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DYSGEUSIA IN PARKINSON´S DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Taste has an extreme importance on individual nutrition, health and quality-of-life status. Parkinson's disease (PD), one of the most frequent neurodegenerative disorders, is becoming a systemic disease with an increasing awareness to the importance of non-motor symptoms for early PD diagnosis and early intervention. Dysgeusia may be a non-motor symptom of PD, similar to olfaction, however its role in PD diagnosis have not been well established yet.

Purpose: To determine whether taste function is impaired in patients with PD.

Research strategy: A systematic review research was carried out on the 30 of November 2015, using PubMed, Cochrane Library, SciELO, Web of Science, Index of Portuguese Medical Journal (IndexRMP.pt) and National Guideline Clearinghouse (guideline.gov). The metaRegister of Controlled Clinical Trials and ClinicalTrials.gov were also searched. We utilized the following equation: ("taste" (MeSH) OR "taste*") OR "dysgeusia" (MeSH) OR "taste disorders" (MeSH) AND ("Parkinson's disease" (MeSH) OR "Parkinson*").

Selection criteria: We have selected original studies conducted with PD patients that investigated the symptoms, incidence, prevalence and severity of taste impairment. There was no restriction on the study design, and publication date or status, but on the PubMed database, we have activated filters concerning to species (humans), and language (English, French, German, Spanish, and Portuguese).

Data Extraction: Independent extraction of articles by 2 authors in accordance with the pre-established selection criteria. A standardized template was filled including the following information: author, year, sample, diagnosis and severity of PD, cognition and therapeutic status, purpose, type of intervention, main results and study limits.

Results: We have found 334 studies by using the keywords and above search criteria. After adjusting for duplicates 173 remained. Out of this total, 125 were excluded by the title, 26 by the abstract, and 11 after we read the full text. Thus, a total of 11 studies were selected and analyzed in this review.

Conclusion: We have observed a lack of standardization on the measurement methods used to assess taste function in PD patients, with great heterogeneity in the participants

samples, which reduces the effectiveness and reliability of the results. Even though, an impairment of taste in PD has been described by the majority of the studies, but the clinical usefulness of taste testing seems to be limited at present, and, therefore, further research is encouraged.

Key-words: Parkinson's Disease, Dysgeusia, Taste Function.

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INTRODUCTION

Background

Taste is a chemosensory function performed by the gustatory system of extreme importance on individual nutrition, health and quality-of-life (QoL) status.[2, 3] It is an important tool for screening soluble and airborne chemicals for food selection, evaluation, and avoidance of potentially toxic compounds, also affect the function of digestive enzymes, and contributes to efficient metabolism, and to the reward system function.[2, 4, 5]

However, in contrast to clinical olfactory testing, where numerous validated tests exist, most gustatory tests are based on chemical stimulus to obtain information about taste threshold, discrimination and/or identification through a variety of systems, e.g. filter paper discs, taste tablets, cotton swabs, edible wafers, taste strips, or liquids, which are either not commercially available or lack available normative data.[3, 6-8] For example ‘‘Whole Mouth Test’’ (WMT), is a rapid screening test for the four basic taste qualities presented at supra-threshold concentrations.[9, 10] But similarly to others tests procedures, this technique do not allow the assessment of single gustatory nerve afferents such as lateralized testing or testing of the anterior two-thirds of the tongue, innervated by the chorda tympani versus the rear of the tongue innervated by the glossopharyngeal nerve.[6] ‘‘Taste Strips Test’’ (TST) is a validated test method for the determination of regional gustatory sensitivity, that uses filter papers impregnated with the same four basic taste qualities but at four different concentrations.[6, 10] In addition to techniques based on administration of chemicals on the tongue, electrogustometry (EGM) provides a rapid measure of taste threshold and facilitates regional testing, being more sensitive to slight taste impairment, but is inappropriate for evaluation of taste qualities other than sour or ‘‘metallic”.[9, 11]

Dysgeusia represents the distortion of the sense of taste, or an abnormality in patient ability to detect the five standard taste stimuli (salt, sweat, sour, bitter, umami) or electric stimuli (EGM).[12, 13] Demonstrating the etiology of a dysgeusia is not an easy task because of the number of anatomical and functional structures involved, and the multi-disciplinary nature its´ etiologies.[13, 14] Although these disorders can have a substantial impact on QoL and may represent significant underlying disease, they are often overlooked by the medical community.[14]

Parkinson's disease (PD), one of the most frequent neurodegenerative disorders - with an estimated prevalence of 31 to 328 per 100,000 people worldwide, is no longer considered

just a motor disorder characterized by extrapyramidal symptoms.[15, 16] Its current diagnosis, based on clinician's recognition of cardinal motor symptoms and response to medication, implies a dramatic delay in diagnosis and prognosis, increasing the risk and effects of disease progression, associated with high economic costs.[15]

