**Original Article**

Continuous follow-up with polaprezinc (zinc-L-carnosine complex) after oral treatment with L-carnosine for pressure ulcers

Kensaku Sakae¹,², Hiroyuki Yanagisawa¹

1 Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, 3-25-8 Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan
2 Department of Psychiatry, Keieikai Yashio Hospital, 1089 Tsurugasone, Yashio-shi, Saitama 340-0802, Japan

**Abstract**
In our previous study, we described how L-carnosine and its zinc complex polaprezinc could be promising novel agents for the oral treatment of pressure ulcers (PUs). For its potency, polaprezinc did not differ significantly from L-carnosine in comparison between treatment groups. Thus, the key question of whether additional zinc confers a benefit was not answered. For patients previously treated with L-carnosine for 4 weeks, in the present study we replaced L-carnosine with polaprezinc to examine the extent to which polaprezinc differs from L-carnosine. Patients received 150 mg/day polaprezinc (containing 116 mg L-carnosine and 34 mg zinc) orally for ≤8 weeks. PU severity was measured weekly using the Pressure Ulcer Scale for Healing (PUSH) score. Ten patients (61.0 ± 11.2 years) orally ingesting standard diets were enrolled. PU stages were III (eight patients) and IV (two). Mean weekly improvement in PUSH score (MWIP) was 1.8 ± 0.9, which was numerically, but not significantly, greater compared with during L-carnosine treatment (P=0.156, 1.3 ± 0.6). Increased MWIP was found in five patients, unchanged MWIP in three, and decreased MWIP in two. One patient dropped out (week 4; pneumonia) and the PUs of the remaining nine patients healed within 8 weeks. Serum level of zinc was 65.3 ± 4.6 µg/dL at baseline and increased significantly from week 1 (P<0.01). The switching treatment from L-carnosine to polaprezinc indicated that orally-administered additional zinc tended to improve PU healing, although statistic power was limited. Further study is needed to test for larger sample sizes as well as for subjects with poorer zinc status, especially those with eating difficulty.

**Key words**: Pressure ulcer, Polaprezinc, Zinc, L-carnosine, Copper, PUSH score

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**Introduction**
Pressure ulcers (PUs) have become a considerable healthcare burden in the aging society worldwide, and the development of new approaches to help with their healing is thus important. Zinc (Zn) has a crucial role in wound healing [1-3], and patients with PUs often have decreased serum levels of Zn [4, 5]. However, the role of oral Zn therapy in the treatment of PUs has not been well investigated [3].

Recently, we described how L-carnosine (CAR) and its Zn complex polaprezinc (PLZ) can be novel agents for the oral treatment of PUs [4, 5]. CAR is an
endogenous dipeptide comprised of β-alanine and L-histidine. PLZ is an artificially produced derivative of CAR in which a Zn ion and CAR are bound in a 1-to-1 ratio to create a chelate compound. PLZ is a widely used medication for gastric ulcers in Japan. For its potency in treating PUs, PLZ did not differ significantly from CAR when comparing treatment groups; thus the key question of whether orally-administered additional Zn confers a benefit was not answered.

For these patients previously treated with CAR, in the present study we replaced CAR with PLZ to examine the extent to which Zn-containing PLZ differs from CAR, with regard to the efficacy for PU healing.

Methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of The Jikei University School of Medicine (Tokyo, Japan), and the Institutional Review Boards of Yashio Hospital (a psychiatric and geriatric facility) and Morinoie Yashio (a nursing home for the elderly), both of which are in Saitama Prefecture, Japan. The study was conducted in accordance with the Declaration of Helsinki (1964) and its subsequent revisions. Before study entry, written informed consent was obtained from patients and their legal guardians. The study was registered in the Clinical Trials Registry of the University Hospital Medical Information Network (number: UMIN000005860).

Patients and study design

The present study was an 8-week open-label follow-up with PLZ for CAR-treated PUs. All 10 patients involved in the present study had been enrolled as a CAR-treatment group in our previous study, in which they orally took 58 mg CAR twice daily for the full 4 weeks of the study period.

