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**REVIEW ARTICLE** 

# Prosthetic Dentistry Treatment Capabilities in Patients with Parkinson's Disease

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**Background:** Parkinson's disease is one the most widespread illnesses in the world, affecting up to 1% of the whole population above 60 years. It is also considered the most frequent movement disorder and the second most common degenerative disease of the central nervous system. The main goal of prosthodontists should be to guarantee a good quality of life for patients ill with Parkinson's disease (PD).

Methods: The PubMed database was used to search the literature published from January 1, 2015 until February 20, 2020. The aim was: 1) To critically review the literature on dental prosthetic treatments that can be done for patients, who have Parkinson's disease; 2) To analyze what is the best time to assign the treatment; 3) To find out how it affects the patients quality of life. Analysis of literature was performed using the PRISMA analysis protocol. Articles were identified in both PubMed and ScienceDirect databases. In each of the studies, we analyzed information for: Prosthetic dental treatment options for patients with PD, most successful approaches to the treatment and factors ensuring good life-quality afterwards.

Results: 15 studies were included in the systematic review, according to inclusion and exclusion criteria. It is suggested, that the best way to restore PD patients' masticatory function, is by using implant-supported fixed prosthesis. Also, removable dentures are a viable restorative option for PD patients, although, reduced biting forces and lower jaw movements need to be taken into consideration. Moreover, before any prosthetic dental treatment, the doctor has to be informed about the patients' medication consumption time, to prevent the occurrence of tremors during the visit. In addition, the most viable treatment plan should always be chosen according to patients' quality of life as one of the main factors. For this reason, it is concluded, that non removable restorations increase the patients' quality of life significantly more than removable ones.

Conclusions: Parkinson's disease affects not only mastication, but also swallowing and verbal functions. In order to improve patients' quality of life, these functions need to be rehabilitated by using implant-fixed dental prosthesis as the best option. Because of functional impairment, prosthodontists should pay attention to keeping the patient in vertical sitting position, strictly control salivation, and also assess patients' medication intake time. Moreover, when helping the patients to clearly understand the treatment plan and maintain good oral hygiene, caregivers' assistance is needed. In addition, during aftercare, an electric toothbrush is recommended, since PD patients have trouble sustaining repetitive motions. This is the best way to ensure a successful prosthetic treatment.

### **Keywords**

Dentistry, Prosthetic, Parkinson's, Treatment, Prosthesis

# **Abbreviations**

PD: Parkinson's Disease; ME: Masticatory Efficiency; IV: Intravenous; GOHAI: General Oral Health Assessment Index; OHRQoL: Oral Health-Related Equality of Life

## Introduction

Parkinson's disease (PD) is one the most widespread illnesses in the world, affecting up to 1% of the whole population above 60 years [1]. It even affects up to 1-2 per 1000 people of the whole population at any given moment [2]. It is also considered the most frequent movement disorder and represents the second most common degenerative disease of the central nervous system [3]. Although the causes of Parkinson's disease are mostly unidentified and unknown, the wide occurrence can be explained by up to 3 times increased risk in population, whose family members and siblings had



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this disease [4]. This disease is usually chronic and causes neurodegeneration in motor and also nonmotor features. This affects not only the patients themselves, but also their families and caregivers, because of restricted mobility and control of their muscles [5]. Various treatment options can help the patient, including drugs, such as dopamine agonists, monoamine oxidase B inhibitors, COMT inhibitors, and Levodopa (L-dopa) formulations [6]. In dentistry, the main goal of prosthodontists should be to guarantee a good quality of life for patients who have PD. One of the most common treatment methods are removable partial dentures, which increase the Oral health-related equality of life (OHRQoL) and also improves patients' masticatory efficiency [7]. It is also very important to evaluate and repair the masticatory function of patient as fast as possible. Patients with Parkinson's disease are sometimes treated with drug L-DOPA, with the international non-proprietary name "levodopa". During those periods, when patient is receiving this treatment, the masticatory function is impaired [8]. There are even incidents, of levodopa-induced buccolingual masticatory dyskinesia [9]. In order to assure a good oral health-related equality of life, patients' oral health needs to be addressed, multidisciplinary approach is essential, and the treatment can be done with either fixed, or removable prosthesis. The aim of this paper was to critically review the literature on dental prosthetic treatments that can be done for patients, who have Parkinson's disease, to analyze what is the best time to assign this kind of treatment and to find out how it affects the patients quality of life.

