosowana była do BMI pacjentów – im wyższe BMI tym wyższa dawka witaminy D_3. Dawki zostały opracowane na podstawie dostępnej literatury [71–74]. Dla BMI poniżej 25 – 4000 jednostek międzynarodowych/dzień (*International Units*, IU), dla BMI pomiędzy 25, a 30 – 5000

IU/dzień, a dla BMI powyżej 30 – 6000 IU/dzień. Pacjenci byli również zachęcani do wykonywania zadanej liczby kroków w trakcie badania, rozpoczynając od 3500 kroków/dzień, aż do 7500 kroków/dzień na koniec trwania badania.

Pacjenci spotykali się z zespołem badawczym trzykrotnie. Na pierwszym spotkaniu (T0) mieli pobieraną krew, podpisywali zgodę na udział w badaniu, wykonywali testy funkcjonalne i otrzymywali jednakowe buteleczki z odpowiednią zawartością w zależności od przydziału do grupy. Na drugim spotkaniu (T1) po sześciu tygodniach ponownie byli zobligowani do pojawienia się, wykonania testów funkcjonalnych, a buteleczki z odpowiednią zawartością były uzupełniane. Po kolejnych sześciu tygodniach na trzecim spotkaniu (T2) ponownie pobierano krew oraz przeprowadzano testy funkcjonalne.

Testy funkcjonalne, które pacjenci wykonywali to Test Wstań i Idź (*Test Up and Go,* TUG), 6-minutowy test chodu (*6 minute walk test,* 6 MWT) i 10-metrowy test chodu (*10 meter walk test,* 10 MWT). W TUG pacjenci siedzieli na krześle, na słowo start musieli wstać, przejść 3 metry i wrócić z powrotem do pozycji siedzącej. Podczas 6 MWT pacjenci chodzili po korytarzu wzdłuż 15-metrowej linii, ich zadaniem było przejść jak największy dystans w czasie 6 minut, nie mogli biegać. 10 MWT polegał na starcie z pozycji stojącej i jak najszybszym przejściu 10 metrów, bez przyspieszania do biegu. Pacjenci przed wykonaniem każdego testu otrzymali instrukcje i omawiano z nimi jak poprawnie wykonać dany test. Jeśli w pierwszej próbie doszło do pomyłki, pacjent miał możliwość powtórzenia testu.

Do zmierzenia stężenia metabolitów witaminy D w surowicy użyto wysokosprawnej chromatografii cieczowej sprzężonej z tandemową spektrometrią mas (*liquid chromatography combined with tandem mass spectrometry*, LC-MS/MS), uzyskano pomiary dla $25(OH)D_3$, $25(OH)D_2$, $24,25(OH)_2D_3$ oraz epi-$25(OH)D_3$. Do pomiaru stężenia markera ogólnego stanu zapalnego – CRP wykorzystano metodę immunoenzymatyczną, użyto zestaw z Demitec hsCRP ELISA Kit, postępowano zgodnie z instrukcją producenta.

Analiza statystyczna została wykonana przy użyciu programu Statistica 13 (Statsoft, Kraków, Polska). Wykorzystano dane pacjentów, którzy ukończyli wszystkie etapy badania. Dane zostały wcześniej przetestowane pod kątem normalności, za pomocą testu W Shapiro-Wilka. Zastosowano statystyki opisowe zarówno dla informacji ogólnych, jak i badania trendów w analizowanych parametrach z wartościami średnimi z 95% przedziałem ufności. Do analizy statystycznej wykorzystano test ANOVA dla powtarzanych pomiarów. Obliczono korelację rang Spearmana. Istotność statystyczną ustalono na poziomie $p<0,05$.

Aby ustalić istotność statystyczną, zastosowano analizę wariancji (ANOVA) z testem post hoc Tukeya.

Nie zaobserwowano różnic statystycznych pomiędzy grupami. Stopień zaawansowania choroby w skali Hoen & Yahr wynosił 2,5 w obu grupach, czas od wszczepienia stymulatora to między 3 a 5 lat, czas trwania choroby między 8 a 13 lat. W stanie bez leków średnia poprawa motoryczna po stymulacji DBS, oceniana za pomocą UPDRS-III, wynosiła 45% (zakres 35-60%). Średnia redukcja dawki leku równoważnego lewodopie wyniosła 35%. Parametry stymulacji były następujące: stymulacja monopolarna u wszystkich pacjentów, częstotliwość 130 Hz, czas trwania impulsu 60 us, natężenie prądu 1,8-3,8 mA i napięcie 1,9-4,2 V.

Wykazano, że przed rozpoczęciem badania w obu grupach stężenie $25(OH)D_3$ było poniżej wartości optymalnych <30 ng/ml. Po 12 tygodniowej suplementacji witaminy D_3 wykazano, że suplementacja dawką dostosowaną do BMI pacjentów wpływa na wzrost stężenia $25(OH)D_3$ do wartości optymalnych, wzrost ten był istotny statystycznie (34,99 ± 12,27 w porównaniu do 25,55 ± 8,94 ng/ml; $p<0,0006$). Różnica między końcowym stężeniem $25(OH)D_3$ w grupie PL a początkowym nie była istotna statystycznie i odpowiednio wynosiła: 19,97 ± 8,48; 21,98 ± 10,91 ng/ml. Zmierzyliśmy również stężenie produktu katabolizmu $25(OH)D_3$ – $24,25(OH)_2D_3$. Wykazano znaczący statystycznie wzrost w grupie VitD (2,77 ± 1,02 w stosunku do 2,09 ± 1,09 ng/ml; $p<0,05$) i porównując stężenie w T2 w grupie VitD do T0 w grupie PL (2,77 ± 1,02 w porównaniu do 1,67 ± 1,15 ng/ml; $p<0,05$). W grupie PL nie wykazano różnic istotnych statystycznie. W stężeniu metabolitu epi-$25(OH)D_3$ wykazano istotny statystycznie wzrost w grupie VitD (1,03 ± 0,37 w stosunku do 1,67 ± 0,70 ng/ml; $p<0,005$) oraz porównując stężenie w grupie VitD w T2 do T0 w grupie PL (1,67 ± 0,70 w porównaniu do 0,83 ± 0,54 ng/ml; $p<0,005$), zauważono brak różnic w grupie PL. Wykazaliśmy bardzo silną, pozytywną korelację pomiędzy stężeniem $25(OH)D_3$ a stężeniami $24,25(OH)_2D_3$ i epi-$25(OH)D_3$ ($p<0,0001$). Do oznaczenia ogólnego stanu zapalnego postanowiliśmy zmierzyć stężenie CRP. Nie wykazano różnic istotnych statystycznie w obu grupach, jednakże w grupie VitD zauważyliśmy trend w kierunku obniżania stężenia CRP w surowicy.

Do sprawdzenia parametrów funkcjonalnych u pacjentów wykorzystaliśmy testy funkcjonalne. Pomiędzy grupami nie było różnic istotnych statystycznie w T0. TUG wykazał istotne statystycznie różnice w grupie VitD. W trakcie trwania badania zmniejszał się czas potrzebny pacjentom do wykonania tego testu, zmiany pomiędzy T0 a T1 i pomiędzy T0 a T2 były istotne statystycznie (13,69 ± 5,10 w stosunku do 11,96 ± 3,44 s,

$p<0,05$; 13,69 ± 5,10 w porównaniu do 11,46 ± 3,80 s, $p<0,005$). W 6 MWT zaobserwowaliśmy istotny statystycznie zwiększony dystans pokonywany przez pacjentów w grupie VitD porównując T0 do T2 odpowiednio (316,68 ± 93,45 do 350,29 ± 96,28 m; $p<0,05$). W grupie PL nie wykazano istotnych statystycznie zmian. W 10 MWT nie zaobserwowaliśmy zmian istotnych statystycznie w obydwu grupach. AF do której pacjenci byli zachęcani podczas tego badania nie była należycie monitorowana dlatego też nie można stwierdzić czy wpływała jakkolwiek na wyniki uzyskane w trakcie eksperymentu.

Podsumowując uzyskane i opublikowane wyniki w ramach przeprowadzonego badania, pozwoliły na zrealizowanie celu drugiego rozprawy. Wykazano, że suplementacja witaminą D_3, dawką dobraną do BMI pacjentów, wpływa pozytywnie na stężenie metabolitów witaminy D w surowicy pacjentów z PD leczonych przy użyciu DBS. W odpowiedzi na suplementację dochodzi do wzrostu stężenia $25(OH)D_3$ do wartości optymalnych z wartości deficytowych. To sugeruje, że dostosowywanie dawki na podstawie BMI w tej grupie pacjentów jest wskazane aby suplementacja była efektywna. Dodatkowym pozytywnym aspektem wynikającym z badania jest fakt, że stężenie $24,25(OH)_2D_3$ jest pozytywnie skorelowane z $25(OH)D_3$ co sugeruje, że mechanizmy obronne, które mają na celu zapobieganie zwiększania stężenia $25(OH)D_3$ do wartości toksycznych działają poprawnie. Trzeci cel został również zrealizowany w wyżej opisanym badaniu. Wykazano, że w wyniku 12 tygodniowej suplementacji witaminą D_3 parametry funkcjonalne u pacjentów z PD leczonych DBS poprawiają się. Czas potrzebny do wykonania TUG jest krótszy niż na początku badania w grupie suplementowanej. Jak już wcześniej wykazano, wyniki tego testu korelują dodatnio z ryzykiem upadków w tej grupie pacjentów [75]. Skrócenie czasu potrzebnego do wykonania tego testu może wiązać się ze zmniejszeniem ryzyka upadków, co w konsekwencji prowadzi bezpośrednio do zmniejszenia ryzyka złamań i zwiększenia samodzielności pacjentów. W 6 MWT dystans pokonywany przez pacjentów w grupie VitD zwiększa się po 12 tygodniowej suplementacji. Im dłuższy dystans są w stanie pokonać pacjenci tym lepsza ich wydolność oraz jakość chodu, co będzie bezpośrednio przekładać się na zwiększoną samodzielność, która prowadzi do zwiększenia jakości życia zarówno u pacjentów jak i u ich rodzin. Nie wykazano zmian istotnych statystycznie w stężeniu markera ogólnego stanu zapalnego – CRP – jednakże zarysował się trend do zmniejszania się stężenia tego markera w grupie VitD. Brak istotności może być spowodowany między innymi zbyt dużymi odchyleniami standardowymi obecnymi w wykonanych pomiarach. Cel piąty można również uznać jako zrealizowany, gdyż wykazaliśmy, że stosowanie suplementacji witaminą D_3 w PD z DBS wpływa na poprawę

parametrów funkcjonalnych co może sugerować, że suplementowanie tej witaminy jest swego rodzaju wspomaganiem leczenia.

3.3 Trzecia publikacja

Druga opublikowana praca eksperymentalna ***Bytowska, Z.K.****; Korewo-Labelle, D.; Kowalski, K.; Libionka, W.; Przewłócka, K.; Kloc, W.; Kaczor, J.J. Impact of 12 Weeks of Vitamin* D_3 *Administration in Parkinson's Patients with Deep Brain Stimulation on Kynurenine Pathway and Inflammatory Status.* Nutrients ***2023****,* 15*, 3839. https://doi.org/10.3390/nu15173839* jest uzupełnieniem badania przeprowadzonego w ramach pierwszej pracy oryginalnej. Aspektem, który został zbadany był wpływ suplementacji witaminą D_3 dawką dostosowaną do BMI pacjentów, na metabolity cyklu kinureninowego i markery stanu zapalnego w PD z użyciem DBS.

W analizie danych w tym badaniu ujęto większą liczbę pacjentów w porównaniu do poprzedniej pracy. Kilku pacjentów wykluczono z poprzedniego badania, ponieważ nie pojawili się na drugim spotkaniu podczas którego były przeprowadzane testy funkcjonalne. W badaniu uwzględniono 15 pacjentów z grupy VitD i 21 z grupy PL. Dawki suplementacyjne były takie same jak w badaniu opisanym w pierwszej pracy eksperymentalnej.

Do oznaczenia stężenia metabolitów witaminy D i metabolitów KP w surowicy użyto wysokosprawnej chromatografii cieczowej sprzężonej z tandemową spektrometrią mas (*liquid chromatography combined with tandem mass spectrometry*, LC-MS/MS), uzyskano pomiary dla $25(OH)D_3$, $24,25(OH)_2D_3$, KYN, KYNA, 3-HK, XANA i PA. Do pomiaru stężenia markerów stanu zapalnego IL-6 i TNF-α wykorzystano metodę immunoenzymatyczną i użyto odpowiednio zestawów z R&D Human IL-6 Quantikine HS ELISA Kit i Biorbyt Human TNF alpha ELISA Kit, postępowano zgodnie z instrukcjami producenta.

Do analizy wykorzystano program statystyczny Statistica 13 (Statsoft, Kraków, Polska). Dane, które zostały wzięte pod uwagę, pochodziły od pacjentów, którzy ukończyli wszystkie interwencje (n=36). Do sprawdzenia normalności danych wykorzystano test W Shapiro-Wilka. Zastosowano statystyki opisowe zarówno dla informacji ogólnych, jak i badania trendów w analizowanych parametrach z wartościami średnimi i 95% przedziałami ufności. Do analizy statystycznej zastosowano ANOVA: test dla powtarzanych pomiarów i jednokierunkowy. Obliczono korelację rang Spearmana. Istotność statystyczną ustalono na poziomie $p<0,05$. Do określenia istotności statystycznej wykorzystano test post-hoc Fishera najmniejszej istotnej różnicy.

Ponownie nie wykazano różnic statystycznych między grupami. Stopień zaawansowania choroby w skali Hoen & Yahr, czas od wszczepienia stymulatora i czas trwania choroby były takie same jak w poprzednim badaniu.

W wyniku pomiarów stężeń metabolitów KP nie wykazano istotnych statystycznie zmian w T0 pomiędzy grupami. Stężenie KYN wzrosło znacząco w grupie VitD (382,14 ± 68,34 w porównaniu do 422,17 ± 109,61 ng/ml; $p<0,05$). Dodatkowo wykazano istotną statystycznie różnicę w stężeniu KYN w T0 w grupie PL w porównaniu do T2 w grupie VitD (364,64 ± 69,83 w stosunku do 422,17 ± 109,61 ng/ml; $p<0,05$). W stężeniu KYNA nie zaobserwowaliśmy znaczących statystycznie zmian, jednak w grupie VitD można było zauważyć trend rosnący (6,60 ± 1,42 ng/ml w porównaniu do 7,29 ± 1,58 ng/ml; $p = 0,067$). Wykazaliśmy istotny statystycznie wzrost w stężeniu 3-HK w grupie PL (7,38 ± 3,92 w stosunku do 8,78 ± 4,93 ng/ml; $p<0,05$). Dodatkowo po zastosowanej suplementacji zaobserwowano istotne statycznie różnice w stężeniu 3-HK między grupami w T2 (6,23 ± 1,73 w VitD w porównaniu do 8,78 ± 4,93 ng/ml w PL; $p<0,05$). Stężenie PA znacząco obniżyło się w grupie PL (4,66 ± 2,03 w stosunku do 3,38 ± 0,84 ng/ml; $p<0,0006$). W grupie VitD nie było różnic istotnych statystycznie. Wykazano istotną statystycznie negatywną korelację między stężeniem 3-HK a $25(OH)D_3$ i $24,25(OH)_2D_3$ ($p<0,05$) oraz istotną statystycznie pozytywną korelację między TNF-α a 3-HK ($p<0,05$). Różnice między początkowym, a końcowym stężeniem 3-HK były istotnie niższe w grupie VitD w porównaniu do grupy PL (-1,14 ± 1,5 w porównaniu do 1,40 ± 2,88; $p<0,005$). Różnice w początkowym, a końcowym stężeniu PA były znacząco niższe w grupie PL w porównaniu do grupy VitD (-1,27 ± 1,74 w stosunku do -0,01 ± 1,20; $p<0,05$). Wykazaliśmy istotne obniżenie się stężenia TNF-α w grupie VitD (7,07 ± 2,30 w porównaniu do 5,98 ± 2,09 pg/ml; $p<0,05$) oraz znaczący wzrost w grupie PL (6,30 ± 2,00 pg/ml w stosunku do 7,23 ± 1,94 pg/ml; $p<0,005$). W stężeniu IL-6 nie zaobserwowano zmian istotnych statystycznie.

Reasumując, uzyskane podczas tej pracy wyniki, pozwoliły na ukończenie realizacji czwartego oraz piątego celu rozprawy doktorskiej. Wykazano, że suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS, doprowadza do regulowania stężenia metabolitów KP. Ustalono, że w wyniku suplementacji stężenie neurotoksycznego 3-HK w VitD obniża się w stosunku do grupy kontrolnej. Dodatkowo wykazano, że stężenie tego metabolitu znacząco wzrasta w trakcie 12 tygodni w grupie placebo, przy jednoczesnym istotnym spadku neuroprotekcyjnego metabolitu PA w tej samej grupie. Zauważono trend wzrostowy neuroprotekcyjnego metabolitu jakim jest KYNA w grupie VitD. Dodatkowo wykazano negatywną korelację pomiędzy 3-HK a

$25(OH)D_3$ i $24,25(OH)_2D_3$ co sugeruje, że deficyt witaminy D w organizmie przyczynia się do zwiększania stężenia neurotoksycznego metabolitu 3-HK. Co więcej wykazano pozytywną korelację pomiędzy TNF-α a 3-HK co wskazuje, że podwyższony stan zapalny jest związany z produkcją i gromadzeniem większych ilości neurotoksycznego metabolitu KP. Ponadto, w grupie VitD zmniejszyło się znacząco stężenie TNF-α przy jednoczesnym znaczącym wzroście w grupie PL. Powyższe dowodzi, że witamina D_3 może mieć działanie neuroprotekcyjne w grupie pacjentów z PD leczonych DBS. Nasze wyniki podkreślają, że niedobory witaminy D oraz zaburzenia w metabolizmie KP są mocno skorelowane z rozwojem PD, co wskazuje, że oba czynniki mogą być związane z patogenezą PD, a suplementowanie i doprowadzanie stężenia witaminy D do odpowiednich wartości może przyczyniać się do wspomagania leczenia i poprawę jakości życia u pacjentów z PD.

4. Wnioski

1. Regularna aktywność fizyczna połączona z odpowiednio dobraną suplementacją pozytywnie wpływa na spowolnienie progresji PD.
2. Suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS doprowadza do wzrostu $25(OH)D_3$ w surowicy do wartości optymalnych (>30 ng/ml).
3. Suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS poprawia parametry funkcjonalne pacjentów, co zmniejsza ryzyko występowania upadków.
4. Suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS obniża stężenie markerów stanu zapalnego w surowicy. W grupie bez suplementacji zwiększa się stężenie neurotoksycznego metabolitu (3-HK) cyklu kinureninowego, a stężenie neuroprotekcyjnego metabolitu (PA) obniża się. Stężenie $25(OH)D_3$ jest negatywnie skorelowane ze stężeniem (neurotoksycznego) 3-HK.
5. Suplementacja witaminą D_3, dawką dostosowaną do BMI pacjentów z PD leczonych DBS, może być rozważana jako wspomaganie leczenia PD ze względu na swoje działanie neuroprotekcyjne.

