INTRODUCTION

Taste is a strong stimulant for saliva secretion. In turn, saliva controls the release, transport and adsorption of taste molecules, as well as their metabolism by enzymatic modification. It also plays a role in the maintenance of taste-sensing cells, and therefore appears to be a key variable in taste perception. Taste perception is important for the differentiation of essential nutrients from harmful and potentially toxic substances. Taste disorders can cause severe health problems, e.g. malnutrition or impaired immunity, and is also associated with impaired mental health and quality of life. Taste disorders can be classified as two types, quantitative disorders and qualitative disorders. Quantitative disorders, a diminished or a completely loss of taste perception, can be assessed psychophysically whereas qualitative taste disorders are characterised by mostly bothersome, completely
subjective complaints that cannot be measured by any technique. In this context, explorations on saliva-related parameters might help investigations on both pathogenesis and assessments of taste disorders.

In our previous cross-sectional research, we examined patients with taste disorders on their taste function and saliva-related parameters and found that scores of a taste function tests correlated negatively with the salivary flow rate and proteolysis, and positively with carbonic anhydrase VI (caVI) and catalase values. Compared to healthy controls, patients with taste disorders exhibited a higher salivary total protein concentration, total anti-oxidative capacity (TAC), proteolysis and salivary flow rate, indicating that assessment of saliva is of high importance in research on taste dysfunction.

For the present longitudinal study, we tracked a small part of these patients to explore how changes of salivary parameters correlate with changes of taste function after a year of zinc therapy, as treatment with zinc has been shown to be the effective therapy of taste disorders. The question was which of these salivary parameters would best reflect the improvement/deterioration of taste function. In addition, it is shown that zinc therapy could improve depression, and mood state also has close relation with complaints of qualitative taste disorders. Hence, changes of Beck Depression Inventory (BDI) scores were also investigated in the current study.

2 | MATERIALS AND METHODS

2.1 | Overall design

We investigated in patients with taste disorders after one-year oral zinc therapy whether there were changes in gustatory function as well as in saliva-related parameters, and if so, whether the change of gustatory function is correlated with changes in saliva-related parameters, such as salivary composition, salivary pH and salivary flow rate.

Before zinc therapy, taste function (evaluated by taste strips) of patients was measured as their baseline taste function. At the same time, baseline salivary parameters (flow rate, total proteins, proteolysis, catalase, total anti-oxidative capacity [TAC], carbonic anhydrase VI [caVI], and pH) were recorded before zinc therapy.

Patients started oral zinc for one year aiming to relieve their symptoms of taste disorders. After one year, patients’ taste function and salivary parameters were re-evaluated with the same methods as return visit data. Thus, the changes of data represented by “Δ” indicating return visit data minus baseline were acquired (Table 1). After we got the Δ taste function (Δ taste strip scores) of patients, patients were divided into two groups based on their Δ taste function for further data analysis. Patients whose Δ taste strip scores were less than 2 points, meaning their taste function decreased after zinc therapy, were labelled as not-improved group (no-group). Those whose Δ taste strip scores were more than or equal to 2 points were labelled as improved group (im-group; Table 1).

In addition, to investigate the relation between taste function and patients’ mental and psychological state as well as the association between patients’ subjective ratings and objective taste function, we also assessed the subjective symptom ratings and Beck Depression Inventory (BDI) scores before and after the zinc therapy.

An additional question related to the investigation of the relation between changes of taste function and changes of smell function which was also evaluated before and after zinc therapy.

2.2 | Participants

A total of 14 patients with taste disorders (6 males, 8 females; age range 40-70, mean age = 58.6 ± 8.6 years, see Table 2) participated in both the first session (baseline) and the return visit session. The diagnosis of taste dysfunction was based on gustatory testing using taste strips and the patients’ self-report. The study was approved by the local Ethics Committee. Written informed consent from all subjects was obtained before the experiment. The participants were asked not to eat for 3 hours before the experiment.

2.3 | Examinations and measurements

2.3.1 | Visual analogue scales

We used 10 cm rating scales, anchored with “not any symptoms” (lowest score “0”) at the left end and “very intense” (highest score “10”) at the right end, to record the intensity of patients’ symptoms of taste disorders at the time of the visit and during the week prior to that. The questions matched with the scales are “How is your symptom at the moment?” and “How was your symptom during the last week?”. For example, if the patient’s chief complaint was an ongoing bitter taste even in absence of a bitter stimulant (phantogeusia), patients sued the rating
scale to describe this symptom. In essence, the symptoms mentioned in the scales aimed at the patients’ chief complaints, the main reason why they came to see a doctor in the smell and taste clinic.