# **Material and Methods**

Our focused questions were:

- To review and analyze the literature on available prosthetic dentistry treatments for patients, who are suffering from Parkinson's disease (PD).
- 2. To review and analyze the literature to evaluate the best prosthetic dentistry treatment timing after consuming PD medication.
- 3. To review and analyze the literature on quality of life of the patients, ill with PD, who have had their mas-

ticatory function restored with fixed or removable dental prosthesis.

# Search strategy

Analysis of literature was performed using the PRIS-MA analysis protocol. The last date of search was 2020 March 1. Article search electronic databases, keywords and filters are described in Table 1.

First, articles were identified in both PubMed and ScienceDirect databases. Keywords "Prosthetic dentistry Parkinson", "Parkinson dental prosthesis", etc. were used, which yielded the most results. During Identification phase, in PubMed, n=60, and in Science Direct n=332 articles. Filters for English language were applied. PubMed articles decreased to n=56, Science Direct had no filter for language. Filters for articles were applied, to be not older than 5 years, clinical trials, controlled clinical trials, meta-analyses and species: Humans. PubMed articles decreased to n=15. Science direct articles were n=85. After screening, we evaluated articles for eligibility.

Full-text articles assessed for eligibility n = 15;

Full-text articles excluded, with reasons n = 88.

From these articles, we reviewed and selected 15 articles, describing prosthetic dentistry treatments, available for patients, who are suffering from Parkinson's disease, their quality of life and the best time to make such treatments possible. Inclusion and exclusion criteria are described in Table 2.

The synthesized results of each article are shown in Table 3. The methodological characteristics of the 15 selected papers were summarized as follows: P-Patients/problem/population, I-Intervention/indicator, C-Comparison, O-Outcome (PICO). Data were collected from the selected articles and arranged in the following fields:

- 1. Author, year-Describes the author and the year of publication.
- 2. Population (P)-Describes the demographic features by which the population was selected, including sample size, age, sex, etc.

Table 1: Search information.

Electronic databases:	• PubMed;		
	Science Direct.		
Keywords:	<ul> <li>Prosthodontics; prosthetic; dentistry; prosthetic dentistry; parkinson; prosthetic dentistry parkinson; parkinson's disease prosthetic dental restorations; parkinson's disease implants prosthetic rehabilitation.</li> </ul>		
Filters:	• 5 years;		
	English language;		
	Clinical trials;		
	Controlled clinical trials;		
	Meta-analyses;		
	Species: Humans.		

Table 2: Inclusion and exclusion criteria.