PD is now considered a complex systemic disease also characterized by the occurrence of a variety of non-motor symptoms (NMSs), that represent an important part of the disease and the recognition of these NMSs is one of the key areas of opportunity for early PD diagnosis and early intervention.[9, 10, 17, 18] Furthermore, contributing to the severity of disability, to institutionalization and to impaired QoL.[17-19] In order to facilitate detection and management of the NMSs in PD two instruments have been developed: (i) the Non-Motor Symptoms Questionnaire (*NMSQuest*) that detects the presence of NMSs and (ii) the Non-Motor Symptoms Scale (*NMSS*) for the evaluation of severity and frequency of various domains of NMSs.[19, 20] However, NMSs remain under-recognized since the clinics focus primarily on the motor aspects of PD and the patients do not report them, because they do not realize that NMSs are connected with PD.[20] The fact that NMS may arise as part of drug related side effects confounds this issue further.[17, 21]

Among them, a deficient olfactory performance is now acknowledged to be one of the prevalent symptoms since the early stages of the disease.[10, 22] Less clear is the incidence, extent and pathophysiology of taste function in PD patients.[9, 22] Inclusion of the item ''change in taste or smell'' in the *NMSQuest* implies that many researchers and clinicians agree that the sense of taste is impaired in PD, but there have been only a few relevant studies, and they have produced conflicting results.[10, 11, 22, 23]

Although there are increasing efforts to develop biomarkers of PD in order to obtain an earlier and more accurate diagnosis of the condition, a recent study reported that up to 20 % of people had been misdiagnosed with PD and are therefore not being treated appropriately [24]. So, it is possible to identify two main problems to date: (i) the correct diagnosis of PD is an important prerequisite for prognostic and therapeutic reasons and is essential for clinical research, and despite all the recent advances in imaging and genetics of parkinsonian disorders, still there is no objective test able to make a definitive diagnosis of Parkinson's disease during life, with the exception of gene testing in a reduced number of cases;[25, 26] (ii) despite intriguing leads, direct testing of preclinical markers

has been limited, mainly because there is no reliable way to identify preclinical disease. (27)

For this reason, the presumed association between dysgeusia and PD has been investigated in this work, trying to elucidate if taste dysfunction in PD could be used as a possible clinical biomarker.

Purpose

The purpose of the present work is to determine whether taste function is impaired in patients with PD by means of a systematic review.

METHODS

Selection Criteria

Types of studies

We selected original studies conducted with PD patients that investigated the symptoms, incidence, prevalence and severity of taste impairment. Additionally, the following types of articles were considered: literature reviews, dissertations, book chapters, case studies, editorials, and guidelines. We excluded original studies that made no reference to the subject of this review in the title, abstract, or full text. Studies focused exclusively on other cases of dementia with Lewy bodies, exclusively on olfactory assessment test, and studies with animals were also excluded.

Types of participants

Studies were included in the review if they had participants with the following characteristics:

(i) Confirmed diagnosis of PD;

(ii) All ages and in all stages of the disease [Unified Parkinson's Disease Rating Scale (UPDRS), and/or Hoehn and Yahr (H&Y) scale];

(iii) Under dopaminergic treatment (e.g. levodopa) or ‘‘naıve’’ patients;

(iv) Compared to a healthy control (HC) group;

(v) Without cognitive impairment;

(vi) Without known ENT disorders and/or major systemic diseases or any condition which could alter chemosensory function. Smokers were not excluded.

Types of Interventions

We considered studies that investigated the epidemiology, symptoms, and severity of taste impairment in PD patients through clinical history, general physical examination, and any kind of taste assessment test (e.g. taste strips, EGM threshold, or questionnaire).

Types of outcome measures

Primary outcome measures: Presence of dysgeusia, detected by any kind of taste assessment test.

Secondary outcome measures: Presence of correlations between age, gender, cognitive function – Mini-Mental Status Examination (MMSE), and/or Montreal Cognitive Assessment (MoCA), and overall disease severity – UPDRS, and/or H&Y scale, PD duration and therapeutic status, prevalence of NMSs, and olfactory assessment testing.

Research Strategy

We followed PRISMA 2015 guidelines for systematic review and meta-analysis and the Cochrane Collaboration definition of both terms. [1, 28, 29]

In order to formulate this literature review, it was sought to answer the following(s) question(s):

(i) How is taste function in PD? And with which frequency is (taste impairment) reported?
(ii) Is dysgeusia an early NMS of PD? And could it be used as a preclinical marker to screening PD?
(iii) Could taste assessment be used as a biomarker of disease progression in subjects with PD?

A systematic review search was carried out on the 30 of November 2015, using PubMed, Cochrane Library, SciELO, Web of Science, Index of Portuguese Medical Journal (IndexRMP.pt) and National Guideline Clearinghouse (guideline.gov). The metaRegister of

Controlled Clinical Trials (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) were also searched to identify ongoing and completed trials. Furthermore, we searched the reference lists of all relevant articles to identify additional published studies for possible inclusion in the review.