5. Podsumowanie

PD jest jedną z najczęściej występujących chorób neurodegeneracyjnych. Na ten moment, z uwagi na to, że nie jest możliwe jej wyleczenie, można działać jedynie objawowo i zmniejszać uciążliwość dolegliwości, które występują w trakcie przebiegu choroby.

W trakcie rozwoju PD zauważyliśmy następujące zmiany metaboliczne w organizmie pacjentów: deficyty w stężeniach witaminy D, podwyższenie stężenia markerów stanu zapalnego, czy też zaburzenia w przebiegu KP. Dodatkowo możemy obserwować pogorszenie parametrów funkcjonalnych u pacjentów, co skutkuje zwiększonym ryzykiem upadków. Celem rozprawy było sprawdzenie czy dopasowana do BMI pacjentów suplementacja witaminą D_3 może wpływać na poprawienie wyżej wymienionych elementów i wspomagać wolniejszy przebieg choroby.

W pracy przeglądowej [32] wykazaliśmy stan wiedzy dotyczący AF i stosowania odpowiednich suplementów diety w PD. Potwierdziliśmy, że regularna AF może przyczyniać się do spowolnienia postępu choroby, jak i wpływać pozytywnie na jakość życia pacjentów. Poprawa wydolności oraz sprawności motorycznej pacjentów przyczynia się do zmniejszenie ryzyka upadków u chorych z PD. Ponadto może poprawiać wydolność u tych pacjentów, poprawiać mobilność czy też dokładność ruchów, a także wpływać pozytywnie na aspekty psychologiczne. Stosowanie regularnej AF i opisanych w pracy suplementów diety w trakcie trwania choroby może wpływać korzystnie na spowalnianie rozwoju choroby.

W pierwszej pracy eksperymentalnej [76] wykazano, że 12 tygodniowa suplementacja witaminą D_3 dawką dostosowaną do BMI pacjentów z PD leczonych DBS, wpływa korzystnie na stężenie $25(OH)D_3$ doprowadzając do optymalnych stężeń (>30 ng/ml) i stężenie metabolitów witaminy D oraz poprawia wyniki testów funkcjonalnych. Biorąc pod uwagę fakt, że znacząco poprawiają się wyniki TUG w grupie suplementowanej można założyć, iż w wyniku suplementacji zmniejszy się ryzyko upadków w tej grupie pacjentów, co znacząco poprawi ich jakość życia. Może także pozytywnie wpłynąć na ich samowystarczalność i niezależność w czynnościach dnia codziennego, przykładowo poprzez zmniejszenie lęku przed samodzielnym wyjściem z domu. Warte podkreślenia jest, że po raz pierwszy wykazaliśmy, iż zmiany te są wynikiem połączenia DBS z jednoczesną suplementacją witaminy D_3 w dawkach dostosowanych do BMI pacjentów. Najistotniejszym wnioskiem płynącym z niniejszej pracy jest prawdopodobieństwo

zmniejszenia ryzyka upadków w tej grupie pacjentów, co może okazać się kluczowe u tych chorych.

W drugiej pracy [35] wykazaliśmy po raz pierwszy, że połączenie leczenia DBS z jednoczesną suplementacją witaminą D_3 dawką dostosowaną do BMI pacjentów, wpływa na stan zapalny oraz KP u pacjentów z PD. Zaobserwowaliśmy istotny spadek TNF-α w wyniku 12 tygodniowej suplementacji witaminą D_3. Dodatkowo w grupie pacjentów bez suplementacji wykazaliśmy wzrost neurotoksycznego metabolitu (3-HK) i spadek neuroprotekcyjnej substancji (PA). W grupie suplementowanej była tendencja wzrostowa w innym czynniku o właściwościach neuroprotekcyjnych (KYNA). Ustaliliśmy, że im wyższe stężenie TNF-α tym wyższa zawartość 3-HK, a im niższe stężenie $25(OH)D_3$ tym wyższe stężenie 3-HK, co może wskazywać, że witamina D_3 prezentuje neuroprotekcyjne właściwości – zmniejszając stan zapalny i zmniejszając zawartość 3-HK w surowicy. Niedobry witaminy D i zaburzenia w KP są mocno ze sobą powiązane i można zaobserwować, że doprowadzenie stężenia witaminy D do wartości optymalnych pozwala na poprawienie wyników u tych pacjentów.

Wyniki badań przedstawione w cyklu prac wchodzących w skład rozprawy doktorskiej wskazują, że połączenie leczenia DBS z suplementacją witaminy D_3 dostosowanej do BMI pacjentów w PD, może przyczyniać się do poprawy jakości życia tych pacjentów – zmniejszając ryzyko upadków. Doprowadza do optymalnego stężenia witaminy D i jej metabolitów we krwi. Dodatkowo pomaga w zredukowaniu poziomu stanu zapalnego i reguluje KP w kierunku neuroprotekcyjnych metabolitów. To pozwala sugerować , że witamina D_3 prezentuje neuroprotekcyjne właściwości i może być stosowana jako wspomaganie leczenia PD. Dodatkowym pozytywnym aspektem jest fakt, że proponowana przez nas suplementacja jest niedroga co może być przychylnie odebrane przez chorych. Wyniki te są pierwszymi, w których wzięto pod uwagę dostosowanie dawki suplementacyjnej do BMI w PD i pierwszymi, w których uwzględniono pacjentów z PD leczonych DBS.

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Review

The Proper Diet and Regular Physical Activity Slow Down the Development of Parkinson Disease

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ABSTRACT: From year to year, we know more about neurodegeneration and Parkinson's disease (PD). A positive influence of various types of physical activity is more often described in the context of neuroprotection and prevention as well as the form of rehabilitation in Parkinson's patients. Moreover, when we look at supplementation, clinical nutrition and dietetics, we will see that balancing consumed products and supplementing the vitamins or minerals is necessary. Considering the biochemical pathways in skeletal muscle, we may see that many researchers desire to identify molecular mediators that have an impact through exercise and balanced diet on human health or development of the neurodegenerative disease. Therefore, it is mandatory to study the potential mechanism(s) related to diet and factors resulted from physical activity as molecular mediators, which play a therapeutic role in PD. This review summarizes the available literature on mechanisms and specific pathways involved in diet-exercise relationship and discusses how therapy, including appropriate exercises and diet that influence molecular mediators, may significantly slow down the progress of neurodegenerative processes. We suggest that a proper diet combined with physical activity will be a good solution for psycho-muscle BALANCE not only in PD but also in other neurodegenerative diseases.

Key words: Parkinson's disease, physical exercise, diet, neuroinflammation, neuroprotection

Neurodegenerative diseases (ND) are one of the main problems of an aging society that relies on neurodegeneration, which leads to neuron death. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD). The economic cost of PD is estimated to exceed $23 billion annually in the United States alone [1]. PD is a complex and highly prevalent neurodegenerative disorder characterized by disabling motor abnormalities such as bradykinesia, postural instability, and gait disorders, often leading to falls [2, 3]. There is also an increased risk of fractures, aggravated disability, poor quality of life, and reduced survival [4]. PD is characterized by the loss of dopamine (DA) due to the degeneration of substantia nigra pars compacta (SNpc) in dopaminergic neurons [5]. Conversely, in PD the early and preferential loss of DA in the dorsal basal ganglia leads to diminished automatic and increased cognitive (frontal cortex) control of motor movements. Consequently, individuals with PD must handle and sustain a more extensive cognitive load to execute either motor or cognitive tasks [6, 7].

It has been found that in PD exercise stimulates DA synthesis in remaining dopaminergic cells and thus reduces symptoms [8, 9]. Moreover, it has been suggested

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that five fundamental principles of exercise enhance neuroplasticity in Parkinson patients. They are as following: (a) intensive activity maximizes synaptic plasticity; (b) activity promotes greater structural adaptation; (c) activity that is rewarding increase DA levels and promotes learning/re-learning; (d) dopaminergic neurons are highly responsive to exercise and inactivity ("use it or lose it"), and (e) where exercise is introduced at an early stage of the disease, progression may be slower [9-11]. Furthermore, exercise may exert its neuroprotective action by attenuating oxidative stress, a mechanism that has frequently been considered in PD genesis. Besides, regular exercise may activate antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) [10] in the CNS, reduce glutamate receptors involved in the excitotoxicity, and downregulate expression of genes involved in apoptosis such as Bcl-x and DP-5. It may also modify the relationship of the DAT transsynaptic against vesicular (DAT/vesicular monoamine transporter), which reduces the susceptibility of dopaminergic neurons to neurotoxins and cytosolic oxidation of DA [11].

During aging, mitochondria become more sensitive to the damages caused by oxidative stress because antioxidant systems are less effective. If mitochondria are not working in the physiological condition, it may lead to lipids and proteins peroxidation [12]. PD patients have more problems with impaired mitochondria than age-matched controls [13, 14]. The loss of mitochondria is associated with DA neurons' loss, which is the major problem in PD. The disruption of mitochondria function is mostly measured by the activity of the electron transport chain (ETC) complexes [12]. The ETC, especially complex I in PD is inhibited by the same toxins, which induce motor dysfunctions and impair dopaminergic neurons. That fact may connect the mitochondrial dysfunction with PD and it is a good direction to investigate if we may stop or slow down this impairment by exercise [12].

Neurodegenerative impairment may connect with a cytokine-induced imbalance in the kynurenine (KYN) pathway. As this pathway provides the primary route for tryptophan (TRP) degradation, it plays a major role in the maintenance of serotonin (5-HT) synthesis and the critical balance between neurotoxic and neuroprotective metabolites. Chronic inflammation is commonly reported in severe cognitive deficits and may contribute to the pathogenesis of each of these disturbances. Consequently, the KYN pathway has become a prospective target for treatment interventions [15]. It is believed that the ketogenic diet, which seems to reduce glucose and calorie intake, may also affect the KYN pathway and brain excitability. It is also known that calorie restriction may have a neuroprotective/antiepileptic effect. KYN, synthesized from TRP, may be transformed into various metabolites. Some of them are considered neuroprotective (e.g., kynurenine acid (KYNA)), while others are neurotoxic (e.g., 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN)). Even though progress has been made in explaining the interaction of metabolites of the KYN pathway in health and disease, questions need to be answered [15].

Alternative strategies with proven anti-inflammatory benefits, such as regular exercise, may provide a simple and effective long-term strategy in treating and preventing associated disorders by influencing enzyme function and helping in the reestablishment of critical protein balances. In recent years, preclinical and clinical studies have highlighted the fundamental influence that the intestinal microbiota exerts on the gut-brain axis, which is now renamed "microbiota-gut-brain axis" [16]. Several microbially-derived molecules may control different gut functions, including metabolic, nutritional, and immune responses, and brain activity, giving rise to a microbiota-mediated bottom-up control of the CNS [17]. The gut microbiota may also indirectly influence glutamatergic pathways along the microbiota-gut-brain axis by controlling TRP metabolism. In the gut TRP, the essential amino acid, contributes to the synthesis of numerous bioactive molecules, including 5-HT, KYN, and indole derivatives, under direct and indirect microbiota control [18]. Microbiota may interact with the nervous system; perhaps the most obvious scenario would be through modulation of host neurotransmitters and/or related pathways. Bacteria have been found to have the capability to produce a range of major neurotransmitters like histamine, DA, gasotransmitters, neuropeptides, steroids, endocannabinoids and others [19].

The beneficial effect of selected physical activity in PD

This paragraph will provide that regular physical activity is one of the most important aspects of healthy aging. Moreover, it was documented that physical activity may prevent and slow down many chronic diseases such as diabetes, strokes, osteoporosis, circulatory and nervous diseases, including PD [20-22]. Pharmacological therapies are primarily used for symptomatic control and provide only short-term benefits before the disease reaches a severe stage. Physical activity and exercise may provide low-cost and universally available aids for current PD therapies. Therefore, studying the effects of physical activity and exercise on PD is substantial [23]. Several large controlled clinical studies have shown that bradykinesia, balance, and muscle strength may be improved by continuous exercise in PD's early stage [24]. In scientific reports, many forms of physical activity that may positively affect patients with PD are described.

Aerobic exercise

One of the most effective aerobic exercise forms is training on a mobile treadmill, where the pace of walking or running and the slope of the surface can be adjusted. It has been shown that aerobic training ameliorates walking in PD patients and improves gait speed, step length, and extends the distance covered [25]. It may also have a beneficial effect on reducing the number of falls and improving a sense of balance. The other data have been reported that aerobic workout strengthens muscles and improves cardiorespiratory fitness [21, 26, 27].

Nordic walking

Nordic walking, a new form of recreational sport, is recently gaining popularity. Although it was established in the 1920s in Finland, fashion has only come to it now. During nordic walking, the whole body is stimulated and engaged in the effort, and the upper limbs are strengthened more than when walking or running without sticks. Therefore, nordic walking is also used to treat patients with PD. It was observed that during the 6-week training, the walking speed has improved, and the quality of life in patients and their families has also effectively augmented [28-33].

Resistance or strength training

Resistance or strength training aim is to increase muscle mass and strength. It is crucial for people who are ill, older or even suffering from PD because due to stiffness and slowness, they are exposed to significant muscle strength deficits. It turns out that the rehabilitation, including resistance training, meaningfully improves muscle strength, mobility, quality of life, and increases lean body mass in PD patients [34-37].

Choreotherapy

Choreotherapy belongs to art therapy. It includes music, expressive movement, and dance. It is a psychotherapy method based on the idea of the indissolubility of the soul and body. It was noted that dance has a beneficial effect on mobility, walking speed, and PD patients' balance. Moreover, it was found that choreotherapy can be an exciting substitute for traditional exercises used so far during rehabilitation [38]. Music, which is an external stimulus, facilitates the beginning of the movement, and the dance itself teaches a precise movement strategy. Dance may also deal with cognitive and psychological symptoms [39]. It has been shown that dance patterns involve motor planning and memory [39] and give an opportunity to practice multitasking, e.g., the spatial and temporal execution of steps in time to the music while ensuring postural stability [40-44].

Tai Chi

Tai Chi is not only a system of stretching, balance, and coordination exercises combined with meditation, but also the art of self-defense. It was developed in the 11th century in China and is based on making slow, harmonious movements that have a positive impact on maintaining good health and well-being, and at the same time achieving control over your own body and mind. Regular exercises have a beneficial effect on stress reduction. Improvements in balance and mobility were noted in PD patients participating in a 12-week study, including 45 minutes session once a week [45]. However, in another study, there was no improvement in the Tai Chi group [46]. Any form of effort adjusted to the disease's stage, physical and mental conditions of a PD patient, can be a source of benefits, not only physical but also psychological. Each physical activity contributes to improving our well-being, which also translates into our health [46-48]. Li and coworkers in cohort analysis showed that the incorporation of Tai Chi in PD patients' daily lives allowed them to stay functionally and physically active. Moreover, it was found the improvement of physical parameters indicated, that Tai Chi have the potential to slow down the progression of PD and delay the administration of levodopa (L-DOPA) [49].

Neuroprotective mechanisms induced by physical exercise

In a narrative review, Paillard et al. [50] summed up the neuroprotective mechanism induced by physical exercise (PE) in subjects affected by PD. The current knowledge about the mechanisms involved in the protective effect of PE against PD relies on data obtained in animal models. It has been shown that PE has a protective effect on the dopaminergic function in PD models by stimulating the expression of several neurotrophic factors and angiogenesis [51]. In response to PE, the concentration of DA increases, and this neurotransmitter's receptors enhance their sensitivity [52]. More precisely, PE reduces the alteration of the dopaminergic neurons in the substantia nigra and contributes toward reconstituting the function of the basal ganglia involved in the motor command by the adaptive mechanisms of DA and glutamate neurotransmission [52]. This action is related to an increased concentration of brain-derived neurotrophic factor (BDNF) [53]. In addition, the hyperexcitability often observed in the basal ganglia is decreased [54].

Diminished loss of the neurons that produce DA is found in PD mice after 18 months of training, as well as

there is observed an improvement of movement-balance coordination [55]. Mechanistic investigations revealed that the neuronal and behavioral recovery generated by PE is associated with an improvement of the mitochondrial function and an increase of BDNF in the cerebral levels and glial-cell-line-derived neurotrophic factors. According to Lau and coworkers, PE protects neurons and mitochondria but also increases synthesis of neurotrophic factors in the substantia nigra (nigrostriatal neurotrophic factors) in PD mice with moderate neurodegeneration [55].

Table 1. The recently published clinical data indicates that physical activity in PD is associated with reduce motion and balance impairments, as shown by the significant improvement in UPDRS III, functional mobility and muscle strength.

Study (ref)	Type of study	Type of excercise	Main outcomes
Leal et al. 2019 [120]	Clinical study on human (H&Y 1-3)	Low volume resistance training (6 months/twice weekly/30-40min/Interval break 1-2min).	The main result of this study shows that low RT volume improves the physical and functional capacity of older patients with PD. RT was efficient in promoting improvements in aerobic endurance, gait speed and balance.
Marusiak et al. 2019 [136]	Clinical study on human (H&Y 1.5-3)	Aerobic interval training (8 weeks/three times weekly/60min/Interval 8x5min, 2min <60rpm 3min >60rpm).	Moderate intensity aerobic interval training by individuals with PD improved psychomotor behaviors, as reflected by bimanual motor control, executive function, and neurological signs of PD.
Silva et al. 2019 [137]	Clinical study on human (H&Y 1-4)	Aquatic dual-task exercise (10 weeks/twice weekly/60min/group classes).	The aquatic exercise program improved the functional mobility, balance and gait of people with PD.
Rawson et al. 2019 [121]	Clinical study on human (H&Y 1-4)	Tango/Treadmill/ Stretching (12 weeks/twice weekly/60min/group classes).	No change in Quality of life scores all 3 group (PDQ-39). SMWT test Tango group improve the most. MDS-UPDRS-III all three group improve but Stretching significant.
Zhu et al. 2020 [138]	Clinical study on human (H&Y 1-3)	Tai Chi (12 weeks/group classes).	After 12 weeks of intervention, participants in both Tai Chi and routine exercise groups gained effects in UPDRS-III, BBS, PDQ-39, PDSS and HAMD compared to the baseline.
Sacheli et al. 2019 [122]	Clinical study on human (H&Y 1-3)	Aerobic exercise (3 months/three times weekly/cycling 40-60min/60%–80% VO2max).	The current study showed that after 3 months of aerobic exercise there was increased rTMS-evoked dopamine release in the caudate and greater activation of the ventral striatum in anticipation of reward. Dopaminergic changes are likely not the only explanation for the benefits of exercise in PD. Other mechanisms may include modulation of neuroinflammation, increases in glial and brain-derived trophic factors and cerebral blood flow.
Fleisher et al. 2020 [139]	Clinical study on human (H&Y 1-3)	Shotokan (10 weeks/twice weekly/60min/group classes).	We found a statistically and clinically significantly improve mention quality of life of 5.9 points on the PDQ-8. There were no changes in physical activity levels compared to baseline as measured by the IPAQ. We found no change in Functional Reach Test, and a small change in Tinetti Mobility Test.
Cherup et al. 2019 [140]	Clinical study on human (H&Y 1-3)	Strength and Power Training (12weeks/twice weekly/60min).	Subjects in both the PT and ST groups demonstrated significant improvements in muscular strength and power, both PRT programs appear helpful in addressing these neuromuscular performance variables.
Vieira de Moraes Filho et al. 2020 [141]	Clinical study on human (H&Y 1-3)	Progressive resistance training (9weeks/twice weekly/50-60min).	The present study highlights the PRT importance on the adjunctive PD treatment due to its efficacy in promoting improvements in the disease motor symptoms with a few weeks of intervention. The significant effects on bradykinesia without an increase in muscle strength, suggest that the intervention promoted neural enhancements in a short term to substantially improve the functional performance of trained individuals.