Inclusion criteria	Exlusion criteria
Articles in English.	Articles older than 5-years-old.
<ul> <li>Case reports, clinical trials, meta-analyses of treatment in English.</li> </ul>	<ul> <li>Articles not covering the prosthetic treatment of patients with Parkinson's disease.</li> </ul>
Articles not older than 5-years-old.	<ul> <li>Articles covering prosthetic dental materials surface treatments.</li> </ul>
<ul> <li>Articles defining prosthetic dentistry treatment possibilities for patients, who have Parkinson's disease.</li> </ul>	<ul> <li>Articles covering other diseases, rather than Parkinson's disease.</li> </ul>
<ul> <li>Articles defining how patient's life-quality changed after dental prosthetic treatment.</li> </ul>	<ul> <li>Articles covering CAD/CAM prosthetic treatments, for patients, who do not have Parkinson's disease.</li> </ul>
<ul> <li>Articles defining what are the best times to administer prosthetic dental treatment according to medicine usage by the patient.</li> </ul>	Articles covering burning mouth syndrome.
<ul> <li>Articles defining best positions for the patients with PD to be held in, when performing prosthodontic manipulations in their mouths.</li> </ul>	<ul> <li>Articles covering dental materials unassociated with prosthetic dental treatment for patients with Parkinson's disease.</li> </ul>
<ul> <li>Articles defining how can the patients life quality be affected by different prosthetic dentistry treatment methods.</li> </ul>	<ul> <li>Articles covering toxicology of dental materials, which have no association with dental Parkinson's treatment.</li> </ul>
<ul> <li>Articles defining and comparing different prosthodontic treatment options for patients, with PD.</li> </ul>	<ul> <li>Articles covering coatings of different surface materials, including dental prostheses.</li> </ul>
<ul> <li>Articles, describing additional non-favorable conditions, affecting patients, with PD, which can interfere and make prosthodontic treatment more challenging.</li> </ul>	Articles covering fluorine intake.

 Table 3: Descriptive characteristics of the reviewed articles based on PICO structure.

Author, year	Population, problem, patient (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Ribeiro, et al. [4]	N = 17 patients were with PD (mean age 69.4 ± 4.7 years).	OHRQoL and ME evaluations before and two months after wearing removable dentures.	The control group consisted of 17 elders (10 men and 7 women; mean age 70.7 ± 4.7 years).	<ol> <li>Controls showed an improvement in ME after insertion of the removable prosthesis.</li> <li>ME was also lower for elders with PD when compared with controls at baseline.</li> <li>After the insertion of removable prostheses, those with PD showed a 76.1% decrease in total OHIP-49 scores (P &lt; 0.05).</li> </ol>
Ribeiro, et al. [5]	N = 17 patients, with PD, (mean age = 69.41 ± 4.65 years).	A kinesiographic device usage to measure the range of jaw motion and movements, while chewing a silicone test material (Optocal).  Masticatory performances and maximum biting forces evaluation.	The control group consisted of 17 patients without PD, (mean age = 70.71 ± 4.65 years).	<ol> <li>In PD group: Decreased range of jaw motions, longer duration and slower velocity of the masticatory cycle (P &lt; 0.05), increased masticatory performance and lower maximum bite force (P &lt; 0.05).</li> <li>No group differences were observed in opening and closing angles (P &gt; 0.05).</li> </ol>
Kaka, et al. [6]	N = 1 patient was with PD, aged 63 years.	Intravenous midazolam sedation to reduce movements before assessing condition of the teeth and mouth.	None.	1. Midazolam reduced her involuntary movements after 2 mg of intravenous sedation.  2. A total of 4 mg of midazolam was needed for sedation during treatment.  3. Supplementary oxygen was needed (2I), due to saturation lower than 90%.  4. Sedation with midazolam was not enough, and general anesthesia was needed in order to complete the treatment.