We used a search strategy with MeSH terms to retrieve topics from the scientific literature and open terms (OT) not found in the MeSH but also relevant to the study and that contributed to expand the search. We utilized the following equation: ("taste" (MeSH) OR "taste*") OR "dysgeusia" (MeSH) OR "taste disorders" (MeSH) AND ("Parkinson's disease" (MeSH) OR "Parkinson*"). There was no restriction on the study design, publication date, and publication status, but on the PubMed database, we activated filters concerning species (humans), and language (English, French, German, Spanish, and Portuguese). No research filters were applied when accessing SciELO, and Web of Science.

Data analysis

A three-step search strategy was utilized in this review: an initial limited search of PubMed was undertaken, followed by analysis of the title and the index terms of studies retrieved using the search strategy. After that, we read the abstracts of those selected based on the relevance of the title.

A second search using all identified keywords and index terms was undertaken across all included databases.

Thirdly, the reference list of all identified reports and articles was searched for additional studies. In case these articles were in accordance with the pre-established inclusion criteria, they were analyzed in their entirety. The full text of these potentially eligible studies will be retrieved to identify studies that potentially meet the inclusion criteria outlined above.

Risk of bias (quality) assessment

Independent extraction of articles by 2 authors in accordance with the pre-established selection criteria. Papers selected were reviewed for methodological validity prior to inclusion in the review by the same 2 authors. Disagreements between the reviewers were resolved through discussion.

Data collection

A standardized template was filled by the data contained in the articles of interest including the following information: author, year, sample, diagnosis and severity of PD, cognition and therapeutic status, purpose, type of intervention, main results and study limits.

RESULTS

Study Selection

Using the above search criteria, 334 studies were returned. After adjusting for duplicates 173 remained. Out of this number, 125 were excluded based on the title, and 26 based on the abstract, as confirmed in Figure 1. Three were conference papers that could not be obtained. The study by Lang *et al.* was available only as an abstract at the time of this review; therefore, full methodology and results were not available for review. The full text of the remaining 22 citations was examined in more detail, which resulted in eleven studies being analyzed in this review (Figure 1). No unpublished relevant studies were obtained. The characteristics of the studies included in the review are listed in Table 1.
The reasons for excluding studies can be clustered into 4 groups, namely: (i) did not included PD patients; (ii) the control group didn´t include healthy subjects; (iii) did not separated the taste and smell disorders as distinct entities; and (iv) without reference to quantitative or qualitative assessment of taste.

Study Characteristics

Participants

All included studies involved patients diagnosed with PD. Four studies specifically stated that the diagnosis was of idiopathic PD. [5, 30-32] The diagnosis of PD was essentially clinical for each of the included studies, as observed in Table 1, with resource to guidelines for PD diagnosis [10, 22, 33, 34] or with the help of medical experts [5, 11, 23, 30-32]. It was noticed the use of imaging technology, and in particular dopamine transporter (DAT) imaging in three studies [30, 33, 34] to support the clinical diagnosis or to establish possible correlations. In terms of severity of PD, a number of scales of evaluating PD motors symptoms and method of reporting (mean, median, range) was not consistent, except for the Breen *et al*. [24], which made no reference to any kind of instrument of PD severity assessment. The majority of the studies rated for the severity of PD with H&Y scale [5, 10, 11, 22, 23, 30-34], not

exceeding the stage III, but four of the studies reported the use of the UPDRS [30, 31, 33, 34] as an additional measure of disease severity (Table 1). Duration of disease ranged widely from 16.4 months to 87.6 months and was reported in all but three studies [22, 24, 33].

The control group of the selected articles is exclusively constituted by healthy subjects, which have been submitted to the same examinations and met the same exclusion criteria as PD patients. The sample of healthy controls were recruited mainly from staff members families of the institutions involved, but also from spouses and close relatives of the participants with PD. Information about sampling source was not available in three studies [10, 11, 30] and the Moberg *et al*. study [31] used a sample from community and local houses of worship.

