Clinics in Surgery

Research Article
Published: 05 Mar, 2019

Collagen Peptide as an Effector in Pressure Injuries Treatment in Older Adult Inpatients

*Yoko Hokotachi[1,2], Masako Itoh[3], Masumi Akasaki[3], Chiho Kai[1,4], Mari Hasegawa[5], Toshihide Tamura[3], Satoshi Uramoto[3] and Teruyoshi Amagai[5]**

[1]Administration Food Sciences and Nutrition Major, Graduate School of Human Environmental Sciences, Mukogawa Women's University, Japan

[2]Department of Clinical Nutrition, Takarazuka Dai-ichi Hospital, Japan

[3]Kikai Tokushukai Hospital, Japan

[4]Department of Clinical Nutrition, Higashi Kobe Hospital, Japan

[5]School of Human Environmental Sciences, Mukogawa Women's University, Japan

Abstract

Aim: To examine the hypothesis that Collagen Peptide (CP) is effective in the treatment of Pressure Injuries (PI) in older adult inpatients.

Methods: This study was a retrospective chart review conducted at a single institution. All consecutive patients who developed PI before or after admission to a single institution between January 2013 and September 2015 were enrolled. Data collected were: 1) characteristics; 2) blood test, CRP, and serum Alb during the period of PI treatment (PPT); 3) PI, evaluated by the DESIGN-R scoring system; 4) nutrition, body weight, BMI at baseline, and energy and protein intake during PPT; and 5) outcomes, the change in DESIGN-R score during PPT (ΔD), ΔD/PPT. Subjects were divided into two groups: with or without CP supplement. All collected data were compared for PI patients in Method 1: PPT ≤ 28 days *vs*. >28 days and Method 2: PPT ≤ 28 days treated with CP *vs*. non-CP.

Results: Among 2,245 included patients, the prevalence of PI and incidence of hospital-acquired PI were 2.93% and 1.69%, respectively. Result 1: PI patients with PPT ≤ *vs*. >28 days had the following characteristics: ≥ 89 years old, lower Alb, and a less severe PI expressed as a DESIGN-R score <10. The outcomes, expressed as PPT/ΔD and ΔD/PPT, were also significantly better. Result 2: the CP-group had a more severe PI and, paradoxically, a significantly lower Alb and Hb at baseline.

Conclusion: From our results, two conclusions were drawn: (1) PI inpatients who healed within 28 days were ≥ 89 years old, had a lower Alb, and had better outcomes, expressed by a significantly shorter PPT/ΔD. (2) PI inpatients treated with CP, who had a more severe PI and, paradoxically, a significantly lower Alb and Hb at baseline, healed within 28 days. In conclusion, CP could be a strategic agent for PI treatment for inpatients ≥ 89 years old, a lower Alb and Hb, and a DESIGN-R score <10 at baseline.

Keywords: Pressure injury; Collagen peptide; Albumin; DESIGN-R

OPEN ACCESS

Correspondence:
Teruyoshi Amagai, School of Human Environmental Sciences, Mukogawa Women's University, Nishinomiya, 663-8558, Japan,
E-mail: amagait@nutrped.com

Received Date: *29 Jan 2019*
Accepted Date: *01 Mar 2019*
Published Date: *05 Mar 2019*

Citation:
Hokotachi Y, Itoh M, Akasaki M, Kai C, Hasegawa M, Tamura T, et al. Collagen Peptide as an Effector in Pressure Injuries Treatment in Older Adult Inpatients. Clin Surg. 2019; 4: 2353.

Introduction

Older adult inpatients have multifactorial comorbidities, medications, and/or physical impairments, leaving them at high risk of pressure injuries. These factors might confer a risk of immobility, due not only to organ-localized functional impairments of bone, muscle, or articular lesions, but also to systemic functional impairments in mental and cardiopulmonary functions and/or perfusion. All these factors have the potential to result in the development of a Pressure Injury (PI). PI is both a physical and a socio-economic burden. In particular, treatment of PI in older patients requires a multifactorial strategy that includes a local dressing and cleansing treatment and general repositioning, early mobilization, and nutrition care [1]. In addition, guidelines state that supplementation with a solution containing 61 g protein per liter (24 energy percent) was more successful in decreasing total pressure injury area than a formula with 37 g protein per liter (14 energy percent) in a geriatric population [2]. One interpretation of this finding is that nutritional support is effective when patients are malnourished. These guidelines also recommend treatment with energy of 30 to 35 kcal/kg body weight-1 day-1 and 1.25 g to 1.5 g protein/kg body weight-1

day-1. In addition, another systematic review reported that arginine-enriched supplements improved the PUSH score [3]. To date, however, use of a nutritional supplement with a Collagen Peptide (CP)-enriched formula for patients with PI has not been extensively examined. Under this context, we examined our hypothesis that CP is more effective in healing PI in older adult inpatients than arginine-enriched nutritional supplementation.