At the end of 4 weeks, the present study started by replacing CAR with PLZ. Patients orally took 75 mg PLZ (which contains 58 mg CAR and 17 mg Zn) twice daily until healing was complete or for ≤8 weeks. Follow-up was conducted from March 2011 to October 2012 at Yashio Hospital or Morinoie Yashio nursing home. PLZ was purchased from Zeria Pharmaceutical Co., Ltd (Tokyo, Japan).

Subjects had to fulfill the following criteria 4 weeks before study commencement: (i) aged ≥20 years; (ii) at least one stage-II, -III or -IV PU for ≥4 weeks according to the classification system set by the National Pressure Ulcer Advisory Panel (NPUAP) and European Pressure Ulcer Advisory Panel (EPUAP); (iii) estimated surface area for one ulcer of ≤24 cm² as calculated using the formula: greatest length (head-to-toe) × greatest width (side-to-side) of the PU; and (iv) capable of oral ingestion.

Exclusion criteria were: (i) clinical suspicion or a diagnosis of osteomyelitis; (ii) diabetes mellitus, peripheral vascular disease, malignant tumor, acute illness (e.g., infection), or other severe diseases; (iii) terminal phase of an illness; (iv) corticosteroid use; (v) receiving tube or parenteral feeding (because all these factors can affect healing, and the capability for providing written informed consent was limited for item (v)); and (vi) complete healing during the 4-week CAR-treatment period before study commencement.

From the CAR-treatment period through to the present-study period, all patients received the same topical treatment and PU care. All patients consumed their own diets and took their own medications without alteration except for temporary antibiotic therapy for the acute infectious complications that developed after study commencement.

The methodology described below is stated in detail in our previous studies. The endpoint for all evaluations (PU severity, weight, dietary intake, blood biochemistry) was complete healing of the PU.

PU care

Several factors that can inhibit healing were addressed prior to the start of the study. Ulcer infection was controlled adequately, and the following were removed by surgical debridement: (i) undermined or hypertrophic wound edges, (ii) hard and fibrotic granulation tissue, (iii) excessive granulation tissue proliferating beyond the edge or much higher than the skin surface, and (iv) necrotic tissue (removed to the maximum extent possible).

All patients received similar PU care to reduce local pressure using a repositioning regimen, an alternating-pressure air mattress on the bed, and a
pressure-redistributing seat cushion when sitting in a chair. Topical treatment was standardized: (i) apply a mixture of sucrose and povidone-iodine (Povidorine Pasta Ointment; TOA Pharmaceuticals Co., Ltd., Toyama, Japan) to the ulcer, (ii) cover with a silver-containing Hydrofiber® Wound Dressing (Aquacel Ag, ConvaTec Inc., Skillman, NJ, USA), and (iii) seal the entire area with an adhesive polyurethane film. Also, during the study, necrotic and excessively granulated tissues were removed as far as possible, with immediate removal of undermining. Repositioning was undertaken carefully, focusing particularly on relief of the shear that often causes undermining.

PU assessment

Well-trained nurses assessed PU severity once a week using the Pressure Ulcer Scale for Healing (PUSH Tool v3.0) [7]. Categorical sub-scores for surface area (length × width) (0 to 10), amount of exudate (0 to 3), and type of wound tissue (0 to 4) were determined and combined to derive a total score from 0 (completely healed) to 17 (greatest severity). Baseline risk for PU development was assessed using the Braden Scale [8]. Six sub-scores (sensory perception, moisture, activity, mobility, nutrition, friction or shear) were determined and combined to derive a total score from 6 (highest risk) to 23 (lowest risk).

Nutritional assessments

Patients were weighed at week 0 and a healing endpoint or at week 8 if the PU had not healed. Dietary intakes were assessed every day during the study period by nurses at breakfast, lunch, and dinner for all patients. Meal ingestion was recorded on a consumption scale of 0 (nothing consumed) to 10 (everything consumed), individually for each food item and caloric beverage. Nurses were well-trained and given visual guidelines for estimating meal intake from a dietitian. Based on these records, mean daily intakes of energy, protein, Zn, copper (Cu), and iron (Fe) were computed manually using the Standard Tables of Food Composition in Japan [9].