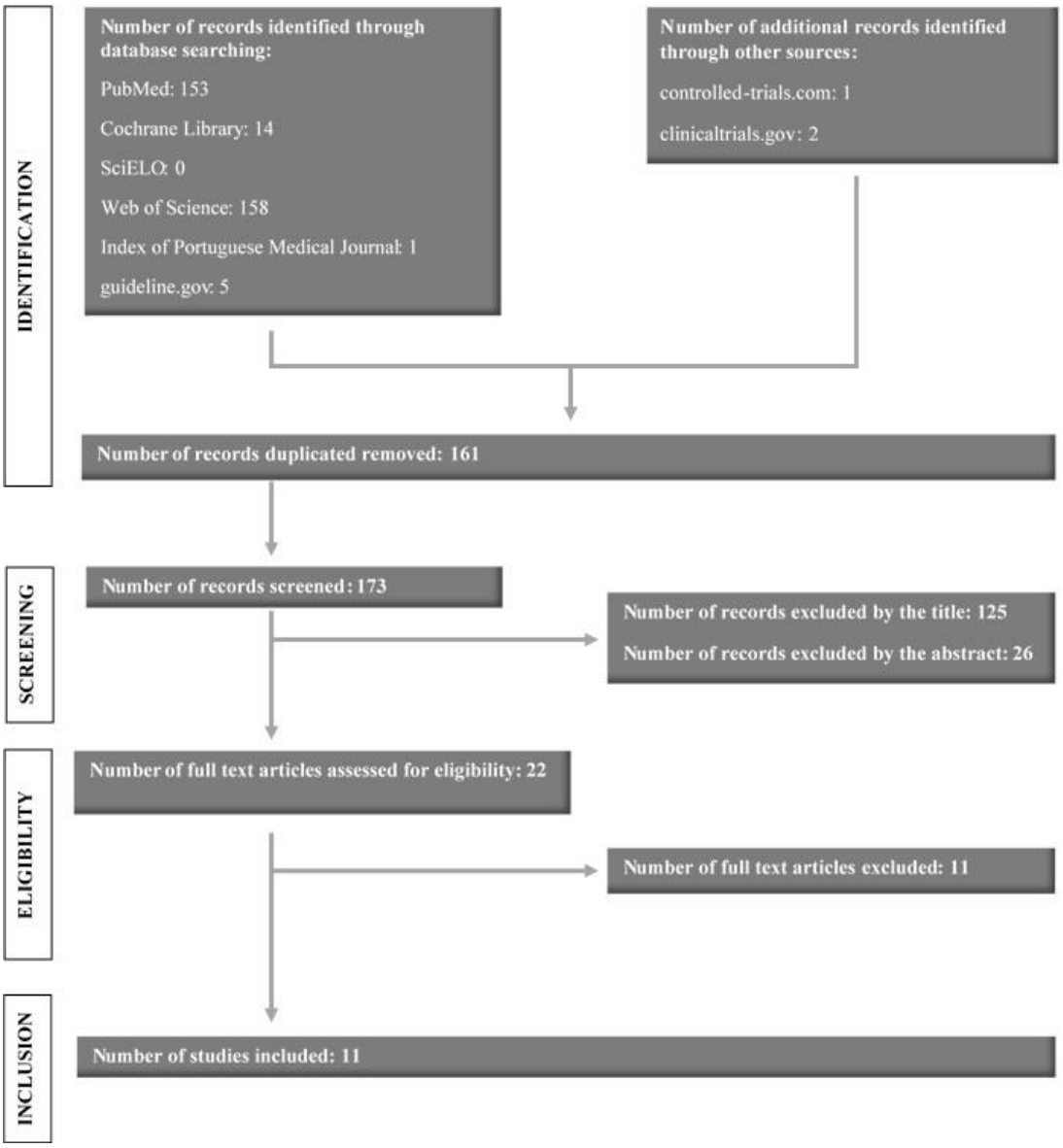

Figure 1 - Search and selection of studies for a systematic review on the model of Cochrane Collaboration [1]

Sample sizes for each of the included studies are also found in Table 1, varying from 40 individuals [5] to 13 310 participants [24]. Most studies recruited less than 150 individuals [5, 10, 11, 30-32, 34] and a higher prevalence of male subjects, taking as example the exclusively male sample in the study of Moberg *et al*. [31]. The mean age of the PD samples ranged from 60.6 ± 6.2 to 74.7 ± 7.7 years, and of healthy controls from 56.3 ± 1.6 to 70.9 ± 8.6 years (Table 1). Eight of the studies have specifically their controls matched by age and gender to PD patients [5, 10, 11, 23, 31-34]. Subjects' cognitive functions were evaluated, as confirmed in Table 1, by administering the MMSE, and in one case also by the MoCA [11], which is more sensitive than the MMSE for detecting cognitive impairment in PD.[35]

However it soon became apparent the lack of consistency in the definition of cognitive impairment/decline, with five articles setting MMSE scores ≥24 [5, 10, 11, 23, 32], and in two others MMSE scores ≥27 [22, 30], and one of them setting up to MMSE scores ≥28 [34].