At another neurological level, aerobic training for PD rats (in sessions lasting 20–60 min) performed 5 days a week for 4 weeks can restore the expression of glial fibrillary acidic protein (GFAP) in the dorsal striatum. That indicates that astrocytes may play a role in producing the beneficial effects of PE in PD [56]. It was suggested that the reduction in GFAP expression is related to the reduced expansion of astrocytes, probably due to an increase in the synaptic function in the dorsal striatum induced by PE [56]. This observation also demonstrates the neuroprotective role of PE.

Furthermore, regular training of rats (from 5 to 23 months of age) for 18 months on a horizontal treadmill at a speed of 20 m/min for 20 min, twice a day, 5 days a week, also had a neuroprotective effect on the cerebellum [57], a part of the brain that is fundamentally involved in the command and control of movement and balance. They also reported that sedentary elderly rats had 11% fewer Purkinje cells (cerebellar efferents) and 9% smaller Purkinje cell soma volumes (p=0.02 for both) than exercising elderly rats, with the latter having the same number of Purkinje cells as young rats (5 months of age) [57].

As summarized in Table 1, recently published clinical data indicate that different kind of PE in PD is associated with significantly reduced motion and balance impairments, as shown by the significant improvement in UPDRS III, stride length, and gait velocity. Moreover, it is shown that regular PE may slow down the disease's progression in patients suffering from PD and may reduce the risk of disease in healthy patients. However, despite many pieces of evidence from animal studies that PE has a beneficial effect in the PD model, there is still little direct evidence from clinical trials data (Table 1), which makes it difficult to propose the appropriate exercise and time duration, and intensity contributes to slowing down the disease progression.

Diet and supplementation in PD

Nutritional habits and diet have a significant impact on the human body at all ages. However, older people, more often than younger people, require individual nutritional intervention because of past or chronic diseases or unhealthy eating habits. A healthy and proper diet is one factor that contributes to a healthy aging process, reducing or slowing down the course of many chronic diseases [58].

Appropriate diet therapy in ND is attributed to the name of a protective factor that reduces the risk of disease or mitigates the course of an already existing disease. On the other hand, a heterogeneous and nutrient-poor diet may disturb homeostasis, increasing the risk of disease or accelerating its course. A shortage of ingredients can be unfavorable, but contaminants found in food have an impact on our health [59]. Contaminants can enter food products from water, soil, air, or when spraying plants. A major problem is the presence of xenobiotics in the aquatic environment, which poses a severe threat to all organisms living in the aquatic environment. These compounds have neurotoxic, immunosuppressive, and hepatotoxic effects [60].

Vitamins of group B and homocysteine

It is worth noting the B vitamins, which play an essential role in homocysteine (Hcy) metabolism. Hcy is an amino acid whose excess in the body may contribute to the progression of many chronic diseases, including ND. An adequate amount of Hcy in the range of 5 to 15 µmol/l ensures the nervous system's proper functioning. A value exceeding the upper limit indicates hyperhomocysteinemia. Hyperhomocysteinemia, associated with reduced levels of methionine synthase (MS), activates the generation of reactive oxygen species (ROS) and limits the action of GPx. It also accelerates the death of dopaminergic neurons [61].

Hcy is a result of denitrification of methionine, an exogenous sulphuric amino acid consumed with food. The resulting Hcy can be subjected to two processes lowering its concentration in blood, consisting of remethylation (second transformation to non-toxic methionine) or transsulformation, where it is rebuilt to cysteine. Remethylation of Hcy into methionine is a process where the methyl group's donor is folic acid, and the cofactor of MS is vitamin B12 (cobalamin) [62]. However, in the process of transsulfuration, the presence of the β-synthase cystathionine cofactor - an active form of vitamin B6 - pyridoxal phosphate - is important. Lack of these cofactors, together with reduced enzyme activity, cause hyperhomocysteinemia. Hcy, which has not undergone any of the two metabolic changes (to methionine or cysteine) is deposited in excessive blood concentrations, which is harmful to our body.

Factors that increase the build-up of higher serum Hcy concentrations include poor eating habits and abnormal lifestyles. It was also noted that smoking and increased consumption of products rich in methionine (dairy products, fish, meat), coffee, and alcohol can increase Hcy levels in the blood. It is worth mentioning that the use of L-DOPA increases the demand for B vitamins and folic acid, hence the importance of adequately planned nutrition in patients suffering from PD [63].

An increased level of Hcy also reduced muscular strength, this leads to a reduction in physical capabilities and thus increases the risk of falls and fractures. Bone is formed through calcium phosphate deposition onto the

protein matrix composed mainly of collagen. It has been reported that hyperhomocysteinemia disrupts the collagen-cross links and impairs bone strength [64]. Therefore, to reduce Hcy in blood, it is recommended to follow a regular physical activity and the methylating diet, influencing DNA methylation, which regulates genes expression.

Antioxidant vitamins

Many scientists focus on studying the effects of antioxidant vitamins on the development and progression of ND. These include vitamins C, E, and A as well as carotenoids, which take part in calming oxidative stress. Vitamins C and E have selected protective properties, protect nerve cells against the harmful effects of inflammation and oxidative stress. Kim and coworkers in 2017 observed decreased levels of α- and β-carotenes and lycopene in plasma, which decreased with the duration of PD. They suppose that this relationship may be related to the progression of ND [65]. In another study, it was observed that an increased supply of vitamin E in the diet lowered the risk of AD development, but its intake together with vitamin C and β-carotene in the form of dietary supplements did not bring such effects [66]. It was noted that a higher intake of vitamin E and β-carotene in the diet was associated with a lower risk of PD, and no correlation with vitamin C was found [67]. Therefore, it is advisable to include fresh fruit and vegetables in the diet, bearing in mind that excess fiber in the diet can significantly reduce the bioavailability of carotenoids and vitamins [68].

Vitamin D

Vitamin D or calciferol is a term covering a group of fat-soluble steroidal organic compounds. There are two forms of vitamin D: ergocalciferol (vitamin D2), found in products of plant origin and yeasts, and cholecalciferol (vitamin D3), found in products of animal origin (fatty fish, fish oil). It is estimated that about 90% of the amount of vitamin D3 necessary for human is delivered from biosynthesis occurring in the skin under the influence of sunlight. Unfortunately, the majority of the population suffers from massive deficiencies of this vitamin. 7-dehydrocholesterol called provitamin D, present in each of us's skin, under the influence of sunlight UVB, is converted into cholecalciferol. Next, cholecalciferol is transferred to the liver, where 25-hydrolase converts it into 25-hydroxycholecalciferol (25(OH)D3). The final synthesis to the active form of vitamin D occurs mainly in kidneys, where 25-hydroxycholecalciferol is enzymatically transformed into 1,25-dihydroxycholecalciferol (calcitriol) via the enzyme 1α-hydroxylase.

The classic effect of vitamin D is to regulate the calcium-phosphate balance. However, recent works show that vitamin D has a pleiotropic effect. For example, vitamin D has an anti-inflammatory effect by lowering the biosynthesis of pro-inflammatory interleukins, which tend to attack myelin sheaths of nerve cells, which is the cause of many ND. Brain function and vitamin D are closely related. Neurons synthesize active vitamin D, which regulates these cells' proliferation in an autocrine manner [69]. This allows the brain to exhibit neuroplastic function through increased neuroprotection. Notably, active vitamin D regulates the expression of many proteins involved in 1) synaptic plasticity, counting drebrin, growth-associated protein 43 (GAP43), and connexin 43, 2) cytoskeleton maintenance, including neurofilament, tubulin, microtubule-associated protein-2 (MAP2), and 3) molecular transport of cell organelles, with creatine kinase, kinesin, RhoA, dynactin [70, 71]. In areas of the brain responsible for DA secretion, active vitamin D affects dopaminergic circuits' function and connectivity [71].

Moreover, recent data from our laboratory showed that optimal concentration in serum 25(OH)D3 decreases oxidative stress, attenuates muscle atrophy, reduces pro-inflammatory markers, and elevates the biogenesis of mitochondria, as well as improves their function [72-74]. Vitamin D supplementation may also have a beneficial effect on aging-related neurodegeneration diseases retardation. Moreover, vitamin D deficiency, diagnosed early and adequately compensated by diet, sun exposure, and supplements, may minimize the risk or prevent the occurrence of many diseases such as PD, SM, AD, arterial hypertension, and atherosclerosis RA, or various types of cancer [75]. In addition, it has been reported that preoperative supplementation with vitamin D induced faster recovery in LBP patients after PLIF surgery [76].

Mediterranean diet

The Mediterranean diet arouses a growing interest and its beneficial effects such as slow down the aging process, reduce the risk of illness, and slow down the progression of chronic diseases, including ND. The Mediterranean diet is a diet and healthy eating habits of Mediterranean countries, including Italians, Spaniards, Greeks, and French. In combine with physical activity, it may bring many health benefits. According to studies, the Mediterranean diet's use significantly improves health conditions and reduces PD and AD incidence by 13% [77]. However, it is worth remembering about the pollution of water reservoirs, as food consumption such as fish and seafood is an essential source of exposure to

various types of xenobiotics. Choose products from the least polluting waters, e. g. oceanic waters.

The Mediterranean diet is rich in fresh vegetables and fruits, cereal products, pulses, olive oil, nuts, cheese and yogurts, fish and seafood, while it is reduced in sweets, eggs, meat (especially beef), and animal fats. Results of FFQ in PD patients may suggest that a diet based on the components mentioned above was associated with lower PD progress rates [78] and a higher age of disease diagnosis [79]. Due to the high consumption of fruit and vegetables, the Mediterranean diet is rich in antioxidants. Despite ambiguous research results, it is recommended to consume products rich in antioxidants, as they may slow down the progression of many diseases [80].

Fatty acids

Studies on the compound and effects of mono- and poly-unsaturated fatty acids (MUFA and PUFA, respectively) on chronic diseases are still ongoing. PUFA include omega-3 and omega-6 fatty acids. Omega-3 fatty acids, which can improve excitability of nerve cell membranes, increase the transmission of nerve impulses, and protection against damage caused by oxidative stress, are essential for the construction and proper functioning of the brain. Moreover, omega-3 fatty acids showed neuroprotective effects in animal models PD [81]. It was observed that people eating at least once a week fatty fish (herring, anchovy, salmon, mackerel) or crustaceans (providing eicosapentaenoic acid and docosahexaenoic acid) reduced the risk of dementia to 60%, including AD [82].

MUFA have a positive effect on the lipid profile, effectively lowering the ratio of LDL cholesterol to HDL cholesterol. Besides, olive oil has anti-cancer, antibacterial, antiviral, and anti-inflammatory effects, which may inhibit the progression of ND. For the most part, PUFA, including omega-3 fatty acids, are also a source of fat. It has been shown that eating fatty fish and seafood more than twice a week reduces the risk of developing AD by as much as 60% compared to people who have eaten it less often [83].

Dairy products

It has been established that dairy products consumed in large quantities may be positively correlated with an increased risk of developing PD, especially in men [84], and faster disease progression [85]. Researchers are trying to determine which mechanism is responsible and which of the specific dairy products in the diet has the greatest impact on PD's development and progression because the results in many studies are not unambiguous. It is believed that consuming large amounts of dairy products causes a decrease in uric acid [85], the decreased concentration of which was observed in patients with PD, and this level decreased with the progression of the disease [86].

Selected nutraceuticals

Nutraceuticals are isolated single substances, pharmaceutical preparations having the character of a paralysis (combining drug and food features), which contain, among others, bioactive ingredients of natural origin, showing pro-health properties [87]. It has been shown that many ingredients of natural origin have a protective effect in the case of ND, and their action consists of modulating multistage signal pathways [88]. Nutraceuticals appear to be a beneficial option for disease prevention and treatment because of their natural origin in the food available and the potential absence of side effects [89]. Polyphenols are known for their antioxidant properties and may be used for ND. Their function is to scavenge ROS, and polyphenols may also chelate metal ions (copper, iron, and other heavy metals), which prevents the formation of hydroxyl radical. Products containing large amounts of polyphenols may increase neurogenesis [90]. There was a significant correlation between the lower risk of developing PD in men who consumed more flavonoids. Such a relationship was not noticed in women. It was also found that higher consumption of anthocyanins, quercetin, and epicatechin reduces the risk of PD progression within 20-22 years of observation [91].

Curcumin, a biologically active colorant obtained from Curcuma, a long oyster, is the main ingredient of the famous spice “curry” and shows a very wide spectrum of pro-healthy effects. In numerous studies, its antioxidant, anti-inflammatory, anticancer [92], and anticoagulant effects were found. It has been noted that the toxicity of ROS and α-synuclein [93] decreases after curcumin administration. In addition, it may increase or stabilize neurogenesis in adults [90].

Luteolin, which belongs to flavones and is found in broccoli, green pepper, celery, and thyme, has a strong neuroprotective effect. Effectively suppresses inflammatory processes of the body, reducing the synthesis of inflammatory mediators [94]. It also has a protective effect against induced cell apoptosis, which makes it suitable for preventing ND or slowing their progression [95].

Genistein, a natural compound of plant origin present in soya, is a phytoestrogen belonging to the group of isoflavones. Many studies have shown neurotrophic and neuroprotective effects of genistein. It has been proven to protect nerve cells against oxidative stress and toxic effects of β-amyloid [96]. In vivo studies proved its

protective effect on dopaminergic neurons in PD model rats [97]. Moreover, genistein's neuroprotective effects on apoptosis induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in black substance neurons [98] were demonstrated. However, the exact mechanism of action of genistein is still unclear. We found that genistein also plays anti-inflammatory effects (data not published yet). Tumor necrosis factor (TNF-α) significantly decreased in AD rats after 4 weeks of genistein's treatment.

Quercetin is one of the most common flavonoids found in food products eaten daily. It shows antioxidant properties related to the ability to scavenge ROS, inhibition of oxidase activity, and anti-inflammatory effects. Besides, it has hepatoprotective and anti-aggregating properties [99]. It is believed that quercetin may be a protective factor in ND in which increased apoptosis of cells leads to AD, PD, Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS) [100], among others.

Resveratrol is a biologically active substance found mainly in red wine and dark chocolate. It is an effective antioxidant and antidepressant with neuroprotective effects. Studies prove that resveratrol may protect dopaminergic neurons in the intracerebral against damage [101]. Its properties, such as ROS capture and anti-inflammatory activity, are well documented [102].

Anthocyanins are a group of flavonic compounds, natural dyes (from orange to violet) found in many fruits and some vegetables. Studies have shown that a high intake of anthocyanins together with diet is associated with risk reduction and inhibition of PD progression [103]. It has been proven that delphinidin, which belongs to anthocyanins, e. g. in blackberries, is the most effective in neutralizing ROS. However, all anthocyanins have neuroprotective properties by inhibiting pro-inflammatory pathways and inducing antioxidative pathways [104].

Ginkgo Biloba is a popular plant that has been used for years to treat memory and concentration disorders. The unique therapeutic properties of ginkgo are distinguished by bilobalide, a biologically active substance belonging to the group of isoprenoids (terpenes). It has an anti-apoptotic effect on neurons' death, which opens up new possibilities in the fight against ND. Besides, it protects neurons from the harmful effects of free radicals, stimulates the release of neuromediators in the brain, and inhibits their breakdown [105].

Ginseng (Panax Ginseng) is a perennial used for centuries in traditional Far Eastern medicine. It contains more than 30 biologically active compounds called ginsenosides, belonging to triterpene saponins [106]. It shows potent anti-inflammatory and antioxidant effects through its influence on nitric oxide production and antioxidant enzymes' activity eliminating ROS. It shows neuroprotective properties in AD, PD, ALS and HD. In PD models, it prevents apoptosis and atrophy of dopaminergic neurons and has a positive effect on synucleinopathy [107].

Caffeine, one of the most popular stimulants, also has anti-inflammatory, antioxidant, and anti-apoptotic effects. Caffeine is believed to reduce PD's risk if used at a dose of 3-5 mg/kg body weight [108]. One glass of freshly brewed coffee is about 90-100 mg of caffeine (or 40 mg/100 ml of coffee). However, it should be noted that excessive coffee intake leads to an increase in blood Hcy concentration, which increases the risk of developing PD and accelerates the already ongoing disease process. In 2016, Lee and his team [109] found out that coffee is not caffeine, but quercetin is a key neuroprotective ingredient.

Capsaicin is an organic compound from the alkaloid group, responsible for the hot and pungent taste of paprika. Studies indicate that a combination of capsaicin and resveratrol treatment has more neuroprotective benefits than a single treatment. Combining these compounds has a protective effect on nerve cells against the toxic effects of glutamate, reducing oxidative stress and apoptosis; both of these compounds may be useful in the treatment of ND [110].

Sulforaphane, an organic sulfur compound found in the highest concentration in broccoli and its sprouts, is a potent antioxidant. Many studies have shown its neuroprotective properties in different models of neurodegeneration. It can increase glutathione levels and enzymes dependent on it; thus, it may be useful in slowing PD progression and other ND by silencing oxidative stress and apoptosis [111].