Blood biochemistry was assessed at week 0 (just before the start of PLZ administration) as well as at weeks 1–4, 6, and 8. If the PU of a patient healed or a patient dropped out at a time point other than that described above, biochemistry data were also obtained at that point. Complete blood count, liver function tests as well as serum levels of transthyretin, C-reactive protein (CRP), urea, creatinine, amylase, electrolytes, uric acid, total cholesterol, high-density lipoprotein cholesterol (HDL-C), Zn, Cu, and Fe were measured. All blood parameters were obtained in the fasted state between 6 am and 8 am. All data were measured by a commercial laboratory (Mitsubishi Chemical Medience Corp., Tokyo, Japan).

Outcomes

The primary endpoint was PU healing as assessed by a change in the PUSH score. Secondary endpoints were changes in nutritional variables (weight, dietary intake, biochemistry).

Statistical analyses

Changes in the PUSH score were tested by the Wilcoxon’s signed rank test. Changes over time in blood parameters were analyzed using a mixed model [10] (covariance structure: compound symmetry), and the Dunnett–Hsu test (adjusted for multiplicity) for pairwise comparisons with baseline. This mixed model was selected to assess repeated-measures data without omitting patients with incomplete data. Changes in weight were tested by the paired t-test. \( P < 0.05 \) was considered significant. Analyses were undertaken using SAS v9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and treatment data for each patient are shown in Table 1. Ten patients were enrolled. Mean age was 61.0 (± 11.2 SD) years and five patients (50%) were male. At baseline, the mean body mass index was 16.52 (± 3.48 SD) kg/m², mean weight was 41.42 (± 7.14 SD) kg, and mean Braden Scale score was 13.9 (± 3.1 SD; range, 9–23). PU stages were III (eight patients; 80%) and IV (two; 20%). PU locations were the sacrum (eight patients; 80%); ankle (one; 10%); and coccyx (one; 10%). Mean weekly improvement in total PUSH score (MWIP), which represented the rate of PU healing, was 1.3 (± 0.6 SD) during CAR treatment. At baseline (start of
Follow-up with polaprezinc after L-carnosine treatment for pressure ulcers

The mean total PUSH score was 6.6 (± 2.8 SD) and mean ulcer area was 1.525 (± 1.088 SD) cm².

Of 10 patients, one patient dropped out of the study at week 4 due to pneumonia. The PUs of the remaining nine patients healed completely within 8 weeks. The MWIP after PLZ treatment was 1.8 (± 0.9 SD), which did not change significantly from the MWIP during CAR treatment (P=0.156). An increased MWIP was found in five patients (50%), an unchanged MWIP in three (30%), and a decreased MWIP in two (20%). Mean change in body weight during the study was −0.28 (± 0.43 SEM) kg with no significant change (P=0.53).

### Table 1: Summary of data relating to demographics and treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Sex</th>
<th>BMI, kg/m²</th>
<th>Weight, kg</th>
<th>Weight change, kg</th>
<th>Braden Scale score</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Stage</th>
<th>Total PUSH score</th>
<th>Ulcer area, cm²</th>
<th>MWIP during L-carnosine treatment</th>
<th>Baseline (at start of polaprezinc treatment)</th>
<th>MWIP after polaprezinc treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>16.2</td>
<td>44.0</td>
<td>−3.1</td>
<td>14</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>III</td>
<td>0.5</td>
<td>3.20</td>
<td>Dropout at week 4</td>
<td>1.3</td>
<td>ℓ</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>16.4</td>
<td>41.5</td>
<td>−1.5</td>
<td>21</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>III</td>
<td>1.8</td>
<td>1.04</td>
<td>4</td>
<td>1.3</td>
<td>ℓ</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>F</td>
<td>13.8</td>
<td>32.7</td>
<td>0.1</td>
<td>14</td>
<td>Dementia</td>
<td>Sacrum</td>
<td>III</td>
<td>1.0</td>
<td>1.60</td>
<td>5</td>
<td>1.4</td>
<td>ℓ</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>M</td>
<td>16.7</td>
<td>47.0</td>
<td>2.0</td>
<td>14</td>
<td>Dementia</td>
<td>Sacrum</td>
<td>IV</td>
<td>2.0</td>
<td>1.26</td>
<td>2</td>
<td>3.0</td>
<td>ℓ</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>17.2</td>
<td>40.8</td>
<td>−0.7</td>
<td>13</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>III</td>
<td>0.8</td>
<td>2.52</td>
<td>8</td>
<td>1.3</td>
<td>ℓ</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>F</td>
<td>16.5</td>
<td>39.6</td>
<td>0.2</td>
<td>16</td>
<td>Schizophrenia</td>
<td>Ankle</td>
<td>III</td>
<td>1.5</td>
<td>0.99</td>
<td>6</td>
<td>1.0</td>
<td>ℓ</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>F</td>
<td>21.9</td>
<td>56.0</td>
<td>−0.6</td>
<td>13</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>III</td>
<td>2.0</td>
<td>0.64</td>
<td>2</td>
<td>2.0</td>
<td>ℓ</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>11.3</td>
<td>32.8</td>
<td>0.7</td>
<td>12</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>III</td>
<td>2.0</td>
<td>0.50</td>
<td>2</td>
<td>2.0</td>
<td>ℓ</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>M</td>
<td>13.0</td>
<td>34.9</td>
<td>−0.1</td>
<td>13</td>
<td>Schizophrenia</td>
<td>Sacrum</td>
<td>IV</td>
<td>1.0</td>
<td>3.22</td>
<td>3</td>
<td>3.7</td>
<td>ℓ</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>F</td>
<td>22.3</td>
<td>44.9</td>
<td>0.2</td>
<td>9</td>
<td>Dementia</td>
<td>Coccyx</td>
<td>III</td>
<td>0.8</td>
<td>0.28</td>
<td>4</td>
<td>0.8</td>
<td>ℓ</td>
</tr>
</tbody>
</table>