Interventions

In general, taste performance can be assessed in the whole oral cavity (WMT) [10, 34] or in particular tongue regions (regional chemical test, or EGM) [5, 10, 11, 22, 30-32, 34]. The latter modality allows the assessment of single gustatory nerve afferents. All these methods rely on subjective responses and need patient's collaboration. In this review, we have noticed a lack of standardization and a broad variation concerning the use of specific taste tests, for example in the EGM test, the stimulus duration was kept at 0.5 s in three of the five studies that use this quantitative method [5, 32, 34], but in the other two the stimulation time was set on 1.5 s [22, 30]. There was a clear preference for quantitative methods, namely regional chemical tests [5, 10, 11, 31, 32], and EGM [5, 22, 30, 32, 34]. The methodology to present tastants used in the analyzed studies varied from filter paper discs [5, 11, 31, 32] to taste solutions in micropipettes [34], syringes [5] or spray [10, 34], for instance. The amount of tastants presented and choice of flavors and exposure periods did not follow any standardization either.

In all conditions where a chemosensory disorder is suspected, both taste and smell should be assessed. In fact, nine studies included in this review were carried out with different smell assessment methods [5, 10, 11, 22-24, 30, 32, 33], where the odor identification tests are

Table 1 - Summary of included studies investigating taste performance in Parkinson's disease

Authors	Year	Sample Size (M:F; mean age[a])		PD Diagnosis	PD Severity	Cognition	Therapeutic Status	Purpose	Type of intervention		Main Results	Study limits
		PD patients	Controls						Smell Test	Taste Test		
Sienkiewicz-Jarosz *et al*. [32]	2005	30 (17:13; 64.0 ± 1.5)	33 (20:13; 64.0 ± 1.3)	Clinic	H&Y stage: 2.1 ± 0.20[b] PD duration: 7.3 years ±0.9[b]	MMSE≥24	All of the PD patients under APA.	To assess taste responses (intensity, and pleasantness ratings and identification) in PD patients.	Self-report	Self-report EGM Filter paper discs Liquid samples	Lower EGM thresholds. Normal taste and enhanced taste acuity for bitter.	Lack of reliability and validity. Examination in "on" state. Discrepancy between EGM and taste intensity results.
Moberg *et al*. [31]	2007	36 (30:0; 74.7 ± 7.7)	20 (20:0; 70.8 ± 8.2)	clinic	H&Y stage: 2.1 ± 0.6 UPDRS motor score: 24.0 ± 11.0[b] PD duration: 6.5 years ±3.7	NA	NA	To examine phenylthiocarbamide (PTC) sensitivity in PD.	NA	Filter paper strips	Higher frequency of PTC nontasters among PD patients.	Small sample size, exclusively male. Age difference between groups. Lack of therapeutic data.
Shah *et al*. [22]	2009	75 (NA)	74 (NA)	clinic	H&Y stage: I-III	MMSE≥27	All of the PD patients under APA.	To determine whether taste is abnormal in PD and explore possible correlations with smell sense or other clinical variables.	UPSIT	EGM	Significant impairment of taste threshold in PD group. No significant effect of age, disease severity, smell sense or levodopa intake.	Lack of demographical data. Examination in "on" state. Taste qualities perception was not explored. "Unorthodox" criteria for taste threshold. Lack of statistical power.
J. Deeb *et al*. [30]	2010	50 (34:16; 63)	NA	clinic	H&Y stage: I-III UPDRS: 32/176	MMSE≥27	Without APA or APA for <3 months prior to enrolment.	To evaluate relationship between odor identification, taste threshold, DaTSCAN and motor function in	Self-rating UPSIT OERP	Self-rating EGM	Impairment of EGM threshold, but no correlation with smell	Taste qualities perception was not explored. Variability on number of

					PD duration: 18.5 months ±3.7			early PD and their diagnostic accuracy.			deficit, and the others test parameters.	subjects recruited for the different tests.
Kim *et al*. (11)	2011	31 (16:15; 67.4 ± 9.7)	29 (11:14; 67.5 ± 9.4)	clinic	H&Y stage: 1.9 ± 0.9 PD duration: 3.9 years ±4.3	MMSE≥24 MoCA	All of the PD patients under APA.	To determine whether taste function is impaired in PD patients, and investigate correlations with olfaction or other clinical variables.	CC-SIT	TST	Impairment of taste function in female PD only, but no correlation with age, disease duration or severity, cognitive function, or olfactory function.	Cognitive performance was difference across patients' gender. TST at the middle of the tongue.
Kashihara *et al*. (23)	2011	285 (120:165; 72.4 ± 9.0)	61 (20:41; 70.9 ± 8.6)	clinic	H&Y stage: 2.5 ± 0.9[c]; 2.7 ± 1.1[d] PD duration: 5.8 years ±5.0[c]; 5.4 years ±3.7[d]	MMSE≥24	APA without any change in the past 3 months.	To investigate the symptoms, frequency, and severity of taste impairment (as well as smell impairment) in PD patients.	Self-report – Clinical interview		Taste perception is impaired in PD. The frequency of smell and taste impairments tended to increase with disease progression.	Only subjective report. Small male sample size in control group.
Breen *et al*. (24)	2012	10 101 (M: 59%; 71 ± 9)	3 209 (NA)	NA	NA	NA	NA	To verify the symptoms, frequency, and severity of NMS in PD, and the moment in which they arose.	Self-completed NMSQuest and quality of life scale (PDQ-8)		NMS increased with disease duration, but was independent of age.	Membership of a charity. Lack of demographic and therapeutic data. Only subjective tests.
Sienkiewicz-Jarosz *et al*. (5)	2013	20 (F: 55%; 60.6 ± 6.2)	20 (F:70%; 56.3 ± 1.6)	clinic	H&Y stage: 1.7 ± 0.15 PD duration: 5.3 years ±0.9	MMSE≥24	All of the PD patients under APA.	To compare pleasantness ratings of sucrose solutions and sweet liking/disliking status in PD patients.	SST	Sucrose solutions. EGM	No differences in EGM thresholds, and pleasantness ratings	Small sample size. The between-group differences.