In the present review, a lot of data from animal studies showed beneficial effects in slowing down the progression of neurodegenerative disorders. Although less evidence comes from selected clinical trials data, which are summarized in Table 2. However, it suggests that the use of dietary supplements may have a positive impact on functional tests and anatomical, and biochemical alterations in PD patients. Absolutely, changes occurring and related to a proper diet and use of supplements are associated with patients, which most of them suffer from obesity, depression and do not exercise at all. In a result, PD patients develop inflammation in their organism. Therefore, a proper diet with supplements and nutraceuticals for patients with PD seems to be the most effective and non-invasive therapy against the disease progression.

Kynurenine metabolites and microbiota

Chronic systemic inflammation is widely accepted as a common risk factor for many diseases (diabetes, cancer, AD, PD, depressions, and others) and has further been observed in several patients suffering from fatigue and cognitive impairments [112]. Studies have shown that inflammatory stimuli, as they appear after acute exercise, activate the amino acid TRP breakdown within the KYN pathway [113]. The KYN pathway includes several enzymes that degrade 95% of the free TRP into diverse bioactive kynurenine pathway metabolites (KPMs), often referred to as kynurenines [114]. Exercise alters skeletal muscle kynurenine metabolism and may significantly change the levels of some of these metabolites both in the periphery and in the CNS [114, 115]. Recently, it was shown that PE leads to a peripheral breakdown of KYN to KYNA by inducing kynurenine aminotransferases (KATs) in muscle tissue [114]. In contrast to KYN, KYNA is unable to cross the blood-brain barrier (BBB).

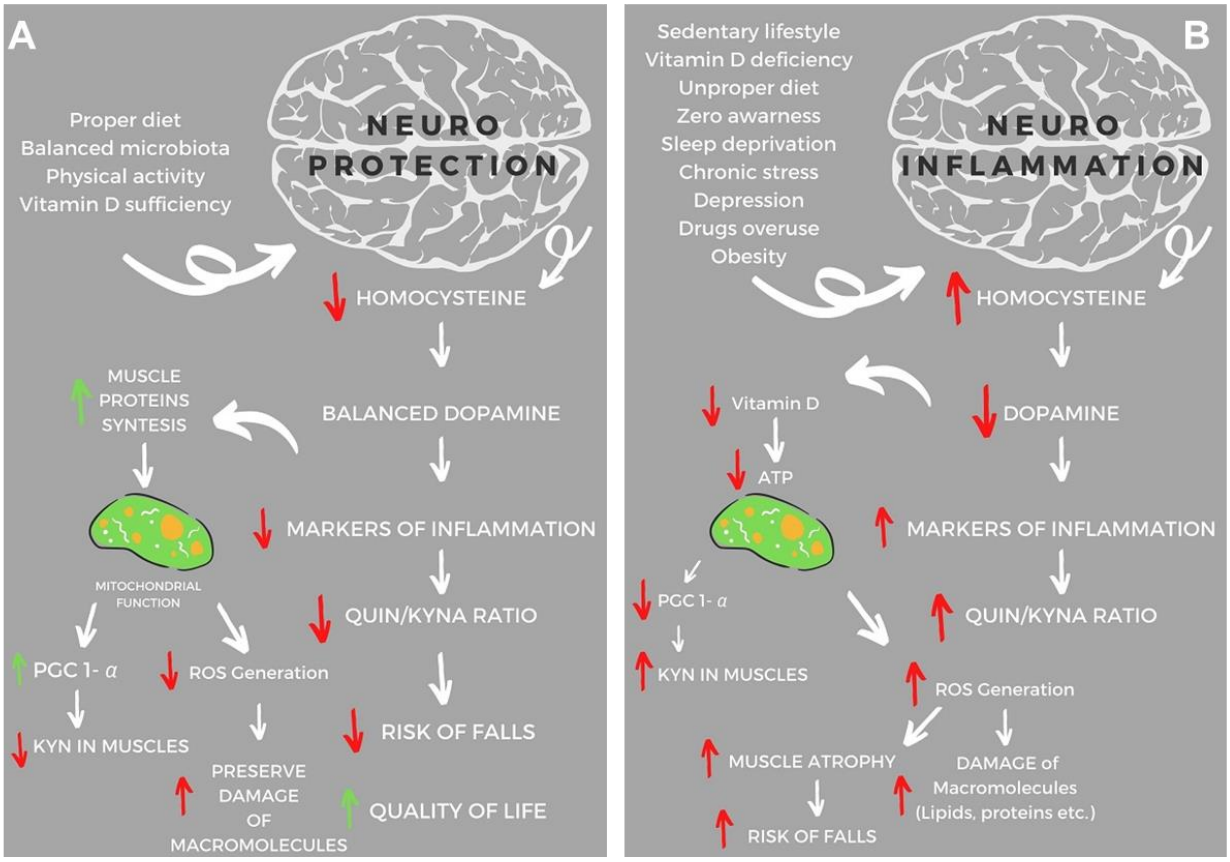

Figure 1. The scheme of neuroprotective and neuroinflammatory factors in PD's. Based on animal and clinical trial studies [120, 138, 140, 146, 147, 151-153] the selected factors may influence on neuroprotection or neuroinflammation in reducing or worsening Parkinson`s decrease. **(A)** The proper diet combined with regular physical activity can lead to neuroprotection and consequently lowering the markers of inflammation and free radicals damage of macromolecules, improving the function of mitochondria as well as reducing the risk of osteoporosis, which is associated with decreasing risk of falls. **(B)** The improper diet and sedentary lifestyle may induce neuroinflammation. In consequences will be observed an increased Hcy level, a strong risk factor for osteoporotic fractures, mitochondrial dysfunction, ROS generation, damage of macromolecules, muscle atrophy and hence a deterioration in the quality-of-life patients. Abbreviation: KYN- kynurenine pathway, KYNA- kynurenine acid, QUIN- quinolinic acid, PGC-1α- peroxisome proliferator-activated receptor-gamma coactivator 1α, ROS-reactive oxygen species, and (indicators: ↓-decrease; ↑-increase).

The link between skeletal muscle, exercise, and KPMs came from the observation that trained muscle (or muscle with high peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) levels) has very high levels of KAT enzymes [114-116]. This enhances peripheral KYN to KYNA conversion and prevents the accumulation of KYN in the brain, which is observed in particular mental health disorders such as stress-induced

depression. Thus, PE reduces the neurotoxic KPMs, which was further described as cognitive dysfunction in neurological diseases [117, 118]. In mice, this detoxification mechanism was shown to reduce KYN-related excitotoxicity, neuroinflammation, and depressive-like behaviors [115]. Since this pathway's activation is extremely dependent on PGC-1α, mice genetically engineered to lack expression of this coactivator in muscle show depressive-like behavior and a reduced capacity to catabolize KYN, even in the absence of any challenge. This highlighted skeletal muscle and exercise as novel regulators of TRP-KYN metabolism, with important systemic consequences [114, 115]. Schlittler and coauthors showed that humans participating in active endurance training display both an increased mRNA genes expression and protein content of the KAT. They also reported that following aerobic exercise, a transient flux of the KYN pathway occurs with a preferential increase in the KYNA concentration (63%) over QUIN (19%), leading to a decreased QUIN/KYNA ratio [116].

Table 2. The selected clinical trials related to the use of dietary supplements on functional tests and biological changes in PD patients.

Study (ref)	Type of study	Treatment	Main outcomes
Postuma et al. (2017) [142]	Randomized controlled trial	2 groups: 1st (n=57) 200 mg of caffeine twice daily in the morning and after lunch 2nd (n=61) 200 mg matching placebo treatment The dose was rising from 50 mg per week to meet the final dose at week 9. The supplementation lasted for 6 months.	No significant motor improvement (MDS-UPDRS III) in both groups.
Simon et al. (2015) [143]	Clinical Trial	groups: - low caffeine intake (≤300 mg daily, n=1288) - high caffeine intake (>300 mg daily, n=261) – based on questionnaire additionally, 10 mg of creatine per day (n=765) or matching placebo treatment (n=770) when ½ patients reached 5 years – the study has ended.	No difference in the disease progression (UPDRS) between groups with different caffeine intake. Increased disease progression (UPDRS) in group taking creatine combined with high caffeine intake.
Postuma et al. (2012) [144]	Randomized controlled trial	2 groups: 1st (n=30) 3 weeks 100 mg of caffeine twice daily upon awakening and immediately after lunch, next 3 weeks 200 mg of caffeine twice daily 2nd (n=31) matching placebo treatment.	Significant improvement in total UPDRS and UPDRS III total after 6 weeks in caffeine group. No difference in depression/PDQ-39.
Fan et al. (2018) [145]	Clinical Trial	10 male patients with idiopathic PD, 28 days of supplementation, 300 mg of blackcurrant anthocyanins twice daily.	Higher cGP concertation in CSF after supplementation – probably because of the uptake form plasma cGP. May be the evidence of oral availability and effective brain uptake.
Tamtaji et al. (2018) [146]	Randomized Controlled Trial	2 groups: 1st (n=20) 1000 mg omega-3 fatty acids plus 400 IU of vitamin E once daily for 12 weeks 2nd (n=20) matching placebo treatment request for no changes in physical activity during supplementation.	In omega-3 plus vitamin E supplementation group significant improvement in total UPDRS compared to placebo group (in UPDRS-part I, in other parts of UPDRS no). Omega-3 fatty acids and vitamin E co-supplementation for 12 weeks in PD patients significantly improved gene expression of TNF-α, PPAR-γ and LDLR and did not have effect on levels of IL-1 and IL-8.
Taghizadeh et al. (2017) [147]	Randomized Controlled Trial	2 groups: 1st (n=30) 1000 mg omega-3 fatty acids plus 400 IU of vitamin E once daily for 12 weeks 2nd (n=30) matching placebo treatment request for no changes in physical activity during supplementation	Omega-3 fatty acids and vitamin E co-supplementation in PD patients had positive effects on UPDRS, hs-CRP, TAC, GSH and markers of insulin metabolism and did not have effect on

		3-day food records and three physical activity records at week 0, 3, 9 and 12.	other markers of inflammation, oxidative stress, and lipid profiles.
Barichella et al. (2019) [148]	Randomized Controlled Trial	2 groups: 1st (n=75) twice daily whey protein-based oral liquid formula enriched with leucine and vitamin D for 30 days 2nd (n=75) standard diet without this muscle-targeted nutritional supplement. Each group received multidisciplinary intensive rehabilitation treatment.	Significant improvement in group receiving muscle-targeted nutritional supplement in 6-minute walking test distance, 4-meter gait speed course, Timed Up and Go test, skeletal muscle mass and skeletal muscle mass index.
Hiller et al. (2018) [149]	Randomized Controlled Trial	2 groups: 1st (n=24) placebo plus 1000 mg calcium carbonate 2nd (n=27) 13600 UI vitamin D plus calcium from Monday to Friday (68000 UI vitamin D per week). Supplementation lasts for 16 weeks.	The concentration of serum vitamin D in vitamin D group has risen and in placebo group was stable. High dose vitamin D supplementation does not improve balance.
Suzuki et al. (2013) [150]	Randomized Controlled Trial	2 groups: 1st (n=55) 1200 UI vitamin D daily for 12 months. 2nd (n=57) matching placebo treatment.	H&Y score worsen in placebo group and was unchanged in vitamin D group. Difference between groups was significant. The same situation in UPDRS part II scores. PDQ-39 score improved in vitamin D group and did not change in placebo group. VDR FokI TT genotype – significant and consistent response to vitamin D supplementation VDR FokI CT genotype – moderate response VDR FokI CC genotype – no significant response.
DiFrancisco-Donoghue et al. (2012) [151]	Randomized Controlled Trial	4 groups: 1st (n=9) vitamin supplementation 5 mg/day of folic acid, 2000 µg/day of cyanocobalamin (vitamin B12) and 25 mg/day of pyridoxal-5'-phosphate (vitamin B6) for 6 weeks 2nd (n=9) exercise group 40 min, twice weekly for 6 weeks 3rd (n=9) exercise + vitamin 4th (n=9) control – normal daily activities.	6 weeks of supplementation – lowered Hcy. 6 weeks of training – increased glutathione levels, improved strength and aerobic capacity. Exercise + vitamin – did not have greater effect of any of the measurements that have been made.
Nascimento et al. (2011) [152]	Controlled Clinical Trial	3 groups: 1st (n=17) PD patients with no physical activity for 6 months. 2nd (n=24) PD patients with aerobic physical activity, 3 times weekly for 60 minutes for 6 months. 3rd (n=19) healthy controls with no physical activity for 6 months.	Hcy levels were lower in PD who participated in aerobic physical activity compared with patients who did not. Also in PD patients who exercised Hcy levels were similar to healthy controls. PD patients who did not exercise received higher doses of L-dopa which can be connected with higher Hcy levels.
Lee et al. (2010) [153]	Randomized Controlled Trial	3 groups: 1st (n=14) Hcy-lowering therapy 5 mg folate, 500 µg mecobalamin 3 times daily 2nd (n=14) α-LA therapy 600 mg α-LA twice daily 3rd (n=13) control group. Every group received 500 mg calcium and 1000 IU vitamin D	Hcy-lowering therapy may prevent bone loss in PD patients taking levodopa.

Another interesting aspect is the role of gut microbiota in ND. In recent years have been reported a lot of data showing that exist a correlation between gut microbiota and neuromodulation. It is clear that intestinal bacteria have the potential to alter neurotransmitter activity, thus interacting with the host nervous system to regulate mental health. A recent systemic review illustrated how exercise contributes to the elevation of the gamma-aminobutyric acid level in the hypothalamus, which is associated with lowered resting blood pressure

and heart rate. Moreover, DA was shown to be synthesized in the gastrointestinal tract during stressful situations. In general, gut microbiota was shown to facilitate the production and regulation of neurotransmitters and hormones, which influenced human well-being, mood, and subjective sense of neurodegeneration [119]. Thus, diet and lifestyle have a substantial impact on the development of PD in aging-related changes. For example, the proper diet and regular physical activity may slow down neurodegenerative changes (Fig. 1A), while the improper diet and sedentary lifestyle lead directly to PD development (Fig. 1B).

Summary

Larger amounts of moderate-to-vigorous PE may slow down disease progression in PD patients [120-122]. It is known that PD patients expend 29% less energy than healthy subjects do, which lead to increased motor deficits and declines in daily activities [123]. PE is a non-pharmacological approach that is usually recommended for PD in order to slow down the deleterious effects of the disease [124]. Findings of some studies show that the beneficial effects of PE are cognitive performances or psychological domains (i.e., attentional capacities, depressive and anxiety symptoms, and mood state) [125]. Multicomponent training improves muscle strength, flexibility, postural balance, walking speed, mobility, functional capacity [126, 127], physical performance, and the activities of daily life [127], especially if the training program lasts more than 10 weeks [128]. Aerobic exercise, stretching, strength training, Qigong, and balance training improve motor function and in particular muscle strength, balance, and walking speed in PD subjects [129, 130]. These physical functioning effects may explain why the quality of life can be improved after only 6 weeks of training [131]. Jang and coworkers in 2018 showed that in PD rats endurance exercise improved mitochondria biogenesis and fusion [132]. Others also reported that, exercise enhanced the biogenesis of mitochondria by inducing the PGC-1α and improving antioxidant systems' effectiveness [124, 132-134]. Based on the described above data and our knowledge, we suggest that NUTRITION combined with ACTIVITY will positively impact BALANCE not only in PD but also in other ND (Fig. 2).

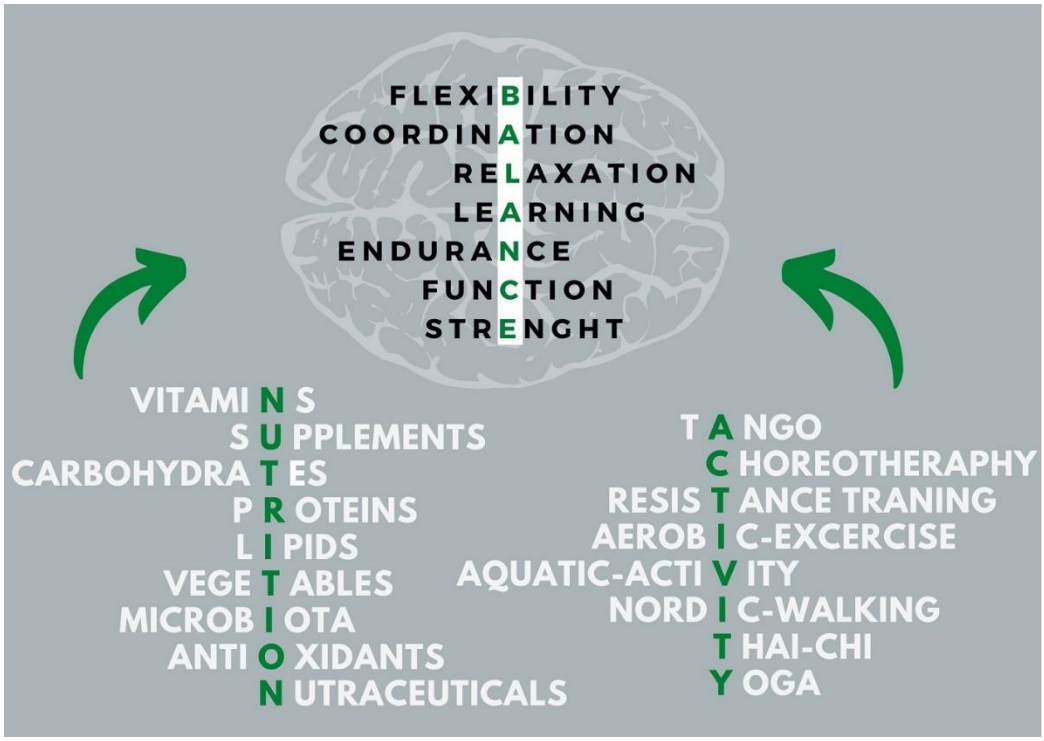

Figure 2. The impact of NUTRITION and ACTIVITY on BALANCE for people with Parkinson's Disease.

Conclusion

In terms of many researchs showing the positive effects of PE and proper diet in PD we have to focus to find the best therapy combining these two elements. On the other side, taking into consideration the individual variability in each human being, the past disease's and the severity of the disease, it is challenging to determine one pattern that

would be effective for everyone. Furthermore, we purpose to look for relationships between external and internal factors affecting the CNS. There are many indications that we are going in the right direction, going from exercise and diet to metabolic pathways leading to the nervous system.

The food and supplements associated with PD progression will probably change over time, with subsequent studies and evaluation of their results. Clinicians now have data to base a recommendation for healthy nutrition, and patients will probably be able to know that their daily choices can influence their progress.

Regular physical activity and a diet rich in the elements mentioned above may slow down the disease's progression in patients suffering from PD and reduce the risk of disease in healthy patients. Although there is still little direct evidence from clinical trials data, related to appropriate exercise and diet, however, it is worth taking such efforts. Preparing individual therapy for a patient with PD in terms of exercise and diet is the most effective non-invasive therapy as of today. Further work on comprehensive therapy for patients should be complementary and include both.