DeMaagd, et al. [8]	Patients, affected with PD, have both symptomatic motor and non-motor features.	Assessing patients' quality of life.	None.	Treatment of symptomatic motor and non-motor features of PD can improve patients' quality of life
Liu, et al. [10]	N = 1, edentulous patient with PD, 6 years after deep brain stimulation (DBS) procedure.	All-on-4 implantation for rehabilitation of edentulous mandible, with a fixed detachable dental prosthesis.	None.	<ol> <li>Implants integrated 4 months after the surgery.</li> <li>1 year after the procedure, soft tissues showed no signs of inflammation.</li> <li>Patient stated that his quality of life has increased considerably.</li> </ol>
DeMaagd, et al. [11]	Population of younger patients with PD (45-55 years-old).	Levodopa therapy.	None.	1. Dyskinesia and dystonia are associated with levodopa treatment. The longer the patient uses this drug, the higher the chance of dyskinesia.
Faggion, et al. [12]	Ensuring good hygiene and reducing inflammatory complications for patients, with neurodegenerative diseases, such as PD.	Restoring chewing function with prosthesis on dental implants, and using.	None.	<ol> <li>It is very important, that the caregivers of the elderly patients also take part in taking care of the prosthesis.</li> <li>Periimplantitis is a very serious disease, which is why, especially for patients, with PD, the number of implants used, should be kept to a minimum.</li> </ol>
Sato, et al. [13]	What the optimal dental prosthetic designs to ensure good quality of life for the patients.	Restoring patients' masticatory function with prosthetic systems that are easy to clean, easy to remove from the mouth, and does not require vigorous cleaning routines.	None.	<ol> <li>Making designs, of prosthesis, that is easier to clean, over aesthetically good-looking ones.</li> <li>Choosing removable prosthesis, instead of non-removable ones, because they are easier to clean.</li> <li>Improve care givers skills of taking care of the elderly patient's prosthesis hygiene.</li> </ol>
Ribeiro, et al. [14]	N = 17; elders with PD (mean age 69.41 ± 4.65 years; 8 women and 9 men).	Prostheses were rinsed in running water for 5 s to remove food debris. Then, 1% neutral red was applied to eight regions of complete dentures. Biofilm presence on the artificial teeth and acrylic resin in each region of maxillary and mandibular prostheses was scored according to the area covered: 0 = no biofilm, 1 = light biofilm (1% to 25% of area), 2 = moderate biofilm (26% to 50%), 3 = heavy biofilm (51% to 75%), and 4 = very heavy biofilm (76% to 100%). After 7, 14, and 30 days, the presence of biofilm on the artificial teeth and acrylic resin of prostheses were reevaluated and positive reinforcement was given to participants.	20 elders without PD (mean age 72.00 ± 5.69; 10 women and 10 men).	<ol> <li>More biofilm was present on the maxillary prostheses of participants with PD than on those of controls at baseline and at 7 and 14 days.</li> <li>Only at 7 days more biofilm was observed on the mandibular prostheses of participants with PD.</li> <li>No difference was observed between groups for maxillary or mandibular prostheses at 30 days.</li> <li>The presence of biofilm on maxillary and mandibular prostheses was reduced over time in both groups (p &lt; 0.05).</li> <li>For the maxillary prostheses, both groups showed hygiene improvement at 7 days, which was maintained throughout the 30-day study period. The mandibular prostheses in the control group showed similar results.</li> <li>The mandibular prostheses of participants with PD showed significant improvement in hygiene only at 14 and 30 days.</li> </ol>