											between the study groups.	Examination in "on" state.
Cecchini *et al*. [10]	2014	61 (32:29; 70.1 ± 8.7)	66 (28:38; 67.0 ± 13.9)	Clinic	H&Y stage: I-III PD duration: 6.2 years ±2.8	MMSE≥24	All of the PD patients under APA.	To examine the taste performance in PD patients.	Self-rating SST	Self-rating WMT TST	Impairment of taste function only with TST. Fair correlation with smell performance and disease's severity.	Discrepancy between TST and WMT results.
Pont-Sunyer *et al*. [33]	2014	109 (M: 69%; 66.6 ± 9.3)	107 (M: 59%; 65.7 ± 7.5)	clinic DaT SPECT	H&Y stage: ≤ 2.5 UPDRS: 18.77±9.6 MDS-UPDRS: 20.77±10.3	NA	Without APA.	To describe the presence and perceived onset of NMS in PD as well as their possible association with motor phenotype.	Questionnaire SST or UPSIT		NMS are common in PD and frequentl in premotor phase. No correlation with motor severity, age, or gender.	Only early stage PD patients. Lack of formal validation of questionnaire.
Doty *et al*. [34]	2014	29 (16:13; 63.1 ± 8.1)	29 (16:13; 62.9 ± 8.1)	clinic SPECT imaging	H&Y stage: 1.4 ± 0.5 UPDRS: 24.9±10.3 Time since diagnosis: 16.4 months ±9.4	MMSE≥28	All of the PD patients under APA.	To establish the influences of PD on taste function, and whether it might be useful in early diagnosis.	NA	WMT Regional chemical taste test EGM	Early stage PD is associated with taste impairment. No association between taste test scores and UPDRS scores, L-DOPA medication, or SPECT.	Small sample, and only early stage PD patients. Not all patients were able to complete both the on- and off-DRM sessions.

NA not available, *H&Y* Hoehn & Yahr scale, *APA* antiparkinsonian agents *UPDRS* Unified Parkinson's Disease Rating Scale, *MMSE* Mini-Mental Status Examination, *MoCA* Montreal Cognitive Assessment, *SST* Sniffin' Sticks Test, *UPSIT* University of Pennsylvania Smell Identification Teste, *CC-SIT* Cross-Cultural Brief Smell Identification Test, *OERP* Olfactory Event-Related Potentials, *EGM* Electrogustometry, *WMT* Whole Mouth Test, *TST* Taste Strip Test, *DaTSCAN* Dopamine transporter scan, *DaT SPECT* Dopamine transporter single-photon emission

[a] SD except when differently specified, [b] SEM, [c] without taste impairment, [d] with taste impairment

prevalent ones, as the *University of Pennsylvania Smell Identification Test* (UPSIT) [22, 30, 33], or *Sniffin' Stick Test* [5, 10, 33].

Patient self-rating scales through self-completed questionnaires [24] or interviews [23] are generating an increased level of interest and importance within the clinical setting, as it could be seen in the four studies [23, 24, 32, 33]. This type of assessment is a subjective report of the patient's sensory perception, as they are not as sensitive as those obtained by as quantitative evaluation. [36, 37]

Outcomes

The main results of this review can be grouped into 5 categories:

(i) A taste impairment in PD patients were reported by all researcher groups with the exception of the studies by Sienkewicz-Jarosz *et al*. [5, 32], that stated an enhanced taste acuity in PD. The taste impairment prevalence rated from 9.1% [23] to 26.7% [22], with unclear significance. Some studies [5, 31, 32, 34] included not only the tastant identification, but also the perceived intensity and/or hedonic ratings of the gustatory samples. Only the Sienkewicz-Jarosz *et al*. studies [5, 32] concluded that PD patients rated lower concentration samples (water and 1% sucrose, or 0.025% quinine) as more intense, and also Doty *et al*. [34] observed a similar phenomenon in the whole mouth test, with PD subjects rating the intensity of the lower concentrations of three of the four target taste stimuli as stronger than did the controls.