Inflammatory (TNF-α, Interferon-gamma, IL-6, IL-17) and anti-inflammatory (IL-10, TGF-β) soluble factors as well as Tryptophan metabolites (TRP, KYN, KYNA, QUIN) that are known to be produced or secreted in response to exercise and that are further suspected to modify immune homeostasis and BBB function (MMP-2, MMP-9) through their inflammatory and anti-inflammatory properties. Studies have shown that regular physical activity positively affects motor and cognitive function in persons with ND. However, the potential mechanisms of exercise-induced changes in immune function remain theoretical constructs as no evidence is available that the achieved improvements will impact the person's everyday life. Further, the influence of varying exercise intensities will provide more detailed recommendations for rehabilitative training programs.

Future directions

In light of the current knowledge, combining proper diet with vitamin D supplementation may have a beneficial effect on muscle function, delaying aging-related ND development. Furthermore, it has been shown that reaching optimal serum concentration of vitamin D in LBP patients reduced markers of oxidative stress [72] and inflammation [74] as well as elevated biogenesis and function of mitochondria, and decreased skeletal muscle atrophy [73]. On the other side, the discovery of vitamin D receptor (VDR) and 1-alfa hydroxylase in skeletal muscle provided evidence showing the beneficial effects of exercise on proper muscle metabolism. Moreover, VDR may potentially regulate local control of vitamin D metabolism in the skeletal muscle. The proper synergistic diet, exercise, and vitamin D interaction towards muscle protein synthesis and mitochondrial function improvement may be manifested by mTOR and FOXO signaling influence on oxidative stress and immunological functions modulation. Further search for knowledge toward proper diet, exercise, and vitamin D impact on brain functions, chronic stress [135], and neuroprotection seem crucial as factors indirectly affect neuromodulation and neurodegeneration, especially in PD.

Conflicts of Interest

The authors declare no conflict of interest.

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Effect of 12-Week BMI-Based Vitamin D_3 Supplementation in Parkinson's Disease with Deep Brain Stimulation on Physical Performance, Inflammation, and Vitamin D Metabolites

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease. To manage motor symptoms not controlled adequately with medication, deep brain stimulation (DBS) is used. PD patients often manifest vitamin D deficiency, which may be connected with a higher risk of falls. We administered a 12-week vitamin D_3 supplementation based on BMI (with higher doses given to patients with higher BMI) to investigate its effects on physical performance and inflammation status in PD patients with DBS. Patients were randomly divided into two groups: treated with vitamin D_3 (VitD, n = 13), and supplemented with vegetable oil as the placebo group (PL, n = 16). Patients underwent functional tests to assess their physical performance three times during this study. The serum 25(OH)D_3 concentration increased to the recommended level of 30 ng/mL in the VitD group, and a significant elevation in vitamin D metabolites in this group was found. We observed significant improvement in the Up and Go and the 6 MWT in the VitD group. In inflammation status, we noticed a trend toward a decrease in the VitD group. To conclude, achieving the optimal serum 25(OH)D_3 concentration is associated with better functional test performance and consequently may have a positive impact on reducing falling risk in PD.

Keywords: Parkinson's disease; vitamin D; deep brain stimulation; inflammation; functional tests

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1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases worldwide. It affects approximately 1–2% of people over 60 years of age, and the number grows with age. In the future, the number of patients with PD is expected to be even higher because of the aging society [1]. Currently, PD is incurable, and the main aim is to alleviate symptoms, ease suffering, and slow down the development of the disease in order to help the patients to cope better with their daily living activities. Symptoms may be divided into motor and non-motor. The main motor symptoms are bradykinesia, postural instability, and resting tremors. Non-motor symptoms include depression, dementia, sleep disorders, and subtle personality changes. In PD, dopamine production is impaired

because of degeneration of the substantia nigra [2–6]. Precursors of dopamine are the most commonly used pharmaceuticals, and L-dihydroxyphenylalanine (L-dopa) is the most widely used [7]. When pharmacological treatment ceases to control symptoms adequately, deep brain stimulation (DBS) is used to mitigate motor symptoms and decrease drug dosage. In PD, electrodes are usually implanted in the subthalamic nucleus [8–10].

Vitamin D is one of the most significant vitamins in our organism. Calcium and phosphate homeostasis are regulated by vitamin D and parathormone [11]. Vitamin D may be synthesized through the skin due to UV-B radiation. Either can be provided with a diet, but it is difficult to achieve acceptable results; thus, dietary supplements of vitamin D3 are usually recommended. After sun exposure, the skin converts 7-dehydrocholesterol to cholecalciferol. It is then hydroxylated to 25-hydroxycholecalciferol ($25(OH)D_3$) in the liver. This metabolite is a non-active form of vitamin D, even though it is used to determine if the deficiency occurs due to longer maintenance in the blood when compared to its active form. It is activated by an enzyme (1α-hydroxylase) to 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), which is an active form. On our latitude, a very common problem is the deficiency of vitamin D due to the low insolation during the year [12–14]. In PD patients, the serum concentrations of $25(OH)D_3$ are lower than in age-matched healthy controls; therefore, supplementation seems to be relevant [15]. Vitamin D deficiency may lead to several disturbances in humans. It can enhance the risk of depression, increase the levels of inflammatory markers, influence muscle weakness, and generate a higher risk of falls in PD patients [13,16].

In patients with PD, inflammation is often increased when compared to healthy age-matched controls [17]. In the study from 2020, researchers demonstrated a correlation between high-sensitivity C-reactive protein (hs-CRP) concentrations and the likelihood of developing PD. Specifically, the higher the levels of hs-CRP, the greater the risk of PD [18]. On the other hand, in the study conducted in 2018, the serum concentration of hs-CRP was lower in the PD group than in the control group [19].

Physical activity is the healthiest and easiest way to improve the quality of daily living in PD patients. Many studies have proven that exercises such as aerobic exercise, Nordic walking, resistance/strength training, choreotherapy, or Tai Chi successfully help slow down the development of PD, but the key is regularity. Physical activity might be low-cost and additional action to support the pharmacotherapy [20].

Therefore, vitamin D_3 supplementation may have beneficial effects on disease progression. Vitamin D deficiency also leads to elevated levels of inflammation. We assume that increasing the serum concentration of $25(OH)D_3$ to the optimum level from the deficiency can reduce inflammation, and improving muscle condition may lower the risk of falls.

Supplementation of vitamin D_3 is still not as common as it should be when talking about PD patients [21]. As mentioned above, patients with PD have a lower serum $25(OH)D_3$ concentration than age-matched healthy controls. Therefore, the doses of vitamin D_3 should be significantly higher than those in healthy people. We suggest that the dosage should be based on the patient's BMI—the higher BMI, the higher percentage of body fat in an organism in this group of patients. We have already checked this relationship in our preliminary study. It is known that a higher fat content in the organism may influence vitamin D metabolism and reduce its beneficial actions; higher doses should be applied in people with overweight or obesity [22].

There are a small number of studies on the application of vitamin D_3 supplementation in PD, particularly when considering PD patients with DBS. If there are any, the dosage of vitamin D_3 is standardized for healthy people—the disease or BMI value is not included in the dose determination [23]. Our research is designed in a way that may help to check how BMI-based supplementation can affect PD.

Therefore, the aim of this study was to explore how a 12-week BMI-based vitamin D_3 supplementation would affect the results of functional tests and serum concentration of vitamin D metabolites and hs-CRP in serum in PD patients treated with DBS.

2. Results

2.1. Demographic Characteristics

Fifty patients were enrolled in this study; however, only twenty-nine completed the intervention. Three of the enrolled patients were excluded because they did not meet the inclusion criteria, and five of them resigned due to the COVID pandemic. During the follow-up, we lost two patients from the VitD group and five patients from the PL group because they did not show up on the second visit for functional tests due to problems with transport. Six patients from the VitD group resigned from this study due to unforeseen circumstances. All patients who completed the intervention were Caucasian and met the inclusion criteria. No statistically significant differences were observed between the groups. The average age was 63 ± 9 years old in the VitD group and 66 ± 6 years in the PL group. The mean height and body mass were respectively 169 ± 12 cm and 78 ± 11 kg in the VitD group, and 174 ± 8 cm and 80 ± 20 kg in the PL group. There were six men (M) and seven women (W) in the VitD group and thirteen M and three W in the PL group. The time from DBS implantation varied from three to five years in both groups. In the off-medication condition, mean motor improvement after DBS stimulation, as assessed with UPDRS part III, was 45% (range 35–60%). The mean L-dopa-equivalent medication dosage reduction was 35%. Stimulation parameters were: monopolar stimulation in all patients, frequency 130 Hz, pulse duration 60 us, current 1.8–3.8 mA (in twenty patients with constant current stimulators), and voltage 1.9–4.2 V (in nine patients with constant voltage stimulators). Hoehn and Yahr's (H&Y) scores in both groups were 2.5. Duration of the disease varies from 8 to 13 years in the VitD and PL groups. In the VitD group, there were three patients with normal weight, eight who were overweight, and two with obesity. In the PL group, there were six patients with normal weight, eight who were overweight, and two with obesity. The characteristics of patients are shown in Table 1.

Table 1. Patient characteristics.

	VitD Group (n = 13)	PL Group (n = 16)
Age (years)	63 ± 9	66 ± 6
Sex	6 M, 7 W	13 M, 3 W
Height (cm)	169 ± 12	174 ± 8
Body mass (kg)	78 ± 11	80 ± 20
DBS implantation	3–5 years ago	3–5 years ago
H&Y	2.5	2.5
Duration of the disease	8–13 years	8–13 years
BMI	≤25 → 3 25–30 → 8 ≥30 → 2	≤25 → 6 25–30 → 8 ≥30 → 2

2.2. Vitamin D Metabolites

The effect of supplementation on vitamin D metabolites is shown in Figure 1. We did not find any statistically significant differences between groups at the T0 in all metabolites. In both groups, at the beginning of this study, 25(OH)D_3 deficiency was found in the serum of PD patients (<30 ng/mL). After vitamin D_3 supplementation in the VitD group, the serum concentration of 25(OH)D_3 reached in T2 34.99 ± 12.27 ng/mL, and it was statically significantly higher as compared to 25.55 ± 8.94 ng/mL at T0 ($p < 0.0006$; Figure 1A). There was also a statistically significant change when compared to the PL group 21.98 ± 10.91 ng/mL at T0 ($p < 0.05$; Figure 1A). We did not find any statistically significant changes in the serum concertation of 25(OH)D_2 in both groups at T0 (0.46 ± 0.33 ng/mL in the PL group and 0.44 ± 0.18 ng/mL in the VitD group) and T2 (0.57 ± 0.45 ng/mL in the PL group and 0.46 ± 0.81 ng/mL in the VitD group) (Figure 1B). The product of catabolism of 25(OH)D_3—24,25$(OH)_2D_3$ was elevated significantly in the VitD group at T2 (2.77 ± 1.02 ng/mL) versus T0 (2.09 ± 1.09 ng/mL) ($p < 0.05$; Figure 1C). There was also a statistically significant change when compared to the PL group of 1.67 ± 1.15 ng/mL at T0

($p < 0.05$; Figure 1C). There was no change in the serum concentration of this metabolite in the PL group at T2 (1.32 ± 0.81 ng/mL) to T0 (1.67 ± 1.15 ng/mL). The last metabolite of vitamin D that we measured was epi-25(OH)D_3. The concentration of epi-25(OH)D_3 was 0.83 ± 0.54 ng/mL and 1.03 ± 0.37 ng/mL, respectively, in the PL and VitD groups at T0, and 0.79 ± 0.54 ng/mL and 1.67 ± 0.70 ng/mL, respectively, in PL and VitD group at T2. We found a significant increase in the VitD group ($p < 0.005$) and a significant change when compared with the VitD group at T2 to the PL group at T0 ($p < 0.005$; Figure 1D). We have also found a strong positive correlation between 25(OH)D_3 and 24,25(OH)$_2$$D_3$ ($p < 0.0001$; Figure 2A), as well as between 25(OH)D_3 concentration and epi-25(OH)D_3 ($p < 0.0001$; Figure 2B).

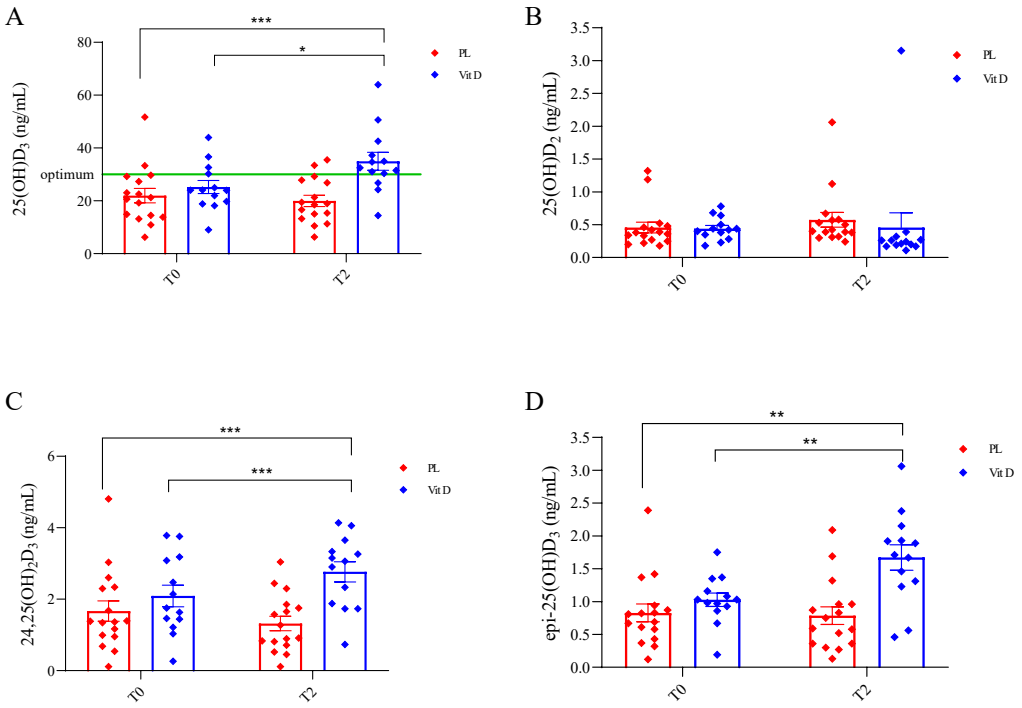

Figure 1. The effect of supplementation on vitamin D metabolites. (**A**) Changes in serum concentrations of 25(OH)D_3. (**B**) Changes in serum concentrations of 25(OH)D_2. (**C**) Changes in serum concentration of 24,25(OH)$_2$$D_3$. (**D**) Changes in serum concentrations of epi-25(OH)D_3. * $p < 0.0006$, ** $p < 0.005$, *** $p < 0.05$. T0—before the supplementation; T2—after 12 weeks of supplementation; PL—placebo group; VitD—vitamin D_3 group; whiskers refer to standard error (SE).

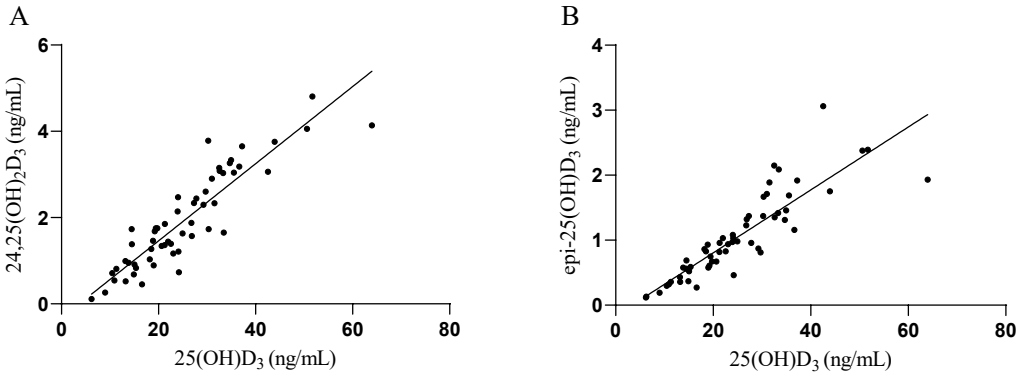

Figure 2. Relationships between (**A**) 25(OH)D_3 and 24,25(OH)$_2$$D_3$; (**B**) 25(OH)$D_3$ and epi-25(OH)D_3. (**A**) Spearman r = 0.9, $p < 0.0001$, 95% confidence interval: 0.83 to 0.94; (**B**) Spearman r = 0.92, $p < 0.0001$, 95% confidence interval: 0.86 to 0.95.

2.3. Functional Tests

The effect of supplementation on functional tests is presented in Figure 3. We did not find any statistically significant differences between groups at the T0 in all tests. In the TUG, we found a statistically significant change in the VitD group after the supplementation when compared with T0 (13.69 ± 5.10 s) to T1 (11.96 ± 3.44 s) ($p < 0.05$; Figure 3A), as well as when compared T0 to T2 (11.46 ± 3.80 s) ($p < 0.005$; Figure 3A). There were no changes in the PL group in this test at all three time points (T0—10.65 ± 2.44 s, T1—10.56 ± 2.73 s, T2—9.86 ± 1.63 s; Figure 3A). In the 6 MWT, we observed significant change when comparing the VitD group T0 (316.68 ± 93.45 m) to T2 (350.29 ± 96.28 m) ($p < 0.05$; Figure 3B), and no changes when considering T1 (339.99 ± 91.43 m). There were no changes in the PL group (T0—381.23 ± 74.74 m, T1—379.99 ± 56.5 m, T2—377.61 ± 75.6 m; Figure 3B). We did not notice any statistically significant changes in 10 MWT at all three time points in the PL and the VitD group, respectively (T1—9 ± 1.59 s, 10.39 ± 3.24 s; T2—8.46 ± 1.00 s, 9.88 ± 2.38 s; T3—8.66 ± 1.43 s, 9.31 ± 2.47 s; Figure 3C).