2.3.2 | Gustatory and olfactory function

Gustatory function of all participants was evaluated by taste strips, details of which are described in our previous study. Orthonasal olfactory function was measured using the extended “Sniffin’ Sticks” test. This test consists of 3 subtests: odour threshold, odour discrimination, and odour identification test. The scores of the olfactory subtests were then summed up building the overall TDI score.

2.3.3 | Saliva collection and biochemical analysis

Salivary parameters including flow rate, total proteins, proteolysis, catalase, total anti-oxidative capacity (TAC), carbonic anhydrase VI (caVI), and pH were selected as they are known to be associated with taste function based on our previous cross-sectional studies. The details of how saliva samples were collected and biochemically analysed were exactly the same as in our previous study.

2.3.4 | Beck Depression Inventory (BDI)

Participants were asked to complete the BDI, which is a widely used, standardised, and validated tool for assessment of depressive symptoms.

2.4 | Statistical analysis

Statistics were performed using spss Version 25.0 (IBM). Paired t tests were used to analyse the differences between the baseline and the return visit data. Independent t tests were used to compare the mean Δ values between groups. For correlation analysis of Δ values, Spearman statistics were used. The level of significance was set at \( P < .05 \).

3 | RESULTS

3.1 | Changes after one-year therapy of oral zinc (Return visit data versus Baseline)

Paired t test was used to compare the mean values of parameters from the baseline and from the return visit. Table 3 shows the parameters whose mean values have significant differences compared with the baseline data.

3.1.1 | All patients

Total patients’ taste and smell function based upon the measurements of taste strips and Sniffin’ Sticks did not change significantly after a year of therapy. Other parameters that did not change were BDI scores, salivary pH, salivary TAC and catalase.

Symptom ratings decreased significantly, indicating improvement of the subjective feelings about the present disease symptoms and symptoms during the week prior to the visit (present: \( P = .021 \), during the last week: \( P = .017 \); see Table 3).

Salivary total protein increased (\( P = .001 \); see Table 3) while salivary flow rate (\( P = .021 \)), proteolysis (\( P = .007 \)) and caVI (\( P = .024 \)) decreased (see Table 3).

3.1.2 | Not-improved group (no-group) and improved group (im-group)

In the present study, 9 patients with decreased taste function (Δ Taste strips score <2) after a year of zinc therapy were thus labelled...
as not-improved group (no-group, see Table 2). Five patients with improved taste function (Δ Taste strips score ≥2) were labelled as improved group (im-group, see Table 2).

The increased level of salivary total protein could be observed in both groups (no-group: P = .017; im-group: P = .005; see Table 3) while the level of salivary proteolysis (P = .036; see Table 3) and caVI (P = .048; see Table 3) decreased in the no-group.

No significant changes of other parameters (smell function, salivary pH, flow rate, TAC, catalase, symptom ratings and BDI scores) were found in im- and no- subgroups using the paired t test.

3.2 | Δ values: no-group versus im-group

Independent t test was used to compare the Δ value between no-group and im-group. The mean Δ salivary pH of no-group (0.2 ± 0.2) was positive and higher than that of im-group (-0.4 ± 0.4) which was negative (P = .003). The data of salivary pH and taste strips scores of each participants was shown in Table 4. No significant differences on any other Δ values between groups were observed.

3.3 | Δ values- correlations

Spearman correlations were used to investigate the correlations between Δ values. Δ BDI was positively correlated with both Δ symptoms ratings (present: P = .002, r = .76; during the last week: P = .0018, r = .62). Δ total taste strip score was negatively correlated with Δ salivary flow rate (P = .039, r = -.56). No other significant correlation pertaining to Δ value was found between other parameters.

4 | DISCUSSION

We observed no significant changes on taste and smell function after one-year zinc therapy using paired t tests. However, the sample size (n = 14) was too small to evaluate the curative effect of oral zinc therapy, also, we were unable to receive a precise documentation of the dose of zinc treatment from each patient. However, zinc therapy was not the primary interest in the present study. We selected subjects with taste disorders treated with zinc because taste function is more likely to change under zinc therapy.9,10 The focus of the present study was to explore the associations between changes of taste function and changes of salivary parameters instead of how zinc therapy would affect taste function or saliva parameters.