BMI, body mass index; PUSH, Pressure Ulcer Scale for Healing; M, male; F, female; MWIP, mean weekly improvement in total PUSH score

### Table 2: Changes in biochemical parameters over the study period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc, µg/dL</td>
<td>65.3±4.6</td>
<td>80.8±4.6**</td>
<td>80.7±4.6**</td>
<td>89.0±5.1**</td>
<td>90.3±5.4**</td>
<td>86.3±8.3</td>
<td>76.2±11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Copper, µg/dL</td>
<td>99.4±6.3</td>
<td>99.2±6.3</td>
<td>98.1±6.3</td>
<td>96.0±6.4</td>
<td>92.7±6.5</td>
<td>98.0±7.6</td>
<td>86.7±9.0</td>
<td>0.210</td>
</tr>
<tr>
<td>Copper/zinc ratio</td>
<td>1.61±0.10</td>
<td>1.25±0.10**</td>
<td>1.24±0.10**</td>
<td>1.11±0.11**</td>
<td>1.10±0.11**</td>
<td>1.16±0.15*</td>
<td>1.16±0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Iron, µg/dL</td>
<td>67.1±8.3</td>
<td>68.9±8.3</td>
<td>61.8±8.3</td>
<td>70.0±9.0</td>
<td>71.5±9.4</td>
<td>80.4±13.1</td>
<td>65.1±17.2</td>
<td>0.820</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.34±0.17</td>
<td>3.43±0.17</td>
<td>3.42±0.17</td>
<td>3.45±0.17</td>
<td>3.48±0.17</td>
<td>3.42±0.22</td>
<td>3.42±0.22</td>
<td>0.611</td>
</tr>
<tr>
<td>Transthyretin, mg/dL</td>
<td>17.68±1.79</td>
<td>18.50±1.79</td>
<td>18.32±1.79</td>
<td>18.66±1.82</td>
<td>19.92±1.83*</td>
<td>17.19±2.03</td>
<td>20.42±2.29</td>
<td>0.117</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.48±0.34</td>
<td>11.74±0.34</td>
<td>11.61±0.34</td>
<td>11.80±0.36</td>
<td>11.78±0.37</td>
<td>11.00±0.47</td>
<td>11.07±0.59</td>
<td>0.381</td>
</tr>
<tr>
<td>Lymphocyte count /mm³</td>
<td>1565.0±217.5</td>
<td>1752.6±217.5</td>
<td>1650.7±217.5</td>
<td>1773.3±224.9</td>
<td>1713.6±228.7</td>
<td>1869.5±275.4</td>
<td>2462.1±330.1*</td>
<td>0.099</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>377.4±50.4</td>
<td>385.3±50.4</td>
<td>367.2±50.4</td>
<td>362.4±52.5</td>
<td>345.5±53.5</td>
<td>407.5±66.0</td>
<td>352.5±80.9</td>
<td>0.348</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>1.563±0.981</td>
<td>1.602±0.981</td>
<td>1.712±0.981</td>
<td>1.529±1.004</td>
<td>1.751±1.016</td>
<td>1.650±1.164</td>
<td>1.554±1.351</td>
<td>1.000</td>
</tr>
</tbody>
</table>

a For simplicity, only the results at weeks 0–4, 6, and 8 are listed.