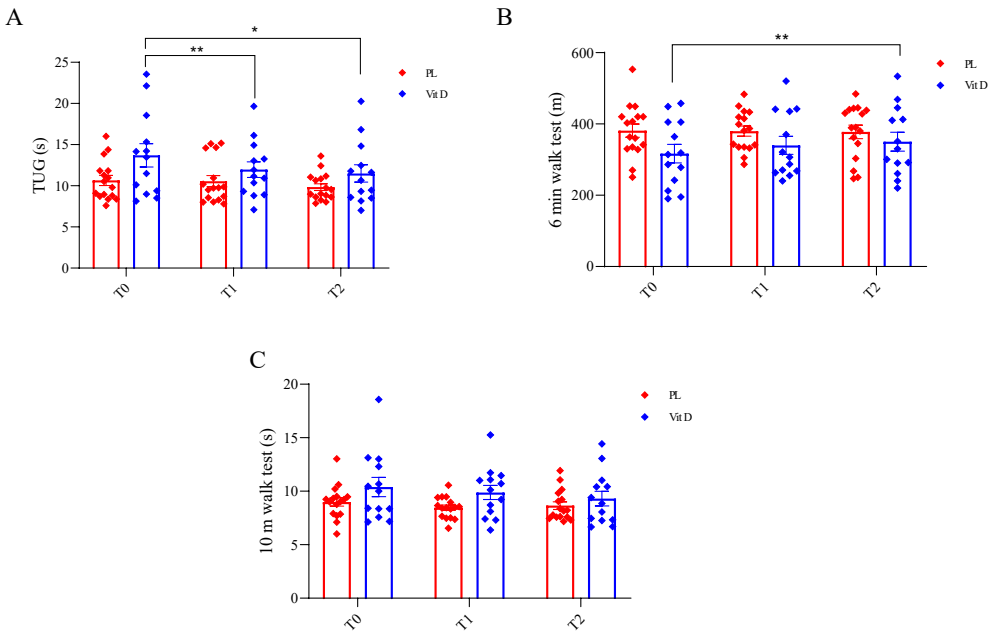

Figure 3. Effect of supplementation on functional tests. (**A**). Changes in time duration in TUG. (**B**). Changes in the distance in 6 min walk test. (**C**). Changes in time duration in 10 m walk test. * $p < 0.005$, ** $p < 0.05$. TUG—test Up and Go; T0—before the supplementation; T1—after 6 weeks of supplementation; T2—after 12 weeks of supplementation; PL—placebo group; VitD—vitamin D_3 group whiskers refer to SE.

2.4. General Inflammation Status

The effect of supplementation on general inflammation status was measured by serum hs-CRP concentration, as shown in Figure 4. We did not observe any significant changes in serum concentration of hs-CRP in both groups; however, we noticed a trend toward a decrease in the VitD group T0 (3091.12 ± 1358.19 ng/mL) vs. T2 (2454.32 ng/mL ± 1325.18) (Figure 4). We did not observe any changes in the PL group (T0—3167.04 ng/mL ± 2103.74; T2—3510.49 ± 1852.66 ng/mL). The lack of significant alteration was probably caused by the large SD, both in and between the groups.

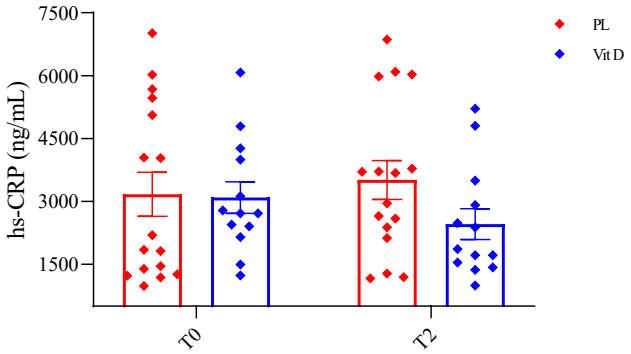

Figure 4. Effect of inflammation on general inflammation status. hs-CRP—high sensitivity C-reactive protein; T0—before the supplementation; T2—after 12 weeks of supplementation; PL—placebo group; VitD—vitamin D_3 group; whiskers refer to SE.

3. Discussion

To the best of our knowledge, this is one of the first studies where PD patients with DBS were supplemented with vitamin D_3, and it is the first when the dosage depends on the patient's BMI. Previous studies showed that patients with PD suffer from vitamin D deficiency and have a lower serum 25(OH)D_3 concentration than healthy age-matched controls [15,24–27], and our results are in line with their outcomes. We found that after supplementation based on patients' BMI, the serum concentration of 25(OH)D_3 increased above the optimum level (30 ng/mL), which shows that considering the BMI when calculating the dosage is a good concept. We also measured the metabolites of vitamin D. 24,25$(OH)_2D_3$ is a product of the catabolism of 25(OH)D_3, and its production is regulated by 25-hydroxyvitamin D-24-hydroxylase. Recently, Couchman and co-workers reported that, usually, it is between 2% and 20% of 25(OH)D_3 (average 10%), but when it comes to the deficiency of 25(OH)D_3, it might become undetectable [28]. In our study, this metabolite was significantly elevated in the VitD group after supplementation and was approximately 8.5% of 25(OH)D_3. In the PL group, it was also detectable but varied around 5.9% of 25(OH)D_3. Another metabolite that we measured was epi-25(OH)D_3, which is a product of the epimerization of 25(OH)D_3. The role of the epimerization pathway has not been sufficiently investigated, but it has been confirmed that 25(OH)D_3 is positively correlated with epi-25(OH)D_3 [29]. Both metabolites increased significantly after supplementation, suggesting that the metabolism of vitamin D was not disturbed by DBS treatment. Strong positive correlations were found between 25(OH)D_3 and 24,25$(OH)_2D_3$, and between 25(OH)D_3 and epi-25(OH)D_3. We also detected that after the supplementation in the VitD group time needed to complete TUG was significantly shorter than at the beginning, which may be related to attenuating the risk of falling. In the 6 MWT, the distance covered by the VitD group improved after the supplementation period, and this alteration also reached significance.

DBS is one of the treatments used to treat motor symptoms in PD [8]. However, most researchers concentrate on PD patients only receiving pharmacological treatment during intervention with vitamin D_3 supplementation [23,30]. We aimed to determine whether DBS influences the efficiency of supplementation. In the current study, before and after the intervention, none of the metabolites differed from those in PD patients without DBS in other studies. PD patients with DBS also suffer from serum 25(OH)D_3 deficiency, and after vitamin D3 supplementation based on patients' BMI, the concentration increased to the optimum level. After DBS was implanted in PD patients, a new, lower dose of L-dopa was established. During L-dopa intake, numerous disturbances occur in organisms. For example, an increase in serum homocysteine (Hcy) concentration may decrease muscle strength and negatively influence bone turnover and, as a result, decrease bone density, which may increase the risk of falls and fractures [20,31]. One of the main roles of vitamin D is to enhance bone density. Combined DBS and vitamin D_3 supplementation may reduce the influence of L-dopa on bones and protect them from fracture. In a study conducted in

a mouse model of Parkinson's disease, the authors suggested that supplementation with vitamin D_3 may decrease the required dosage of L-dopa and reduce its side effects. The mice were treated for two weeks after the induction of PD with 6-hydroxydopamine (6-OHDA) and vitamin D, L-dopa, or vitamin D + L-dopa for 21 days. Vitamin D was found to reverse the effects of 6-OHDA on dopamine metabolism, including behavioral deficits and oxidative stress. Dopamine metabolism also increases the effect of L-dopa [32]. In another study on patients with psoriasis, vitamin D supplementation reduced the concentration of Hcy after three months of administration [33]. Although we did not measure Hcy concentrations in our study, the results from other studies suggest that vitamin D supplementation may have beneficial effects on these parameters in patients with PD. Further studies are required to confirm this phenomenon. Regarding motor symptoms, a study by Habibi et al. showed that vitamin D did not help reduce dyskinesia induced by L-dopa [34].

Recently, we showed that vitamin D deficiency is associated with many disorders in the organism, including muscle atrophy [35] which may lead to an increased risk of falls. In a 2019 study, the authors indicated that PD patients with lower concentrations of vitamin D had a higher frequency of falls [26]. Moreover, Nocera et al. reported that shorter TUG test time in PD patients was associated with a lower risk of falls [36]. In our study, the supplementation time needed to complete the TUG was significantly shorter than at the beginning, which may be related to a decrease in the risk of falling. We also assessed the 6 MWT, which may be associated with the cardiovascular, respiratory, and locomotor systems in the elderly population [37], including PD patients. Moreover, the gait speed (m/s = distance (m)/360 (s)) can be calculated from the test results, and a speed less than 1 m/s is correlated with a higher risk of falls in the elderly population [38]. In one study, 2021 results of the 6 MWT improved after vitamin D_3 supplementation in older adults [39]. Our results showed that after the supplementation, the distance reached by the patients was also significantly improved. Moreover, gait speed improved in the supplemented group, and it was also near the statistically significant difference (2.6% improvement compared to −1.0% in the placebo group). The last test we conducted with our patients was the 10 MWT, which has been frequently used in PD because of its high test-retest reliability [40]. In this test, we did not find any statistically significant differences.

Patients with PD are often non-active [41]. Therefore, we prompted them to increase their daily activities by walking a determined number of steps per day. Unfortunately, we did not have a professional device to control performance; therefore, we did not include physical activity in our results. We may assume that, when the steps are monitored, the results would be even better in functional tests when combined with vitamin D_3 supplementation. In our review from 2021, we presented that regular physical activity is one of the most available and low-cost additions to PD therapy [20].

Dopamine loss is observed in PD due to the degeneration of the substantia nigra [4]. Studies on the effects of vitamin D on dopamine levels in patients with PD are scarce, and patients treated with DBS are virtually non-existent. Therefore, when we consider studies on animal models, we find some interesting results. In a study that we have already mentioned from 2022 in the 6-OHDA-induced PD mouse model, the authors reported that vitamin D treatment protected dopamine metabolism. Improvement in dopamine metabolism was observed in all groups, and the best results were observed in the group that received vitamin D + L-dopa [32]. In a study conducted in 2022, the authors showed that vitamin D_3 supplementation combined with exercise in hemiparkinsonian rats reduces the effects of 6-OHDA. It was reported that vitamin D_3 supplementation elevated dopamine concentration and attenuated oxidative stress in the brain [42]. Smith and co-workers reported that long-term treatment with vitamin D_3 improved dopamine metabolism and increased the concentration of dopamine in the striatum of rats with PD induced by 6-OHDA [43]. Moreover, a study from 2018 showed similar results, indicating that vitamin D supplementation may reverse the effect of the 6-OHDA lesion, which is a decrease in dopamine. They also pointed out that vitamin D supplementation had anti-inflammatory effects [44]. Furthermore, in our previous study, it was shown that reaching an optimal

serum concentration of 25(OH)D_3 in patients with low back pain reduced markers of inflammation and decreased the intensity of pain [45]. In contrast, in a review from 2016, the authors showed that vitamin D did not have anti-inflammatory properties. They suggested that this ability may be more noticeable during sudden inflammation than during diseases that last a long time [46]. However, several studies have reported higher levels of inflammation markers in patients compared to healthy matched controls. [17,18,47]. In addition, Song with co-workers found that in PD patients, regardless of the onset age of the disease, the concentration of hs-CRP was higher than that in the control group [48]. A study conducted in 2019 investigated blood biomarkers that could be useful in predicting PD prognosis, revealing that higher hs-CRP and lower vitamin D concentrations are associated with worse daily living activities [49]. Moreover, in the study, in older adults, the authors showed that elevated ultra-sensitive CRP was associated with falls [50]. In the present study, we estimated hs-CRP, the general inflammation status in PD patients. After vitamin D_3 supplementation in PD patients, we observed a trend toward a decrease in serum hs-CRP. However, it did not reach statistically significant differences. Therefore, it is substantial to note that the lack of significant changes in hs-CRP levels in PD patients could be attributed to a massive standard deviation and a small patient population or other unknown factors. On the other hand, from a biological perspective, a decrease of approximately 1000 ng/mL in PD patients after 12 weeks of vitamin D_3 treatment compared to the PL group is noteworthy.

There are several important limitations of this study. First, the sample size is small as recruitment of PD patients with implanted DBS was challenging during the covid pandemic. Nevertheless, only 29 patients without missing data were included in the final analysis. Consequently, although the power of statistical analysis was compromised, the differences between groups proved to be sufficient to show statistical significance. Second, there is a lack of a true control group without DBS to check the impact of the stimulation on the supplementation. Third, we did not measure the complex of B vitamins, which are tightly associated with L-dopa treatment and might influence the results of functional tests. Fourth, patients did not have a dedicated device to control the number of steps per day; they used their mobile phones. Because of that, the quality of control of whether they performed the required physical activity is limited. Therefore, further studies are needed to confirm these results and broaden the investigation process.

4. Materials and Methods

4.1. Design of the Study

This study was a randomized, double-blind, placebo-controlled clinical trial (NCT04768023) with a 12-week supplementation of vitamin D_3 in PD treated with DBS. This study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk; the approval number is NKBBN/522-648/2019, date of approval 3 December 2019. Patients were recruited from the neurosurgery unit of the Hospital of Nicholas Copernicus. After recruitment, patients were randomly assigned to receive vitamin D_3 (VitD) or a placebo (PL). They were divided into 1:1 ratios. The randomization was made with Excel random number generator. The identical bottles with vitamin D_3 and placebo received numbers from 1 to 42. The randomization and product allocation were conducted by an independent researcher who was not engaged in any other study procedure. Patients and investigators were blinded to the intervention assignment during this study. All patients and personnel involved in the data analysis were blinded until the database was analyzed and the intervention assignment was relevant. The unblinding was performed after all data analyses.

4.2. Participants

Patients were recruited by invitation from the Hospital of Nicholas Copernicus from the Neurosurgery Unit. The recruitment was from November 2019 to February 2022. The intervention was made during the fall/winter season to avoid the sun exposure

that is possible during the spring/summer season. Fifty patients were enrolled in this study (Figure 5).

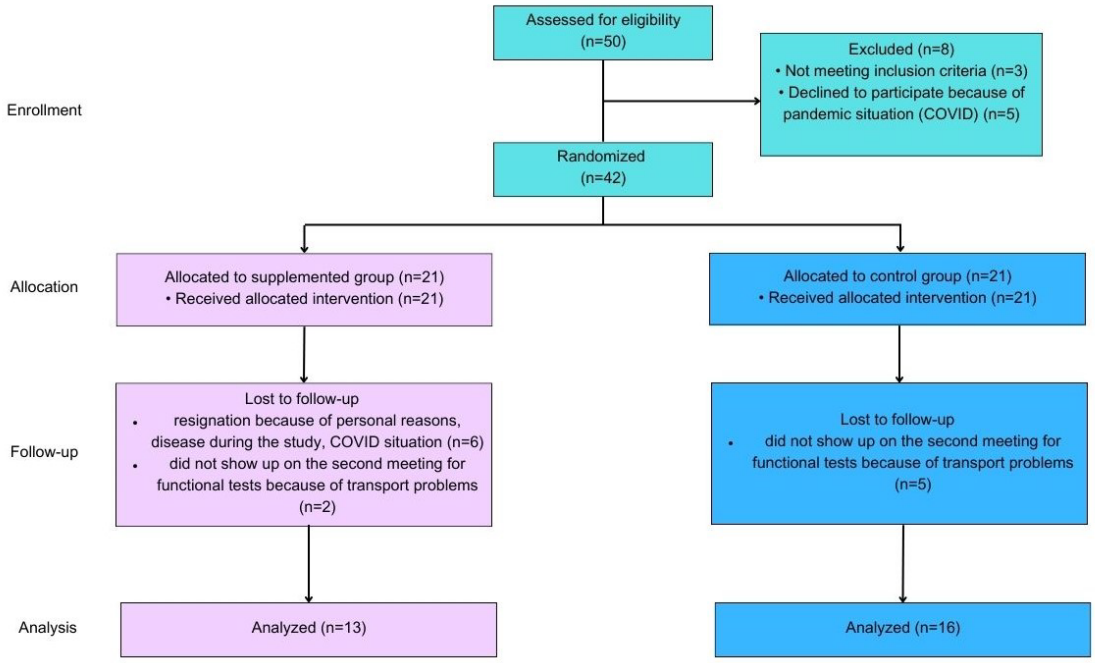

Figure 5. Flow diagram of this study.

The inclusion criteria were: agreement to take part in research, subthalamic nucleus deep brain stimulation (STN-DBS) treatment, lack of supplementation of vitamin D_3 before the research, no serious comorbidity (tumor, cerebrovascular disease, cardiorespiratory compromise, forced dementia, etc.), and declaration of involvement.

4.3. Intervention

Supplementation lasted for 12 weeks for all groups. Supplementation of vitamin D_3 was based on the participants' Body Mass Index (BMI). The BMI was measured by using the TANITA scale. The doses were set based on the literature. The recommended dose for healthy young adults is 1000–2000 International Units (IU)/day [51]. For obese and overweight individuals, the doses are higher and range between 2500 and 4800 IU/day [52–54]. Taking these recommendations into consideration, along with the fact that serum concentration in PD patients is insufficient and lower than in healthy age-matched controls, the following doses were prescribed: for BMI under 25, 4000 International Units (IU)/day; for BMI between 25 and 30, 5000 IU/day; and for BMI over 30, 6000 IU/day. The placebo group received a matching placebo treatment. Vitamin D_3, as well as the placebo, were in the same bottles with no labels on them. Patients were prompted to complete 3500 steps per day in the first week of the research and finish the research by completing 7500 per day.

4.4. Visit Program and Material Collection

There were three meetings with the patients. During the baseline visit (T0), there were blood collections, patients signed the agreement to take part in the research, then performed functional tests, and finally, received their first supplementation bottles. During the second visit after six weeks (T1), the functional tests were performed, and supplementation was replenished. On the third visit after six weeks (T2), the blood was collected for the second time, and functional tests were performed again. The visit programme is shown in Figure 6.

Figure 6. Visit programme.

The blood was collected into test tubes with a clot activator, then centrifuged at 4000× *g* for 10 min at 4 °C. The obtained serum samples were aliquoted and stored at −80 °C until the analysis.

4.5. Functional Tests

The functional tests that we assessed were: the test Up and Go (TUG), the 6 min walk test (6 MWT), and the 10 m walk test (10 MWT). All tests were performed during the on-phase of the usual anti-PD medications. All tests were explained and demonstrated before they were performed. If the first attempt was successful, then the patient followed the next attempt. If any mistake appeared, the patient waited for a minute and tried again. During every meeting, the procedure of each test was explained to the patients. In the TUG, patients were instructed to stand up from the chair, walk 3 m, turn around, return to the chair, and sit down as fast as possible without running. The 6 MWT was administered in a 15 m line in a corridor. Patients were instructed to go back and forth, without running the 15 m line, as far as possible in 6 min. The total distance was measured after 6 min and then used for the analysis. In 10 MWT, we measured the time needed to walk through 10 m from a standing position.

4.6. Measurement of Vitamin D Metabolites

The vitamin D profile was estimated in serum by the mass spectrometry method. We apprised level of 25(OH)D_3, 25(OH)D_2, 24,25(OH)$_2D_3$, and epi-25(OH)D_3. The isotope dilution method by liquid chromatography combined with tandem mass spectrometry technique (LC-MS/MS) was used. All samples were prepared and analyzed with the Eksigent ExionLC analytical HPLC system with a CTC PAL autosampler (Zwinger, Switzerland) combined with QTRAP® 4500 MS/MS system (Sciex, Framingham, MA, USA).