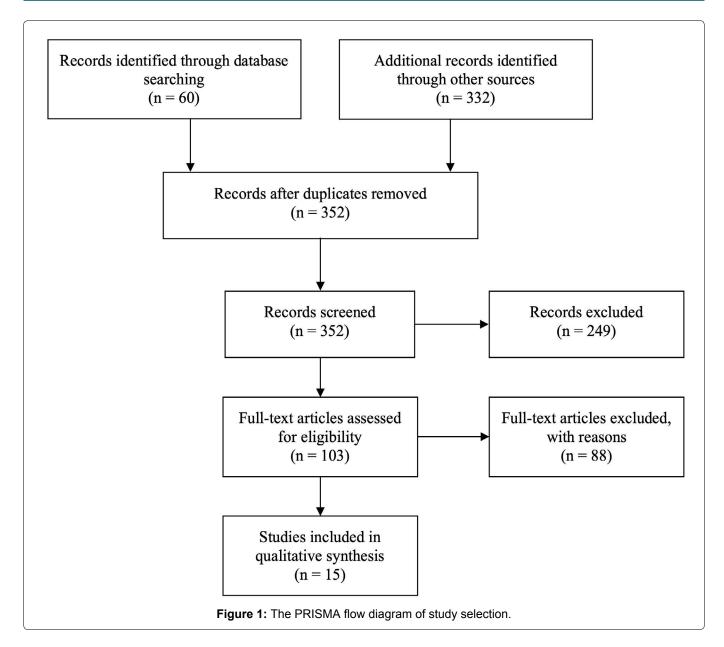
Fukuoka, et al. [15]	N = 24; PD patients (12 men, 12 women; mean age ± SD: 70.4 ± 7.9 years; age range 54-89 years).	Tongue pressure when swallowing 5 mL of barium on video fluorography was measured using a sensor sheet with five sensors. The maximal magnitude (kPa), duration(s), time to peak pressure(s), and pressure gradient (kPa/s) of tongue pressure were analyzed.	Dysphagic PD group (n = 9) and non- dysphagic PD group (n = 15).	There was no significant difference in maximal tongue pressure between both groups.      The dysphagic PD group had prolonged duration of tongue pressure and time to peak pressure and a reduced pressure gradient compared with the non-dysphagic PD group.
Rodrigues Ribeiro, et al. [17]	N = 11. Partially (n = 7) or totally (n = 4) edentulous patients had received rehabilitation with new removable dental prostheses.	Masticatory function was evaluated by mandibular movements, maximum bite force (MBF), and masticatory performance (MP). Mandibular movements reflecting jaw range of motion (ROM) and jaw movements while chewing silicone test material (Optocal), were evaluated using a kinesiograph. MBF was assessed by strain sensors, and MP was determined using the median Optocal particle size (X50) after 40 masticatory cycles.	Evaluations were carried out 30 min before levodopa intake (off-period) and within a 3-day interval 1 hour after levodopa intake (on-period).	During the levodopa off-period, elders showed decreased ROM during protrusion and lateral movements, while no difference was found in maximum opening and mandibular movements during chewing. MBF was lower and X50 was higher during the off-period, indicating worse mastication.
Fereshtehnejad, et al. [18]	Patients with dementia and PD have less dental care visits, than people, who are not affected by these diseases.	The rate of dental visits changes, after the patients were diagnosed with PD.	None.	<ol> <li>The rate of dental visits per year decreases to 0.8 3 years after the diagnosis of dementia.</li> <li>Caregivers of elderly, affected with dementia and PD should be informed, about the assistance that is required.</li> </ol>
Suttrup, et al. [19]	Patients who suffer from PD frequently develop dysphagia.	Impaired swallowing.	None.	1. Swallowing difficulties complicate medication intake, lead to malnutrition and aspiration pneumonia, therefore - reduce patients' quality of life.
Ribeiro, et al. [20]	N = 17 (mean age $69.59 \pm 5.09$ years) patients with PD.	Objective assessment: Remaining teeth, DMFT, VPI, salivary flow rate, removable prosthesis conditions. Subjective assessment: Self- perception of oral health using GOHAI index.	N = 20 (mean age 72.00 ± 5.69 years) healthy volunteers.	<ol> <li>There were no group differences in the number of remaining teeth, DMFT, VPI or salivary flow rate (p &gt; 0.05).</li> <li>GOHAI scores were low for the PD group and moderate for controls (p = 0.04).</li> <li>Elders with PD have similar oral health to controls.</li> <li>Although all elders had few remaining teeth, high DMFT and high VPI, PD elders had more negative self-perceptions of their oral health than did the controls.</li> </ol>

DBS: Deep Brain Stimulation; DMFT: Decayed, Missing and Filled Teeth; GOHAI: General Oral Health Assessment Index; MBF: Maximum Bite Force; ME: Masticatory Efficiency; MP: Masticatory Performance; OHIP: Oral Health Impact Profile; OHRQoL: Oral Health Related Quality of Life; PD: Parkinson's Disease; ROM: Range of Motion; VPI: Visible Plaque Index.

- 3. Intervention/Indicator (I)-Defines the disorder diagnostic parameters and research methods used.
- 4. Comparison (C)-Reveals whether a control group was used and describes its features.
- 5. Outcomes (O)-Describes the resulting outcomes according to the targets of the study.