In our study, we found that Δ salivary flow rate was negatively correlated with Δ taste strip scores, indicating that when the salivary flow rate increased, the taste strips would decrease, and vice versa. This is in accordance with our previous cross-sectional research, that is, the taste strip score correlated negatively with the salivary flow rate, and patients with taste disorders exhibited a higher salivary flow rate compared to healthy controls.6

| Group | Self-report | Age | Diagnosis | TS 1 | TS 2 | Δ TS |
|-------|-------------|-----|-----------|------|------|------|
| im-   | Taste loss after surgery | 47 | Hypoguesia | 18  | 22  | 4    |
| im-   | Salty dysgeusia | 68 | Idiopathic dysgeusia + hypoguesia | 8   | 10  | 2    |
| im-   | Metal dysgeusia | 58 | Idiopathic dysgeusia + hypoguesia | 4   | 9   | 5    |
| im-   | Sweet, salty dysgeusia | 58 | Idiopathic dysgeusia | 13  | 23  | 10   |
| im-   | Taste loss | 70 | Idiopathic hypoguesia | 11  | 17  | 6    |
| no-   | Salty dysgeusia | 40 | Idiopathic dysgeusia | 20  | 18  | -2   |
| no-   | Sweet dysgeusia | 56 | Idiopathic dysgeusia + hypoguesia | 11  | 2   | -9   |
| no-   | Salty dysgeusia | 50 | Idiopathic dysgeusia | 15  | 4   | -11  |
| no-   | Bitter dysgeusia | 56 | Idiopathic dysgeusia | 14  | 12  | -2   |
| no-   | Salty dysgeusia | 62 | Idiopathic dysgeusia | 17  | 7   | -10  |
| no-   | Taste loss | 66 | Idiopathic hypoguesia | 14  | 13  | -1   |
| no-   | Bitter dysgeusia | 68 | Idiopathic dysgeusia | 26  | 22  | -4   |
| no-   | Bitter dysgeusia | 61 | Idiopathic dysgeusia | 26  | 18  | -8   |
| no-   | Sour, metal dysgeusia | 61 | Idiopathic dysgeusia | 25  | 20  | -5   |

Abbreviations: Im, Improved group; No, Not-improved group; TS 1, Taste strips scores of baseline; TS 2, Taste strips scores of return visit.
When we reviewed other studies investigating the relationship between taste function and salivary flow rate, we did not find an uniform picture. Gustatory loss can be accompanied by increased, decreased, or unchanged salivary flow rates and the correlations has been reported to vary for different taste qualities. For example, one study showed that there was a negative correlation between salt perception and salivary flow rate, whereas no correlation was found for bitterness or sweetness, and contradictory results were reported for sourness. Other studies showed that bitter taste sensitivity correlates positively with unstimulated saliva flow rate. In addition, also a negative correlation has been observed for sourness and salivary flow rate.

One reason for this inconsistency of results may relate to the different methods used in the respective studies. For example, results may differ when taste function was evaluated by self-ratings or chemosensory tests, whether salivary flow rate was assessed as stimulated or unstimulated, or whether participants were healthy or patients with taste disorders. Hence, when considering the relationship between salivary flow rate and taste function, individual taste qualities (sweet, salt, sour, bitter) could be studied and discussed separately using comparable techniques in future studies (unfortunately, individual taste qualities could not be analysed in a meaningful way in the present study). Moreover, considering that the salivary pH and the salivary buffer capacity are highly dependent on the salivary flow rate (they increase when the salivary flow rate increases and vice versa), there could be also an optimal range of salivary flow rate for the best taste sensitivity.

Salivary pH is maintained at a relatively constant level, ie 6.5-7.4, buffering acids and thereby diminishing the rate of dental demineralisation. Several previous investigations showed that salivary pH interacts with the salivary flow rate and is important for sour and sweet taste perception. In the present study, Δ salivary pH was found to be significantly different between two groups - salivary pH tended to increase in no-group while it decreased in the improved group (Table 4), indicating that the increased taste sensitivity might be accompanied by decreased salivary pH during the zinc therapy. However, more research is needed to confirm this tendency.

In some previous investigations, proteolytic activity of human saliva plays a role in the perception of bitter, fatty, and salty stimuli and enhanced in-mouth proteolysis is a key peri-receptor factor. However, further studies are needed to confirm this hypothesis.