4.7. Measurement of C-Reactive Protein

The measurement of C-reactive protein was made by using a Demeditec hsCRP ELISA Assay Kit (DE740011, DEMEDITEC Diagnostics GmbH, Kiel, Germany) according to the manufacturer's instructions. All of the samples were analyzed in a microplate reader, Thermo Scientific Multiscan Go (Thermofisher Scientific, Vartaa, Finland). We followed the instructions.

4.8. Statistical Analysis

For the analysis, we used the statistic program Statistica 13, StatSoft Inc., (Tulsa, OK, USA). We took into consideration only full data from patients who completed all interventions (n = 29). Data were previously tested for normality using the Shapiro–Wilk W-test. The descriptive statistics for both background information and examination of the

trends in the analyzed parameters with mean values of 95% confidence interval were used. The ANOVA test for repeated measures was used for the statistical analysis. Spearman rank correlation was calculated. The statistical significance was set at $p < 0.05$. To establish statistical significance, we applied an analysis of variance (ANOVA) with Tukey's post hoc test.

5. Conclusions

The present findings indicate that 12 weeks of vitamin D_3 treatment in patients with PD with implanted DBS induces changes in the concentration of vitamin D serum metabolites and improves functional tests. These changes may have beneficial effects with an attenuated risk of falls, which is a common problem in PD. It is worth emphasizing that these changes are associated with the dose of vitamin D_3 and are dependent on the patient's BMI (the higher the BMI, the higher the dose). Although these changes occurred, there was no difference in the serum hs-CRP concentrations between the groups. This study shows for the first time that the cumulative effect of DBS implementation and BMI-based vitamin D_3 supplementation on selected blood markers and functional tests might have positive effects on reducing the number of falls, which seems to be essential for PD patients.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/522-648/2019, 3 December 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Author Konrad Kowalski was employed by the company Masdiag-Diagnostic Mass Spectrometry Laboratory, Stefana Żeromskiego 33, 01-882 Warsaw, Poland. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of 12 Weeks of Vitamin D_3 Administration in Parkinson's Patients with Deep Brain Stimulation on Kynurenine Pathway and Inflammatory Status

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Abstract: The current study aimed to investigate whether a 12-week Body Mass Index (BMI)-based (the higher the BMI, the higher the dosage) vitamin D_3 administration may affect both the kynurenine pathway (KP) and the inflammatory state in Parkinson's disease (PD) patients with deep brain stimulation (DBS) and may be useful for developing novel therapeutic targets against PD. Patients were randomly assigned to two groups: supplemented with vitamin D_3 (VitD, n = 15) and treated with vegetable oil (PL, n = 21). Administration lasted for 12 weeks. The isotope dilution method by LC-MS/MS was applied to measure KP and vitamin D metabolites. Serum concentrations of cytokines such as IL-6 and TNF-α were measured using ELISA kits. After administration, the serum concentration of TNF-α decreased in PD patients with DBS. Moreover, in KP: 3-hydroksykynurenine (3-HK) was increased in the PL group, picolinic acid was decreased in the PL group, and kynurenic acid tended to be higher after administration. Furthermore, a negative correlation between 3-HK and $25(OH)D_3$ and $24,25(OH)_2D_3$ was noticed. Our preliminary results provide further evidence regarding a key link between the KP substances, inflammation status, and metabolites of vitamin D in PD patients with DBS. These findings may reflect the neuroprotective abilities of vitamin D_3 in PD patients with DBS.

Keywords: Parkinson's disease; deep brain stimulation; vitamin D; kynurenine pathway; inflammation

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1. Introduction

The population of people ages 65 and above is widely associated with neurodegenerative disorders, the second most widespread being Parkinson's disease (PD). According to World Health Organization, the number of patients suffering from this disease was over 8.5 million in 2019. It is marked by motor symptoms including resting tremor, bradykinesia, and rigidity as well as non-motor symptoms, such as dementia, depression, sleep disturbances, among others. During disease progression, dopamine production drops due to the degeneration of substantia nigra pars compacta [1,2]. Although the disease is incurable, effective symptomatic therapies exist. Pharmacological treatment usually includes dopaminergic medication, with the precursor of dopamine, L-dihydroxyphenylalanine

(L-dopa), being the most popular drug [3]. When medical therapy becomes ineffective, patients undergo deep brain stimulation (DBS) surgery. This type of treatment improves the motor symptoms, allowing for a reduction in the drug dosage [4].

Vitamin D is often described as one of the most relevant vitamins in the human body. It plays multiple roles, e.g., maintaining the calcium and phosphate balance, helping the immune system to differentiate, and increasing bone mineralization [5,6]. The synthesis of vitamin D_3 (cholecalciferol) runs from 7-dehydrocholesterol percutaneously following sun exposure, followed by hydroxylation to 25-hydroxycholecalciferol ($25(OH)D_3$) occurring in the liver. This is the inactive metabolite widely used to assess deficiency due to the prolonged persistence in the blood, contrary to the active form, 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), produced by the enzyme 1α-hydroxylase. Vitamin D deficiency is common at our latitude (49°00′–54°50′ N, 14°07′–24°09′ E) in Poland, Europe, a result of the limited number of sunny days during the year, particularly during the autumn-winter season [6–8]. PD patients have lower concentrations of vitamin D than their healthy age-matched controls; therefore, supplementation becomes essential [9]. Vitamin D deficiency is detrimental for humans, including the increased risk of developing depression, muscle atrophy, and possibly undergoing falls [10,11].

Supplementation of vitamin D_3 is not popular among patients with PD. It is already known that PD patients suffer from a deficiency of vitamin D and have lower concentrations than healthy age-matched controls. Therefore, the doses for patients with PD should be expanded versus those for healthy people. In this study, we propose Body Mass Index (BMI)-based administration. A higher BMI is often associated with a higher content of body fat, which influences the distribution of vitamin D. Fat reduces the beneficial actions of vitamins [12].

Research on the supplementation of vitamin D_3 in PD patients is scarce, especially those with implanted DBS. The dosage in the available research is determined for healthy people [13]. In our previous study, we took into account that the content of fat affects vitamin D metabolism, and therefore determined the doses based on the patient's BMI [14].

The main route of tryptophan metabolism is the kynurenine pathway (KP). It is activated by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). Tryptophan is converted to N-formyl-kynurenine and then quickly to kynurenine (KYN) due to N-formyl-kynurenine's instability. Subsequently, KYN may be catabolized to 3-hydroksykynurenine (3-HK), kynurenic acid (KYNA), and anthranilic acid (AA). KYNA has neuroprotective properties. 3-HK, which is neurotoxic, is transformed into 3-hydroxyantrhranilic acid (3-HANA) and then catabolized to quinolinic acid (QUIN) or picolinic acid (PA), the first of which is neurotoxic, and the second may be neuroprotective. 3-HK may also be converted to xanthurenic acid (XANA) which also has neurotoxic properties. The kynurenine pathway is often disturbed in PD [15–19].

In PD patients, the markers of inflammation are often elevated compared with the healthy age-matched controls [20]. In a study conducted in 2019, the authors found that plasma concentration of tumour necrosis factor-alpha (TNF-α) was relevantly higher in PD patients than in controls [21]. Another study showed higher levels of pro-inflammatory cytokines such as interleukin-1β, interleukin-2, and interleukin-6 (IL-6) in the PD group compared to the control group. Furthermore, the level of anti-inflammatory cytokine interleukin-10 was lower in the PD group, although the change was not statistically relevant [22].

In our previous study [14], we demonstrated that BMI-based vitamin D_3 administration improved physical performance in PD patients undergoing deep brain stimulation. Based on these findings, the current study was designed to explore whether vitamin D_3 administration may affect both the kynurenine pathway and the inflammatory state in PD patients with DBS and may be useful for developing novel therapeutic targets against PD, which are independent of the dopaminergic system.

2. Materials and Methods

2.1. Design of the Study

This study was a randomized, double-blind, placebo-controlled clinical trial (NCT04768023) with 12 weeks of vitamin D_3 administration in patients with PD who underwent DBS. The research has been approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk, the number of approval: NKBBN/522-648/2019, date of approval: 3 December 2019. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All patients signed the consent to participate in the study and were informed of their right to resign at any point during the trial. The recruitment took place at the Neurosurgery Unit of the Nicholas Copernicus Hospital in Gdansk. Patients were divided into two groups in a 1:1 ratio to receive vitamin D_3 (VitD) or placebo (PL). An Excel random number generator was used for the randomization. Vitamin D_3 and placebo were placed in identical bottles labeled only with numbers and featuring no additional information. Product allocation and randomization were conducted by an independent researcher. Personnel involved in the data analysis and patients stayed blind until the database was examined for analysis. When all the data were analyzed the unblinding occurred.

2.2. Participants

The administration was planned for the autumn–winter season to prevent the confounding influence of sun exposure. The inclusion and exclusion criteria of PD patients and other relevant details were described by Bytowska et al. [14]. In total, 50 patients were recruited in the study. Three of them were excluded for not meeting the inclusion criteria and five were precluded by cause of resignation due to the COVID-19 pandemic. There were 42 patients who were randomized into VitD and PL groups. All patients (n = 21) from the PL group completed the intervention. Six patients from the VitD group resigned during the intervention due to the COVID-19 pandemic that progressed during the study, personal reasons, or illness during the study (Figure 1).

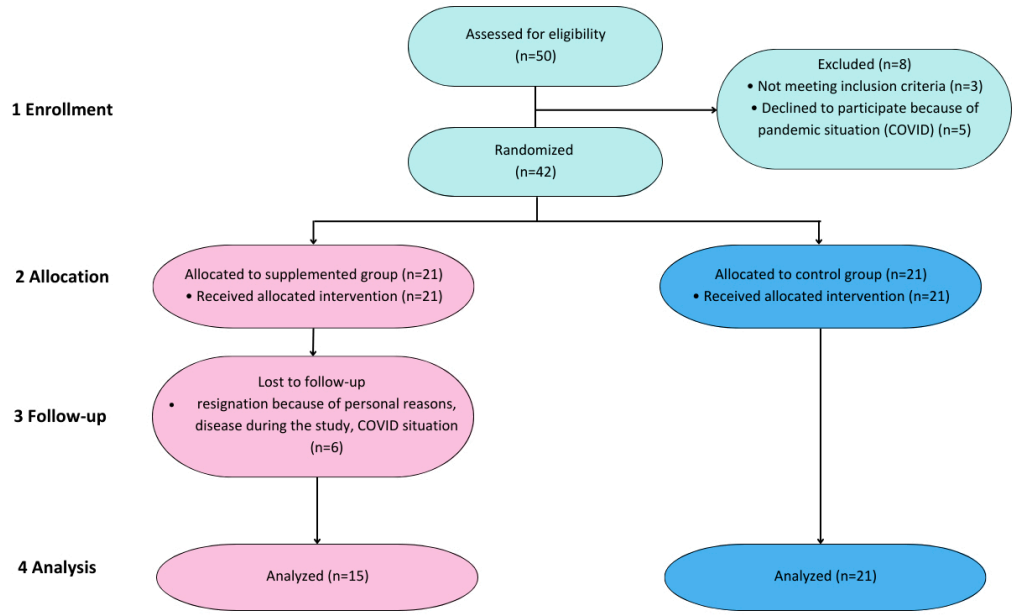

Figure 1. Flow diagram of the study.

2.3. Intervention

The administration period was 12 weeks. The dosage of vitamin D_3 was based on the patient's BMI as follows: for normal weight (BMI below 25, 4000 International Units

(IU)/day), for overweight (BMI 25–30, 5000 IU/day), and for obesity (BMI above 30, 6000 IU/day). Patients from the PL group received a matching placebo treatment.

2.4. Visit Programme and Material Collection

Patients were asked to meet with the investigators three times over the aforementioned administration period. The baseline visit (T0) included blood collection, signing of the consent forms, and the distribution of the administration bottles. Over the course of the second meeting, conducted six weeks after the start of the study, the administration bottles were refilled, and the dosage was corrected if necessary. The administration bottles were sent to patients unable to physically attend the second meeting. During the third meeting (T1), conducted 12 weeks after the start of the study, blood was drawn again. Telephone contact was maintained with patients between the meetings.

Blood was drawn into test tubes with a clot activator, then centrifuged at $2000\times g$ for 10 min at 4 °C. The received serum samples were divided and stored at −80 °C until the analysis.

2.5. Measurement of Vitamin D and Kynurenine Pathway Metabolites

The vitamin D profile and kynurenine pathway were measured in serum by the mass spectrometry method. We estimated the concentration of $25(OH)D_3$, $24,25(OH)_2D_3$, 3-HK, KYN, KYNA, XANA, and PA. The isotope dilution method by liquid chromatography combined with tandem mass spectrometry technique (LC-MS/MS) was applied. All samples were set up and analyzed with the Eksigent ExionLC analytical HPLC system with a CTC PAL autosampler (CTC Analytics AG, Zwingen, Switzerland) coupled with QTRAP® 4500 MS/MS system (Sciex, Framingham, MA, USA).

2.6. Assessment of Inflammation Markers

The assessment of IL-6 was made by using an R and D Human IL-6 Quantikine HS ELISA Kit (HS600C, R&D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. The measurement of TNF-α was made by using a Biorbyt Human TNF alpha ELISA Kit (orb50111, Biorbyt Ltd., Cambridge, United Kingdom) according to the manufacturer's instructions. All of the samples were analyzed in a Thermo Scientific Varioskan LUX multimode microplate reader (Thermofisher Scientific, Vartaa, Finland).

2.7. Statistical Analysis

For the analysis, the statistics program Statistica 13 was used. Only complete data, from patients who finished all interventions (n = 36), were taken under consideration. The Shapiro–Wilk W-test was used to proofread data for normality. The descriptive statistics for both background information and examination of the trends in the analyzed parameters with mean values and 95% confidence intervals were used. The ANOVA test for repeated measures and the one-way ANOVA test were applied for the statistical analysis. Spearman rank correlation was calculated. The statistical significance was established at $p < 0.05$. To determine statistical significance, we used the post hoc Fisher's Least Significant Difference test.

3. Results

3.1. Demographical Characteristics

Fifty patients were recruited in the study; thirty-six completed the intervention. All patients were Caucasian and fulfilled the inclusion criteria. No statistically relevant changes were detected among the groups. The mean age was 64 ± 9 years in the VitD group and 65 ± 6 years in the PL group. There were eight men (M) and seven women (W) in the VitD group and 17 M and four W in the PL group. The average body mass and height were correspondingly 78 ± 12 kg and 169 ± 11 cm in the VitD group and 80 ± 20 kg and 169 ± 15 cm in the PL group. The Hoen and Yahr (H and Y) score was 2.5 in both

groups; the duration of the disease was between eight and thirteen years in the VitD and the PL group. DBS implantation in both groups was performed 3–5 years ago. The patients' characteristics are shown in Table 1.

Table 1. Patients' characteristics.

	VitD Group (n = 15)	PL Group (n = 21)
Age	64 ± 9 years	65 ± 6 years
Sex	8 M, 7 W	17 M, 4 W
Height	169 ± 11 cm	169 ± 15 cm
Body mass	78 ± 12 kg	80 ± 20 kg
H&y	2.5	2.5
Duration of the disease	8–13 years	8–13 years
Time from DBS implantation	3–5 years	3–5 years
$25(OH)D_3$ T0 (ng/mL)	24.25 ± 9.23	18.99 ± 10.95
$25(OH)D_3$ T1 (ng/mL)	34.12 ± 10.75	18.38 ± 11.98
$24,25(OH)_2D_3$ T0 (ng/mL)	2.05 ± 1.25	1.43 ± 1.11
$24,25(OH)_2D_3$ T1 (ng/mL)	2.85 ± 1.02	1.31 ± 1.21
BMI	≤25→4 25–30→8 ≥30→3	≤25→8 25–30→10 ≥30→3

3.2. Kynurenine Pathway

The effect of vitamin D_3 administration on the kynurenine pathway is presented below. KYN concentration increased significantly in the VitD group during the administration (382.14 ± 68.34 versus 422.17 ± 109.61 ng/mL, $p < 0.05$; Figure 2a). Additionally, a relevant difference between the PL group at T0 and the VitD group at T1 (364.54 ± 69.83 versus 422.17 ± 109.61 ng/mL, $p < 0.05$; Figure 2a) was noted. There were no significant alterations in KYNA concentrations observed in both groups. However, although an increasing trend in the VitD group was observed (6.60 ± 1.42 versus 7.29 ± 1.58 ng/mL, $p = 0.067$; Figure 2b), there was no notable difference in the PL group (7.23 ± 2.10 at T0, 7.00 ± 2.43 ng/mL at T1; Figure 2b). A statistically higher 3-HK concentration was found in the PL group 7.38 ± 3.92 at T0 versus 8.78 ± 4.93 ng/mL at T1 ($p < 0.05$; Figure 2c). Moreover, 3-HK differed significantly at T1 between groups: 6.23 ± 1.73 in the VitD group versus 8.78 ± 4.93 ng/mL the PL group (Figure 2c). There was no notable difference in XANA concentrations in the VitD group (2.64 ± 1.15 at T0, 2.72 ± 1.25 ng/mL at T1) and in the PL group (3.19 ± 1.43 at T0, 3.21 ± 1.60 ng/mL at T1) (Figure 2d). The PA concentration decreased significantly in the PL group (4.66 ± 2.03 compared to 3.38 ± 0.84 ng/mL, $p < 0.0006$; Figure 2e). In the VitD group, no differences were observed (4.03 ± 1.43 at T0, 4.01 ± 1.14 ng/mL at T1; Figure 2e).

A negative correlation between $25(OH)D_3$ and 3-HK ($p < 0.05$; Figure 3a), and between $24,25(OH)_2D_3$ and 3-HK ($p < 0.05$; Figure 3b), was found. Furthermore, a positive correlation between TNF-α and 3-HK ($p < 0.05$; Figure 3c) was noticed.

Additionally, the differences in the delta of KYNA, 3-HK, and PA were examined between groups. In KYNA there was no significant difference, but a strong trend $p = 0.062$ (0.69 ± 1.54 in the VitD group compared to −0.23 ± 1.31 in the PL group; Figure 4a) was observed. The delta of neurotoxic 3-HK was relevantly downregulated in the VitD group as compared to the PL group (−1.14 ± 1.5, 1.40 ± 2.88, respectively; $p < 0.005$; Figure 4b). The delta of the neuroprotective metabolite of KP, PA, was statistically relevantly reduced in the PL group as compared to the VitD group (−1.27 ± 1.74, −0.01 ± 1.20, respectively; $p < 0.05$; Figure 4c) in PD patients with DBS.