Changes over the study period were tested (including the data at non-listed time points) by a mixed model; pairwise comparisons with week 0 were made using the Dunnett–Hsu test (*P<0.05, **P<0.01 vs. week 0).

Data represent the least squares means ± SEM.
Table 2 shows the changes in key biochemical parameters over the study period. Serum levels of Zn increased gradually and significantly toward week 4 ($P<0.01$) and decreased thereafter toward week 8, but maintained higher levels than those at baseline. Serum levels of Cu showed no significant changes ($P=0.210$). Hence, the Cu/Zn ratio in serum decreased significantly ($P<0.001$). Serum levels of Fe showed no significant changes ($P=0.820$). Serum levels of alkaline phosphatase (ALP) were slightly above the reference range (RR: 100–325 IU/L) at baseline and showed no significant changes ($P=0.348$). Serum levels of albumin and transthyretin were below the RR (albumin, 3.8–5.3 g/dL; transthyretin, 22–40 mg/dL) and those of CRP were above the RR ($\leq 0.30$ mg/dL), with no significant changes. Complete blood count (including hemoglobin level and lymphocyte count), liver function tests (except albumin and transthyretin), levels of urea, creatinine, amylase, electrolytes, uric acid, total cholesterol, and HDL-C showed little deviation from RRs during the study, with no significant changes (only part of data shown). Table 3 shows the mean daily dietary intakes of energy, protein, Zn, Cu, and Fe over the study period.

### Table 3 Mean daily dietary intakes during the study period

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy kcal</td>
<td>1,535.8 ± 352.9</td>
</tr>
<tr>
<td>kcal/kg body weight</td>
<td>38.03 ± 11.14</td>
</tr>
<tr>
<td>Protein g</td>
<td>62.53 ± 15.93</td>
</tr>
<tr>
<td>g/kg body weight</td>
<td>1.55 ± 0.50</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>7.39 ± 2.97</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>0.876 ± 0.237</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>8.99 ± 3.50</td>
</tr>
</tbody>
</table>

Data are means ± SD

Discussion

In our previous study, the effect of CAR as an oral treatment for PUs was pronounced. However, an augmented effect upon addition of Zn to CAR in the form of a Zn-CAR complex was not clear. Similarly, the present study failed to show a clear benefit of this complex because the rate of PU healing increased by 1.4-fold after the switch from CAR to PLZ, but the difference was not significant probably due to a small sample size, and only 50% of the PUs of patients improved.

The effect of oral Zn therapy on PU healing has remained unsolved since the first clinical trial was conducted in the 1960s; only a few clinical trials have investigated the effect of oral therapy of Zn alone for PU healing and none have demonstrated a positive effect \[^{[3, 11-13]}\]. In recent years, high-protein/energy beverages enriched with Zn have been used more often for PU treatment. In addition, a large randomized trial revealed the effect of such a beverage enriched with a mixture of arginine, Zn, and antioxidant vitamins \[^{14}\]. However, the independent role of Zn in these formula diets is not known.

In general, it is accepted that, in the presence of Zn deficiency, Zn confers a beneficial effect. Unfortunately, a sensitive and specific biomarker of Zn status has not been identified. Measurement of the serum level of Zn has been the most frequently used approach. However, the serum level of Zn does not necessarily reflect the total Zn content in the body because it declines with metabolic conditions unrelated to Zn status (e.g., infection, inflammation, stress, trauma) due to redistribution of Zn from the serum to other tissues in response to metabolic need \[^{15, 16}\]. Therefore, the diagnosis of Zn deficiency requires a combination of biochemical tests, assessment of dietary intake of Zn, and the clinical response to a Zn load \[^{17, 18}\].