(ii) No significant association was observed between taste impairment with older age, male gender, smoking habits and deterioration of cognitive function. All of these factors are known confounders in chemosensory impairments. Kim *et al*. and Kashihara *et al*. reported a taste impairment in female PD only [11, 23].

(iii) In general, taste impairment was not associated with PD characteristics such as disease duration or severity, age of onset, levodopa intake and treatment duration, or DAT imaging. Nevertheless, three studies described statistically significant associations between the frequency of taste impairment and disease progression [23], TST and disease's severity [10], and non-motor symptoms with disease duration [24].

(iv) The contradictory findings, whereas Sienkiewicz-Jarosz *et al*. and Doty *et al*. studies have found no differences in electrical thresholds of PD patients [5, 34] or lower thresholds

in PD patients than in controls [32], Shah *et al.* [22] and J. Deeb *et al.* [30] studies founded significant deficits in PD patients on both anterior (CN VII) and posterior (CN IX) regions of the tongue. Cecchini and coworkers [10] revealed conflicting results with taste strips score being significantly lower in PD patients than controls, while WMT showed no differences. Whereas another study [34] that used the WMT demonstrated that identification test scores for all stimuli were lower for the PD patients than for controls.

(v) A severe disorder of smell identification was founded in almost all PD patients of the totality of studies included in this review that assessed olfactory function, with higher frequencies than taste impairment in PD. Smell and taste dysfunction were not found to correlate (Table 1) in the majority of the studies, except by Deeb *et al.* [30] that found a significant correlation between smell and taste self-ratings and Cecchini *et al.* [10] that report a marginal significance between TST and SST scores. Some articles conclude that a taste test is important in confirming a diagnosis of PD in conjunction with smell identification tests, in other words that the combination of all the available tests (smell, taste, and DaTSCAN) would support a definitive diagnosis of PD [22, 30].

DISCUSSION

The taste impairment in PD seems to be present, even though the variety of methodologies employed to investigate the gustatory function, and the heterogeneity of the clinical characteristics of control and patients' samples. However, the results still generate a lot of controversy and speculation in the scientific community regarding its significance, its severity, its consistency, and its clinical utility. Moreover, no evidence of correlations between taste function in PD patients and their demographic characteristics, dopaminergic processes or another clinical variable have been highlighted.

Taste sense may be altered by concomitant mental and physical conditions such as depression, altered salivation, poor oral hygiene, gastrointestinal diseases, zinc deficiency, antiparkinsonian or other medications and smoking. [10, 11, 22, 23, 30, 32] Since taste function is known to be more vulnerable to drug side effects than olfactory function, it may be a relevant issue in PD patients without smell impairments. [10]

The selected studies in this systematic review emphasized the naive state of the current knowledge, with the most varied and different hypotheses being placed and tested. Consequently, results are sometimes difficult to understand. For future academic and clinical purposes, we decided to present the main theories on the following groups:

(i) Taste impairment and anatomical explanations

At present, the topographical significance of taste impairment in PD is unclear. [9] But the main theories are based in anatomic explanations, as shown below, with some authors claiming that taste impairment is independent of olfactory dysfunction, as the first- and second-order neurons for taste are totally separate from the olfactory route, and others arguing that taste impairment is a consequence of olfactory dysfunction.

The independent abnormalities of both smell and taste in PD most plausibly relate to their separate anatomical pathways, although in clinical practice smell loss is frequently associated with subjective complaint of impaired taste which rarely was confirmed by actual measurement, as in J. Deeb *et al.* study [30] where more than half of the PD patients reporting abnormal taste had normal thresholds but abnormal smell function. [22, 30, 32] On the other hand, also it could be possible to explain the PD patients with complaints of taste dysfunction, but without smell impairment. [23]

Alternatively, in PD the solitary tract nucleus is spared until much later in PD, but the rostral part of the dorsal vagal motor nuclear complex (DMNC) which is damaged early, merges with the salivatory nuclei which receive afferent fibers from all three taste nerves (CN VII, IX and X). Hence, Lewy pathology in DMNC might change saliva consistency and possibly elevate taste threshold, with resultant deterioration in taste appreciation. [22, 30]

The opposite theory can be explained framed in the context of PD as it is conceivable that some form of central reorganization in PD diminishes taste appreciation in the presence of a smell defect.[22] Or PD-related neurodegenerative changes responsible for taste impairment may progress in parallel and concomitantly with subclinical neurodegenerative change for smell impairment dysfunction. [23] Explaining why both taste and smell impairments were tended to occur more frequently at advanced disease stages and corroborating the results in Kashihara *et al.* study [23], where PD patients with smell impairment

showed a higher frequency (25%) of taste impairment when compared with patients without smell impairment (9%).