#### **Results and Discussion**

The flow diagram of study selection is shown in Figure 1. Of the total of 392 studies identified through the search in the databases, 15 articles were included for the systematic review.



# Prosthetic dentistry treatments, available for patients, who are suffering from Parkinson's disease

During any prosthetic dental treatment, especially in challenging cases, like PD, it is very important, to maximize the functional, phonetical and aesthetical results. Ribeiro, et al. had observed, that PD has association with impaired masticatory function-reduced lower jaw movements and maximum biting forces [5]. One of the ways to treat PD patients is their masticatory function rehabilitation with prosthesis on implants. Liu, et al. suggested using All-on-4 prosthetic dental treatment, by making a fixed detachable dental prosthesis on 4 implants in the patients' mouth. It proved to be a good choice, with no complications after1-year follow-up, no loss of bone around the implant was present. The soft tissues were also found in good condition [10]. Packer analyzed PD patients and their prosthetic dental treatment plans. In one of the cases, dentures, with removable LOCATOR® abutment systems held for 8 years, but the retentive elements needed to be chosen carefully [11]. Patients, with PD, can have some difficulties in removing the prosthesis from the mouth, if the retentive inserts are too tight, so it is always wise to choose the lighter ones. Also, the inserts in the removable denture, should be used with an angle placement capability, because it may be hard for the PD affected patient to insert them in only one way. It should also be mentioned, that patients with PD have a lower implant survival rate-82%, so treatment should be planned accordingly. Furthermore, the number of implants, that are used to treat prosthetic problems in PD patients, should be kept to a minimum, because of the increased chance of negative outcomes, such as periimplantitis [12]. Nevertheless, two-piece implants are more viable option for prosthetic treatment, than a one-piece system, because, if needed, an implant can be put to sleep [13].

Removable dentures can also be used to treat patients with PD. Although, authors Ribeiro, et al. have observed, that patients with PD have had more biofilm accumulation on their prostheses, compared to non-PD patients. During their research, results were more apparent on the maxillary prosthesis [14]. Also, Fukoka, et al. used video fluorography, which led them to

results, that dysphagic PD patients have prolonged duration of tongue pressure, and the time that they take to reach maximum pressure is longer. This may cause problems for the patient, in holding the removable denture in its place [15]. In 2017, scientists Ribeiro, et al. did a research, where they measured Masticatory efficacy (ME), which was calculated according to patients bite force and jaw movements amplitude, and came to a conclusion, that removable dentures improved ME in elder individuals, but it not quite reached the levels of control group [4].

# Evaluation of the best prosthetic dentistry treatment timing after consuming PD medication

Kaka, et al. described a case with two patients, who suffered dyskinesias, which main relief of symptoms were observed from 30 to 60 minutes after taking medication and their symptoms started reappearing 3 hours after (in this case, the drug that was used was co-careldopa). Also, the same scientists suggested, that for longer treatment periods, a small dosage of Intravenous (IV) midazolam sedation can help reduce the symptoms [6]. Moreover, Boyd, et al. described, that when the patient uses anti-PD drugs (like levodopa, which enhances brain levels of dopamine), it can cause nausea and vomiting, which may aggravate any prosthetic procedure inside the patient's mouth [16]. According to Ribeiro, et al. the prosthodontist needs to evaluate, that during the levodopa "on" periods, the masticatory function of the patient is impaired, and it need to be taken into consideration, if any of the procedures involve these types of movements [5]. Also, the same scientists, Ribeiro, et al. came to a conclusion, that before patients take in levodopa, their mandible range of motion is reduced during specific movements, in this case, protrusion and laterotrusion [17]. It should also be noted, that patients, who have PD, may need a lot of visits for review, and alterations of prostheses. Packer treated 4 patients with PD, and a total of 116 visits were required through a 10-year period [11]. Also, the patient can have impaired swallowing, therefore, dentists should always be careful in leaning back the patient in the chair, which means, that vertical position is more favourable [16]. It should also be noted that the procedure of Deep brain stimulation (DBS) before any kind of prosthetic dental treatment improves patients resting tremor, which helps the clinicians in their work, for example-registering occlusion or taking impressions [10].