In the present study, the baseline serum level of Zn was 43–95 (mean, 65) μg/dL. According to the lower cutoff of the serum level of Zn of 80 μg/dL in blood sampling in the morning proposed by the Japan Society for Biomedical Research on Trace Elements \[^{19, 20}\], eight of all 10 patients were deficient in Zn. The baseline Cu/Zn ratio in serum was 0.87–2.33 (mean, 1.61). Cu absorption from the intestine is augmented in the Zn-deficient state \[^{17, 21, 22}\], so such a state may be characterized by an elevated ratio of Cu/Zn in serum (≥1.5) accompanied by a lowered serum level of Zn (<80 μg/dL) \[^{17, 23}\]. According to this criterion, six of 10 patients were deficient in Zn. In addition, an analysis in 2014 stated that the cutoff for the serum level of Zn as a marker of severe
deficiency of Zn was 50 μg/dL [24]. According to that value, only one of 10 patients were severely deficient in Zn.

ALP is a Zn-dependent enzyme. However, ALP activity is unlikely to be a useful biomarker of Zn because the results of a systematic review in 2009 indicated that changes in Zn intake do not have a significant effect on ALP activity [16]. In our patients, ALP activity was slightly above the RR before and after treatment with PLZ.

Dietary intake of Zn was 4.2–13.7 (mean, 7.39) mg/day. The recommended dietary allowance (RDA) of Zn for healthy individuals (developed by the Food and Nutrition Board at the Institute of Medicine of the National Academies) is 8–11 mg/day [25]. Individuals with PUs are likely to need more Zn, but evidence for a specific reference value is lacking. Dietary intake of energy and protein was 38.03 kcal/kg/day and 1.55 g/kg/day, respectively, which met the RDA for individuals with PUs according to international guidelines (30–35 kcal/kg/day and 1.25–1.5 g protein/kg/day, respectively) [26]. Accordingly, our patients did not seem to be severely malnourished (probably because we included only subjects capable of oral ingestion of standard diets). Likewise, our patients may have not been severely deficient in Zn. There is a possibility that greater response to a Zn load for PU healing may be observed in subjects with a more severe Zn deficiency. In future studies, it would be very interesting to test for subjects with eating difficulty and poorer Zn status, especially those with appetite loss or receiving enteral feeding who have PUs more frequently.

A mouse study on Zn transporters demonstrated that impaired homeostasis of Zn results in skin fragility and decreased dermal stromal collagen [27], suggesting that Zn deficiency predisposes to PUs by external pressure being applied over a bony prominence. Therefore, many patients with PUs may already be suffering from Zn deficiency. Indeed, PU patients often have reduced serum levels of Zn, even though such a reduction reflects ostensible decline by metabolic redistribution of Zn in addition to a pure deficit of Zn. Conversely, even in patients who maintain a relatively high level of Zn, Zn deficiency is not ruled out because there are variations among individuals for the serum level of Zn associated with the development of deficiency symptoms [24].

Numerous basic and clinical studies have shown that Zn has a critical role in wound healing. Therefore, generous provision of Zn is recommended in conditions involving Zn deficiency. Thus, PLZ would be more advantageous than CAR for PU treatment. However, a decrease in the serum level of Cu should be considered in high-dose, long-term oral Zn therapy. PLZ contains 34 mg Zn and our patients ingested a total of 41.39 mg/day Zn from the diet and PLZ, whereas the tolerable upper-intake level of Zn is 40 mg/day [25]. In the present study, serum levels of Cu tended to decrease (but not significantly) ~8 weeks after PLZ treatment.

Taken together, our results of switching treatment from CAR to PLZ indicated that orally-administered additional Zn tended to improve PU healing, although statistic power was limited in this small sample size. Further study is needed to test for larger sample sizes as well as for subjects with poorer Zn status, especially those with eating difficulty. A greater benefit may be found in such a patient population. PLZ is a promising new agent for the oral treatment of PUs. PLZ is a tablet and easy-to-use compared with high-protein/energy beverages. Oral agents are not available for PU treatment, so accumulation of further evidence on PLZ is encouraged.

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Conflict of interest
The authors declare that they have no conflict of interest.

References