Since olfactory loss leads to a decrease in taste and trigeminal functions, it can also be possible that the altered sense of smell itself produces a taste impairment secondarily in some patients as a result of chemosensory interaction since olfactory loss leads to a subtle but significant decrease in taste function and decreased trigeminal function. [10, 22, 23, 30].

(ii) Dopamine reward hypothesis

Knowing that midbrain dopaminergic neurons constitute a critical part of the brain reward system and the rewarding properties of any stimulus are a direct consequence of dopamine release evoked by this a striatum stimulus in the striatum. [5] Therefore, it could be hypothesized that dopamine deficits, as it occurs in PD, may produce anhedonia, a condition defined as a decreased experience of pleasure after presentation of natural or "chemical" rewards.[38] Or in other words, if dopaminergic dysfunction in the PD subjects could lead to any obvious alteration in perceived pleasantness/aversiveness of gustatory stimuli, that could explain the taste impairment results. [5, 32]

(iii) Single tastant ageusia

In their investigation, Moberg *et al.* hypothesized that PD patients would show a differential pattern of phenylthiocarbamide (PTC) tasting status, since abnormalities in the function or expression of G protein-signaling pathways (responsible for PTC perception), have been implicated in PTC perception and also in dopamine expression and regulation in PD. As phenotypic variation in PTC sensitivity is genetic in origin, this may represent a surrogate risk factor for the development of PD. [31]

(iv) Loss of the epidermal nerve fibers and Meissner corpuscles

Recently, Kim and coworkers [11] reported that recently has been demonstrated the loss of the epidermal nerve fibers and Meissner corpuscles in skin biopsy specimens from patients with PD. It cannot be ruled out that similar pathologic changes occur in the oral cavity mucosa of PD patients and that this contributes to the observed taste dysfunction.

(v) Ageing-related taste impairment

The current literature suggest that in contrast to olfaction, which deteriorates markedly with age, taste perception function declines during the healthy ageing process, although the extent of decline is variable between studies. [39][40]

However, in Shah *et al*. study [22] was reported that there was only a marginal evidence of age-related decline for taste and only for PD patients, not controls. Although the resistance of taste function to ageing effects to some tastants deserves more investigation, it may partially explain the taste impairment found in the studies of this review.

The majority of the above hypothesis suggest that taste impairment in PD is a hallmark of pathologically advanced disease. It is not surprising that studies enrolling patients in the early phase [30, 34] only detected a taste dysfunction in a subgroup of patients while studies performed in advanced PD disclosed a marked impairment. This is in contrast with smell dysfunction, which represents an early marker of PD. [10]

Because olfactory testing shows a similar sensitivity to the more sophisticated and expensive DaT-SPECT [30], it may be used as screening tool to identify patients with pre-motor PD. Shah *et al*. [22] and Deeb *et al*. [30] combined taste and smell tests, concluding that taste testing alone could not be used to diagnose PD, but an abnormality of both smell and taste would support a diagnosis of PD (predicted positive value superior to 94.5%). Conversely, normal olfactory and taste test in suspected PD would call for a diagnostic review (false negative value of 22.2%) [22].

LIMITATIONS

Some clinical variables were not included in this review, namely, marital status, education degree, weight, and height, number and quality of chronic medical conditions, mean age of PD diagnosis and mean age of motor symptom onset, alcohol use disorders identification test (AUDIT) score, beck depression inventory (BDI), adding sugar to caffeinated beverages, and sweet craving on the day of testing. Thus, although some of the studies included in the analysis reported risk associated with these variables, a combined risk estimate is unlikely to be representative of the full published literature on these factors.

Not all studies reported estimates of risk adjusted for confounders (e.g., smoking). However, where such adjustments have been made, we have not included these data in the analysis.

Clinical variables should be dichotomized, to allow them to be employed in combination for largescale screening. So here's another example that represents the heterogeneity of results, with many of the variable to be presented by dose.

Also it would be important, in light of the current scientific knowledge, that one of the inclusion criteria consisted of all patients completed the NMSQuest, a validated tool for detection of NMS in PD.

Diagnosis of secondary, familial or atypical Parkinsonism according to the available clinical criteria, and present or past therapy with neuroleptics should be specified from the beginning as exclusion criteria, since it could overpower the results.

We restricted our search to non-demented subjects, but without a well-defined set point, leaving space for the inclusion of subjects in early dementia on some studies.

Finally, it’s important to verify the lack of ongoing studies in subjects at risk for developing PD and long-term follow-up of cohorts of incident PD cases, as it will contribute more-objective data on the clinical profile of the premotor phase and the clinical significance of NMS at the time of diagnosis.

CONCLUSION

Taste dysfunction is included among the possible non-motor manifestations of PD. Taste testing is a possible biomarker of disease progression, indicating advanced cortical disease.

Different testing methods and patient heterogeneity difficult the interpretation of results and the clinical usefulness of taste testing.

Taste testing should be included in multicenter studies of the PD to better evaluate its possible role as a PD biomarker.

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