### TABLE 3  The mean values of parameters of both return visit session and baseline session

|                        | Improved group (n = 5) | Not-improved group (n = 9) | Total (n = 14)           |
|------------------------|------------------------|---------------------------|--------------------------|
|                        | Mean ± SD              | P value                   | Mean ± SD                | P value       | Mean ± SD              | P value       | Mean ± SD              | P value       |
| Taste strips Baseline  | 10.8 ± 5.3             |                           | 15.9 ± 6.7               | .021           | 0.6 ± 0.2              | .005           | 1.1 ± 0.2              | .004           |
|                        | Return                 | 16.2 ± 6.5                | 12.9 ± 7.2               |               | 0.4 ± 0.2              | .001           | 1.1 ± 0.3              | .024           |
| Flow rate (mL/min) Baseline | 0.8 ± 0.5            |                           | 0.6 ± 0.3                |               | 0.6 ± 0.4              | .021           | 1.5 ± 0.7              | .001           |
|                        | Return                 | 0.3 ± 0.1                 | 0.4 ± 0.2                |               | 0.4 ± 0.2              | .001           | 1.4 ± 0.6              | .024           |
| Total protein (mg/mL) Baseline | 0.6 ± 0.2            | .005                      | 0.7 ± 0.5                | .017           | 0.7 ± 0.4              | .001           | 1.4 ± 0.6              | .001           |
|                        | Return                 | 1.2 ± 0.2                 | 1.5 ± 0.7                |               | 1.4 ± 0.6              | .024           | 1.1 ± 0.3              | .007           |
| Proteolysis (IU) Baseline | 11.6 ± 12.9           | .036                      | 12.6 ± 13.4              | .007           | 1.1 ± 0.2              | .004           | 1.1 ± 0.3              | .007           |
|                        | Return                 | 1.1 ± 0.2                 | 1.1 ± 0.4                |               | 1.1 ± 0.3              | .004           | 1.1 ± 0.3              | .007           |
| CaVI (ng/mL) Baseline  | 1.6 ± 1.4              | .048                      | 3.2 ± 3.5                | .024           | 0.9 ± 0.3              | .048           | 1.3 ± 1.2              | .021           |
|                        | Return                 | 4.1 ± 4.0                 | 1.5 ± 0.5                |               | 4.7 ± 3.3              | .017           | 5.2 ± 3.4              | .007           |
| Current symptoms Baseline | 7.4 ± 2.1             |                           | 7.0 ± 2.1                | .021           | 6.8 ± 2.1              | .048           | 5.2 ± 3.4              | .024           |
|                        | Return                 | 6.1 ± 3.7                 | 4.7 ± 3.3                |               | 5.2 ± 3.4              | .017           | 6.0 ± 3.9              | .007           |
| Last week symptoms Baseline | 7.8 ± 1.6             |                           | 7.4 ± 1.5                | .017           | 7.2 ± 1.4              | .017           | 5.1 ± 3.5              | .021           |
|                        | Return                 | 6.0 ± 3.9                 | 4.6 ± 3.3                |               | 5.1 ± 3.5              | .017           | 1.3 ± 1.2              | .001           |

Note: Paired t test was used to compare the mean values of parameters from the baseline and from the return visit, both in the total sample and in improved and not-improved group. Significant P values which means there were significant differences between baseline and return visit on the mean values of each group or total patients are given in the table.
One hypothesis is that the mucosal pellicle forms a barrier that controls the accessibility of tastants to the receptors. A thinner or looser pellicle due to higher proteolytic activity would then be associated with a facilitated tastant-taste receptor interaction. In the present study, for the no-group whose taste strip scores decreased, their salivary proteolytic activity also decreased combined with increased salivary total protein (Table 3), which support this hypothesis. However, we also observed an increased salivary total protein without concomitantly decreased salivary proteolysis in the im-group whose taste strip scores increased (Table 3). This difference might be explained by the small sample size in the im-group (n = 5) which did not reflect the significant changes in proteolysis. The overall contradictory results on the relation between taste function and salivary proteolysis might also be interpreted in light of the differences between correlations with individual taste qualities (sweet, salt, sour, bitter). In our study, the taste strip score represents the combined function of the four basic tastes, but the negative correlation may exist only between salivary proteolysis and a specific taste quality, such as bitter as shown in previous studies.

CaVI (gustin) in saliva has been associated with the growth and development of taste buds and a lower CaVI concentration is associated with lower levels of total parotid salivary zinc in subjects with reduced taste function. Our previous cross-sectional study also found there was a positive correlation between the CaVI concentration and taste scores. What we found in present study, patients in no-group showed a significant decreased CaVI concentration, is also in accordance to these findings. Although, for total patients, there was no significant change in taste function after one-year zinc therapy, the improvements of symptoms of total patients were significant. It is not unusual that the patients’ subjective complaints about taste disorders symptoms are not paralleled by their objective taste capacities. Qualitative taste disorders which can only be diagnosed by self-report do not have to coexist with quantitative taste disorders, and for quantitative taste disorders, many individuals do not even notice their taste deficiency. A study on 48 patients with qualitative dysgeusia showed that two thirds experienced spontaneous resolution of the dysgeusia (evaluated by self-ratings), with an average duration of 10 months and mood state (evaluated by BDI scores) related to resolution rates. In the present study, we found that ΔBDI scores were positively correlated with Δtaste disorder symptom ratings, ie, when taste disorder symptoms improved, patients’ depressive symptoms also improved and vice versa. This suggests that, psychotherapy might help these patients to feel better, without necessarily improving their gustatory sensitivity.