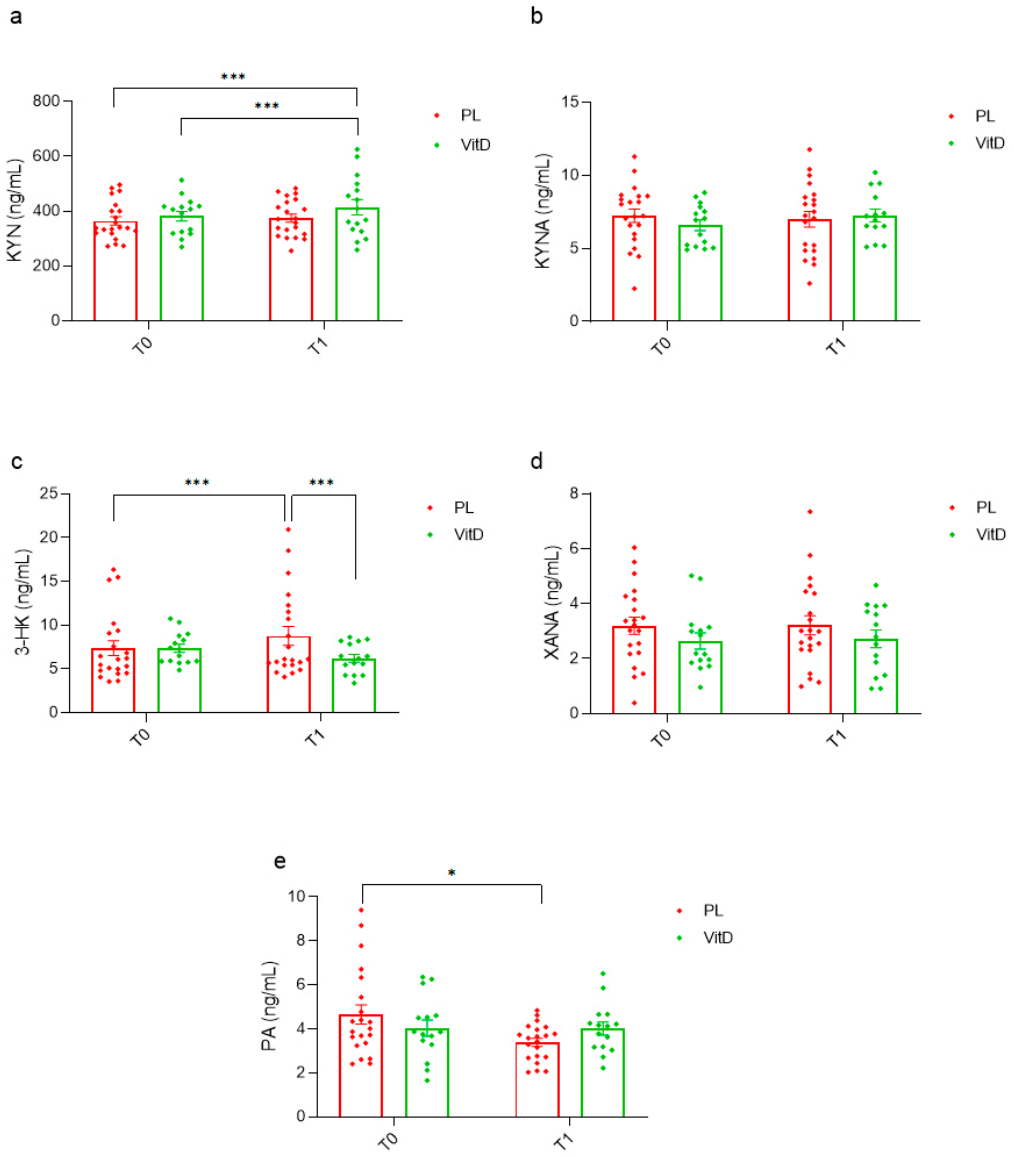

Figure 2. The impact of vitamin D_3 administration on kynurenine pathway metabolites. (**a**) Changes in serum concentration of KYN. (**b**) Changes in serum concentration of KYNA. (**c**) Changes in serum concentration of 3-HK. (**d**) Changes in serum concentration of XANA. (**e**) Changes in serum concentration of PA. * $p < 0.0006$, *** $p < 0.05$, T0—before the research, T1—after 12 weeks of administration, VitD—vitamin D group, PL—placebo group, KYN—kynurenine, KYNA—kynurenic acid, 3-HK—3-hydroksykynurenine, XANA—xanthurenic acid, PA—picolinic acid, whiskers refer to standard error (SE).

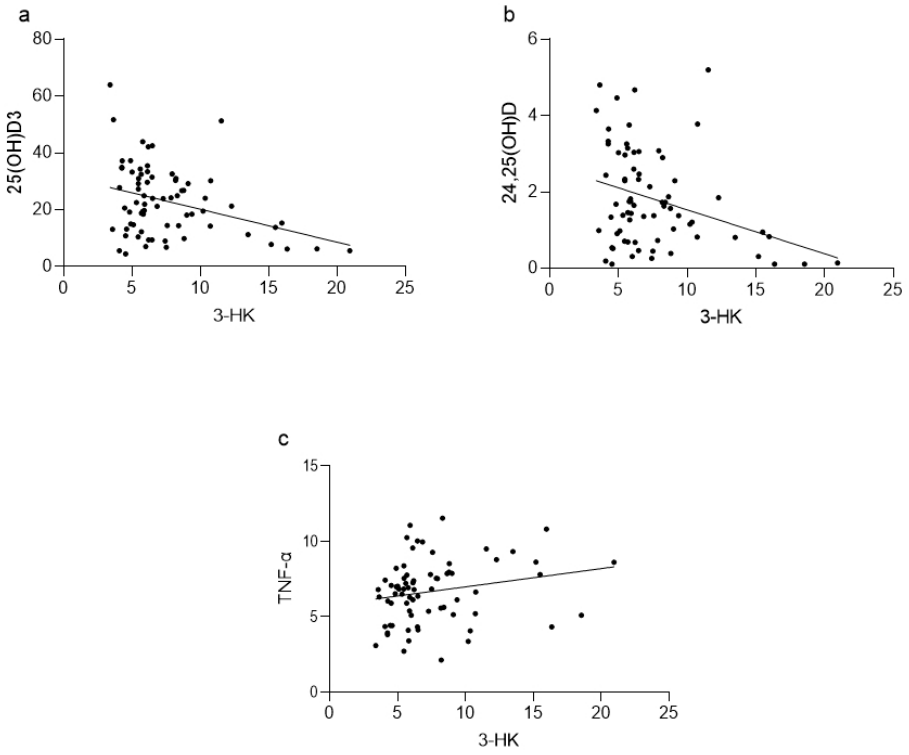

Figure 3. Correlations among (**a**) 25(OH)D_3 and 3-HK; (**b**) 24,25$(OH)_2D_3$ and 3-HK, and (**c**) TNF-α and 3-HK. (**a**) Spearman r = −0.2421, $p < 0.05$, 95% confidence interval: −0.45 to −0.004; (**b**) Spearman r = −0.26, $p < 0.05$, 95% confidence interval: −0.47 to −0.03, (**c**) Spearman r = 0.2530, $p < 0.05$, 95% confidence interval: 0.01571 to 0.4633. KYNA—kynurenic acid, 3-HK—3-hydroksykynurenine, TNF-α—tumour necrosis factor-alpha.

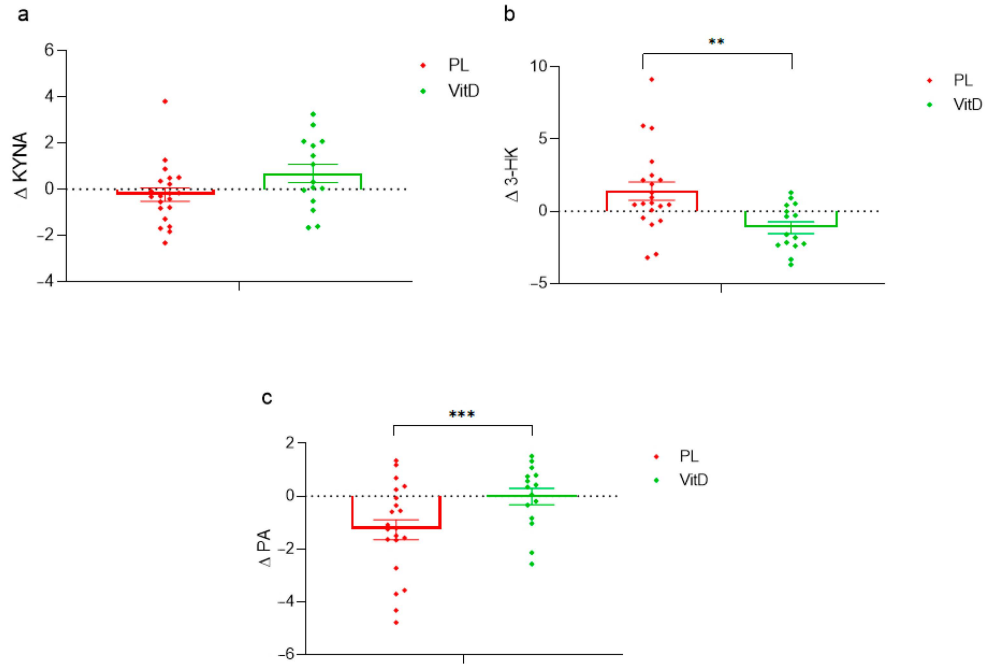

Figure 4. The effect of supplementation on Δ in KYNA, 3-HK, and PA between VitD and PL group. (**a**) Difference of Δ in KYNA. (**b**) Difference of Δ in 3-HK. (**c**) Difference of Δ in PA. ** $p < 0.005$, *** $p < 0.05$, Δ—delta, VitD—vitamin D group, PL—placebo group, KYNA—kynurenic acid, 3-HK—3-hydroksykynurenine, PA—picolinic acid, whiskers refer to standard error (SE).

3.3. Inflammation Status

The changes in inflammatory markers concentration after vitamin D_3 supplementation are presented in Figure 5. No meaningful differences in IL-6 serum concentration (Figure 5a) were observed. In the VitD group the value was 1.80 ± 0.75 at T0 and 1.98 ± 0.87 pg/mL at T1, and in the PL group 2.24 ± 0.97 at T0 and 2.35 ± 1.45 pg/mL at T1. In TNF-α, a statistically marked reduction in the VitD group (7.07 ± 2.30 versus 5.98 ± 2.09 pg/mL, $p < 0.05$; Figure 5b) was found. Moreover, there was a statistically relevant increase in the PL group (6.30 ± 2.00 compared to 7.23 ± 1.94 pg/mL, $p < 0.005$; Figure 5b).

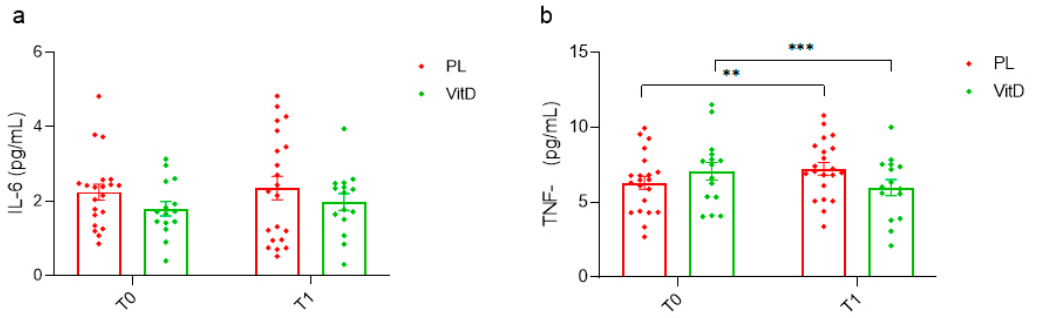

Figure 5. The impact of vitamin D_3 administration on inflammation markers. (**a**) Changes in serum concentration of IL-6. (**b**) Changes in serum concentration of TNF-α. ** $p < 0.005$, *** $p < 0.05$, T0—before the research, T1—after 12 weeks of administration, VitD—vitamin D group, PL—placebo group, IL-6—interleukin 6, TNF-α—tumour necrosis factor-alpha, whiskers refer to standard error (SE).

4. Discussion

Recently, we reported that a 12-week BMI-based vitamin D_3 administration improved physical performance in patients with PD who underwent DBS. Moreover, the overall inflammatory state measured with high sensitivity C-reactive protein after the administration showed a decreasing trend [14]. In the current study, our goal was to expand our research and investigate whether BMI-based vitamin D_3 supplementation in DBS PD patients can modify the KP and its impact on selected inflammatory markers. We found that after vitamin D_3 administration based on the patient's BMI, the serum concentration of TNF-α decreased in PD patients with DBS. Furthermore, we observed in KP that the neurotoxic substance 3-HK was enhanced in the PL group, the neuroprotective metabolite PA decreased in the PL group, and another neuroprotective metabolite KYNA tended to be higher after supplementation in patients with PD who underwent DBS. We also discovered that the delta of KYNA and PA were upregulated, and the delta of 3-HK was downregulated in the supplemented group. In PA and 3-HK the difference in delta between the groups was statistically significant, and in KYNA we observed a strong trend between groups. Furthermore, we not only noticed a negative correlation between $25(OH)D_3$, $24,25(OH)_2D_3$, and 3-HK but also a positive correlation between TNF-α and 3-HK. Our results provide further evidence concerning a key link between the KP substances, inflammatory states, and metabolites of vitamin D in PD patients with DBS. Overall, the gathered data suggest that both vitamin D deficiency and dysregulation of KP metabolites are closely associated with PD development and progression. Our initial findings indicate that the vitamin D-kynurenine pathway may be associated with the pathogenesis of PD. Consequently, this approach can potentially offer a novel therapeutic strategy that does not solely target dopamine metabolism.

The activation of KP is primarily driven by the liver, and the majority of its metabolites originate from peripheral tissues. However, under specific physiological conditions such as aging or certain pathological conditions such as blood–brain barrier (BBB) damage, these metabolites have the potential to cross the BBB and affect the central nervous system. Moreover, it is also known that the KP is often disturbed in PD. Substances from KP such as 3-HK and XANA are known to be neurotoxic, whereas KYNA and PA are usually

characterized as neuroprotective. In the literature, it was reported that during states of elevated inflammation, there is a diversion of tryptophan away from serotonin production toward the KP [16,23–25]. In the present study, we observed a relevant increase in KYN serum concentration in the VitD group after vitamin D_3 administration. Our results are in line with a study conducted in 2017 [26], where the authors demonstrated higher KYN concentrations in patients with PD compared with healthy controls. However, other results are in contrast—lower KYN concentrations were observed in PD patients than in the control group [27]. KYNA concentrations are lower in PD patients than in healthy controls [27–29]. Nonetheless, some authors reported increased concentrations of KYNA in PD [26]. This indicates that the results are inconsistent among researchers of PD. However, it is difficult to consider whether our results are consistent with or contrary to those reported by others because our PD patients were treated with DBS. We are very far from any speculation, but stabilization of L-dopa dosage resulting from DBS treatment might potentially influence the concentration of KP metabolites. In our study, we did notice a trend toward increasing KYNA concentration in the VitD group ($p = 0.067$). 3-HK concentrations are often elevated in PD patients [24,30] suggesting that the KP in PD is more likely to play a neurotoxic rather than neuroprotective role during disease progression. Kynurenine-3-monooxidase which is responsible for converting KYN to 3-HK can be activated by inflammatory factors [16]. Our results showed a significant increase in the 3-HK concentration in the PL group whereas after administration in the VitD group, it remained at comparable levels. Moreover, after the administration, the 3-HK concentration was significantly lower in the VitD group than in the PL group. Furthermore, we found a negative correlation between 3-HK and $25(OH)D_3$ and 3-HK and $24,25(OH)_2D_3$. Although the KYN concentration was relevantly lower in the PL group, the concentration of neurotoxic 3-HK was higher in this group. It might be an effect of the neuroprotective role of vitamin D_3. Another metabolite that we measured was PA, which plays a neuroprotective role. The concentration of PA significantly decreased in the PL group.

Inflammation that is connected with age may stimulate the activation of KP. Moreover, the expression of IDO, which is the first enzyme of KP, can be influenced by inflammatory cytokines such as IL-6 and TNF-α [31,32]. This may reflect an increased risk of neurodegenerative disorders. In a review from 2016, researchers found that IL-6 and TNF-α concentrations were higher in PD patients than in healthy controls [20]. Xiromerisiou et al. showed that in the advanced stages of the disease (H and Y > 2) concentration of TNF-α is elevated [33]. Depression is a common non-motor symptom in PD. It was reported that TNF-α concentrations in the cerebrospinal fluid of depressive PD patients are higher than those in PD patients without depressive symptoms [34]. After the intervention, we found a marked reduction in TNF-α serum concentration in the VitD group and a relevant increase in the PL group. Furthermore, an increased production of the neurotoxic metabolite 3-HK may be triggered by inflammatory factors. The higher concentration of 3-HK was associated with higher TNF-α in the PL group. We found that these parameters are correlated. Our preliminary data indicate that vitamin D plays a neuroprotective role, particularly in reducing the concentration of 3-HK. This effect is notable when the concentrations of serum $25(OH)D_3$ reach optimal levels. In our previous study, we found that administration attenuated the general inflammation status, although the effect was not significant [14].

The study has some limitations. Firstly, the sample size is small because the recruitment of PD patients during the pandemic was impeded. Secondly, we did not measure the tryptophan concentrations but the kynurenine pathway is described as the main catabolism pathway (>95%) of tryptophan [16]. Thirdly, we did not have any food questionnaires, although patients claimed that they did not change their diet habits during the study.

5. Conclusions

In the current research, we observed a decrease in the concentration of the inflammatory marker TNF-α after vitamin D_3 administration in PD patients with DBS. Furthermore, we found that the neurotoxic metabolite of KP, 3-HK, increased in the PL group, while the

neuroprotective metabolite, PA, decreased in the same group. Interestingly, there was a tendency for the neuroprotective metabolite KA to be higher in the VitD group. Taken together, our findings may reflect the neuroprotective abilities of vitamin D_3 in patients with PD who underwent DBS. The deficiency of vitamin D and disturbances in the kynurenine pathway are closely connected with the development of PD. Our preliminary data strongly support the notion that vitamin D, in conjunction with the kynurenine pathway, may be associated with the pathogenesis of PD.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: Author Konrad Kowalski was employed by the company Masdiag-Diagnostic Mass Spectrometry Laboratory, Stefana Żeromskiego 33, 01-882 Warsaw, Poland. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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