# Quality of life of the patients, ill with Parkinson's disease, who have had their masticatory function restored with fixed or removable dental prosthesis

One of the main goals of treating patients with PD is to ensure the correct treatment for symptomatic motor and non-motor features of the disease [8]. Fereshtehnejad, et al. in their nationwide study examined individuals with dementia and Parkinsonism, which showed their

reduced abilities in utilizing dental care. The most affected groups of patients either had mixed dementia or dementia in the context of Parkinsonism [18]. It should also be noted, that patients, who have PD often develop dysphagia, which can cause serious side effects, such as inability to take medication, malnutrition, and one of the most serious complications-aspiration pneumonia which furthermore reduces the patients' quality of life. For these types of situations, prosthesis on implants is one of the main treatment possibilities, in order to restore patients' masticatory function, and also improve their everyday life quality [19]. Liu, et al. concluded, that rarely, removable denture is a valid type of restoration, because of the involuntary tongue movements, and sialorrhea, which reduces the prosthesis ability to hold well onto the gums, without any additional attachments. Also, relining did not fix the problem. The most favorable type of treatment for this situation is an implant fixed dental prosthesis, rather than an implant-retained overdenture [10].

Patients with PD also usually have a lot of non-favorable conditions, such as xerostomia or sialorrhea. They can also experience nausea, vomiting, which can have negative impact on patients' oral health. It is difficult, for PD patients to brush their teeth, because of the required sustained repetitive motions, therefore, electric toothbrush is recommended, which greatly increases the patients' quality of life [16]. Also, not only the doctors, but also the caregivers should be involved in the prosthetic dental treatment, by learning how to take care of prosthesis on implants [12].

Ribeiro, et al. study evaluated 37 patients (17 of them were ill with PD) according to the General oral health assessment index (GOHAI) who had removable dentures, and the results have shown, that GOHAI Index was low in the PD group of patients, compared to control group, which index was moderate [20]. By making non-removable, all-on-4 implant systems, scientists Liu, et al. observed, that life quality greatly improves with these types of prosthetic restorations, compared to removable ones [10].

### **Conclusion**

- According to the article data, the most successful form of prosthetic dental treatment for PD patients is implant supported fixed prosthesis. Nevertheless, during regular visits, patient's tissues, around the implant-prosthesis system, should always be evaluated for inflammations in order to avoid peri-implantitis. As an alternative, removable dentures can also be taken into consideration, as a viable prosthetic treatment option for PD patients. Although, in comparison to non-PD individuals, the accumulation rate of biofilm, on removable prosthesis, is higher in the PD patients;
- 2) Also, for PD patients, the total number of visits to

the prosthodontist should be kept to a minimum. Drug consumption time should always be taken into consideration. The procedures should be scheduled 60 to 90 minutes after taking PD medications (e.g. *levodopa*). This way it is easier to perform manipulations in the oral cavity since the muscle tone, which resists to jaw opening, is minimized and uncontrolled tremor is avoided;

3) In order to increase prosthetic treatment longevity and to guarantee a good quality of life for PD patients, it is very important, that the aftercare includes patients' relatives or caregivers. They should help the patient to clean their teeth and prosthesis, since PD affected individuals have difficulties in sustaining repetitive motions. In addition, an electric toothbrush is recommended, due to more effective results, compared to regular flossing and using a standard toothbrush.

# **Ethics Approval**

NA.

# **Funding**

NA.

# **Conflicts of Interest**

The authors have no actual or potential conflicts of interest.

# **Authors Contribution**

Authors have contributed equally to this research article.

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