One study investigating subjects with oral sensory complaints (OSC) including burning mouth syndrome, idiopathic taste aberrations and xerostomia indicated that salivary and taste analyses were helpful in distinguishing healthy subjects from subjects with complaints. In the present study, we could observe both improvement of symptoms of taste disorders and changes of saliva-related

| Group  | Baseline pH | Return visit pH | ΔpH | Baseline Taste strips | Return visit Taste strips |
|--------|-------------|-----------------|-----|----------------------|--------------------------|
| no     | 7.20        | 7.40            | +0.2| 20                   | 18                       |
| no     | 6.90        | 6.70            | −0.2| 11                   | 2                        |
| no     | 6.70        | 6.80            | +0.3| 15                   | 4                        |
| no     | 6.70        | 6.60            | −0.1| 14                   | 12                       |
| no     | 6.50        | 6.40            | +0.1| 17                   | 7                        |
| no     | 6.30        | 6.30            | 0.0 | 8                    | 13                       |
| no     | 6.40        | 6.40            | 0.0 | 4                    | 13                       |
| no     | 6.30        | 6.30            | 0.0 | 2                    | 23                       |
| no     | 6.10        | 6.10            | 0.0 | 10                   | 22                       |
| no     | 6.30        | 6.30            | 0.0 | 8                    | 23                       |
| no     | 6.90        | 6.90            | 0.0 | 10                   | 22                       |

TABLE 4 The changes of salivary pH and taste strips scores compared with baseline of each participants.
parameters of total patients (Table 3, Total). However, the sample size was small and a healthy control group was missing. Hence we cannot conclude that the improvement of complaints could be reflected by saliva-related parameters. Still, the results suggest that salivary parameters may be useful in the distinction between healthy subjects and patients with qualitative taste disorders and thus call for more investigations on saliva testing as an objective measurement to evaluate either taste dysfunction or taste complaints.

Because of the high rate of dropouts, there are only 14 samples in the present study and the etiologies and subtypes of their taste disorders are heterogeneous. As is shown in Table 2, the first patient’s hypogeusia is reported after a surgery while other patients’ taste disorder (either dysgeusia or hypogeusia or both) are idiopathic. Theoretically, saliva parameters could change in order to compensate for the recovery of taste function (secondary change). However, changes of salivary parameters could also be the primary cause of taste disorders (primary change). Samples in current study exhibit heterogeneity but they are too small to be divided into subgroups which could be analysed separately. Thus, based on the present work, several directions can be suggested for future studies to investigate the association of changes between saliva-related parameters and taste function. At first, larger sample sizes are needed. The presently observed changes in saliva-related parameters such as total protein, proteolysis, salivary flow rate, and pH, could be the priorities to be studied. More patients with taste disorders with different etiologies and subtypes should be included. Healthy controls plus a group of untreated patients would also be desirable. As mentioned above, studies found that individual taste qualities could be influenced by saliva differently. Hence, the suggestion would be to not only measure general function, but also measure sensitivity for specific taste qualities (sweet/sour/salty/bitter) using validated assessment tools. At last, when measuring taste function with psychophysical tests, it is also important to record taste complaints with symptom scales so that the association between taste complaints and salivary parameters could be studied in greater detail.

5 | CONCLUSION

The present longitudinal results suggest that changes of both taste function and taste complaints were accompanied by changes in salivary parameters, indicating that salivary parameters have the potential to be useful in the diagnosis of patients with qualitative taste disorders and that assessment of saliva is of importance in research on taste dysfunction.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

YZ and TH drafted the article. VKD collected the data and saliva samples. GF, FN and HB analysed the saliva samples. YZ analysed the data. All authors revised it critically for intellectual content and approved the final version of the manuscript.

ETHICS APPROVAL

All investigations were conducted in accordance with the Guidelines for Biomedical Studies Involving Human Subjects (Helsinki Declaration). The study protocol was approved by the Ethics Committee at the University Clinic “Gustav-Carl-Carus” of the “Technische Universität Dresden” (ethics protocol number EK320082014). Consent to participate and publication: Written informed consent was obtained from all participants prior to their inclusion.

DATA AVAILABILITY STATEMENT

All data and material are available upon request.

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