Methods

This study was conducted as a retrospective chart-review at a single institution. All consecutive patients that developed PI before or after admission between January 2013 and September 2015 were enrolled. Exclusion criteria were (1) liver dysfunction, defined by a serum AST or ALT above 1.5 times the upper institutional limit or a total bilirubin concentration ≥ 1.5 mg/dL; and (2) renal dysfunction, defined as a serum creatinine concentration ≥ 1.5 mg/dL. This study was approved by the ethics committee of the studied institution. Given the nature of this study, the requirement for informed patient consent was considered not necessary. Data from all subjects were collected during the period of PI Treatment (PPT) between the start and end day of PPT. The collected data were categorized into the following five parameters: (1) characteristic parameters, including age, sex, primary diagnosis, and Charlson Comorbidity Index (CCI) to estimate the severity of comorbidities at admission [4], body weight, body mass index (BMI, kg/m^2) at baseline and at the end of PPT, body weight change during PPT; (2) blood test parameters, including highest C-Reactive Protein (CRP), frequency of CRP ≥ 6.0 mg/dL, a level reported for a biomarker for bacterial infection in older inpatients [5], and the lowest serum Albumin (Alb) concentration during PPT; and (3) a Pressure Injury (PI) parameter, including site of PI and the DESIGN-R score. This scoring system was developed to predict the clinical course of healing using the following six acronym components: Depth (D), Exudates (E), Size (S), Inflammation/Infection (I), Granulation tissue (G), and Necrotic tissue (N). Pockets (P) is additionally added to the acronyms when an undermining pocket is identified during repeated weekly evaluations. The R in "DESIGN-R" is for rating system [6]. All scores of E, S, I, G, N, and P, except D, were summed to indicate the severity of PI, with a larger score indicating a greater severity and zero indicating that the PI was completely healed. Then, the cumulative energy and protein intake during the first 14 and 28 days of PPT were divided by ΔD to evaluate the efficacy of nutritional supplementation with CP compared to without CP. This indicates the number of days required to reduce by one point the DESIGN-R score, expressed in units of kcal or g /ΔD. In other words, a smaller energy or protein amount to achieve a one-point reduction of DESIGN-R score is more effective or efficacious; (4) nutritional parameters, including energy and protein intake during PPT, whereby energy and protein intakes were summed in cumulative amounts during the first 14 and 28 days of PPT, and then the calculated energy and protein deficits were defined as actual intake minus the target amount. Energy and protein deficits were expressed as ΔE and ΔP, respectively. Here, targets of energy and protein intake were set at 25 kcal/kg and 1.0 g/kg of actual body weight per day, respectively; and (5) outcome parameters, including (a) time-related outcomes, calculated as PPT divided by ΔD (days/points), the total length of stay in hospital (days) after the start of PPT (LOS) [7,8]. LOS was divided by ΔD (days/points); and (b) nutrition-related outcomes, including energy and protein efficacy to achieve PI healing. Cumulative energy and protein intakes were divided by ΔD to determine how much energy and protein was necessary, and both were expressed in units of kcal or g/points of ΔD, respectively. Under these circumstances, the following two assumptions were set: local perfusion and the impairment of mobility. Both must be considered as major risk factors for PI [9]. In the present study, both factors were the same in all subjects, because all subjects had to use mobility aids, such as a walking stick, frame, or wheelchair, or were bedridden. In addition, their nursing care was considered to be similar because they were all cared for under a standardized protocol, and all nursing care was supervised by nursing staff that were registered by the Wound, Ostomy, Continence (W.O.C.) association. In addition, the contents of CP and non-CP formulae were shown (Table 3).

Subject divisions

Subjects were divided by two methods into two groups according to two categories. The first category was by the duration of PPT, such as PPT <28 or <14 days. The second category was the use of CP supplement. In these two analyses, all subjects were compared in all collected data to identify the factors that shorten PPT and to examine the efficacy of CP supplement in PI treatment. A high efficacy of CP supplement was expected in older patients, especially for less severe PI with PPT <28 days. In the subject categorization, PI patients with PPT ≤ 3 days were included in the non-CP group because this period was considered to be too short to examine the efficiency of a particular nutritional supplement. CP supplement is commercially available and is designed to provide an additional amount of 10 g of CP per package. Nutritional information about the CP and non-CP nutritional supplements is shown in Supplementary (Table 1).

Method 1: Comparison of all data in PI patients with PPT ≤ 28 *vs.* >28 days

All included subjects were divided into two groups, PI that healed ≤ 28 days *vs.* >28 days, to recognize which factors were associated with shorter PPT. These two groups were then compared for all collected data, including outcome parameters and energy or protein intake efficacy (Figure 1).

Method 2: Comparison of subjects with PPT ≤ 28 days treated with CP *vs.* without CP (non-CP)

Data of subjects with PI that healed within 28 days of PPT observed in Method 1 were compared with data in patients treated without CP to examine the efficacy of CP as a strategic agent for PI treatment (Figure 1).

Statistical analysis

Correlations between the number of days for healing of Pressure Injuries (PPT) and changes in DESIGN-R score during PPT (Δ DESIGN-R) were analyzed by linear regression analysis. Data are presented as median and interquartile range for continuous variables and as number and percentage for categorical variables. The two groups in the three methods were compared using the Mann-Whitney U test for continuous data and Fisher's exact test for categorical data. The nonparametric test was used for continuous variables because the relatively small sample size would underestimate the distributional assumptions of parametric tests. Statistical analyses were performed using SPSS Statistics software version 21 (IBM, Armonk, NY, USA). P<0.05 was considered to be statistically significant.

Results

Subject characteristics for all patients are summarized in (Table 1). The median age of all subjects was 88 years old (82, 93) and body weight at baseline was 40.4 kg (35.6, 47.2), expressed as median

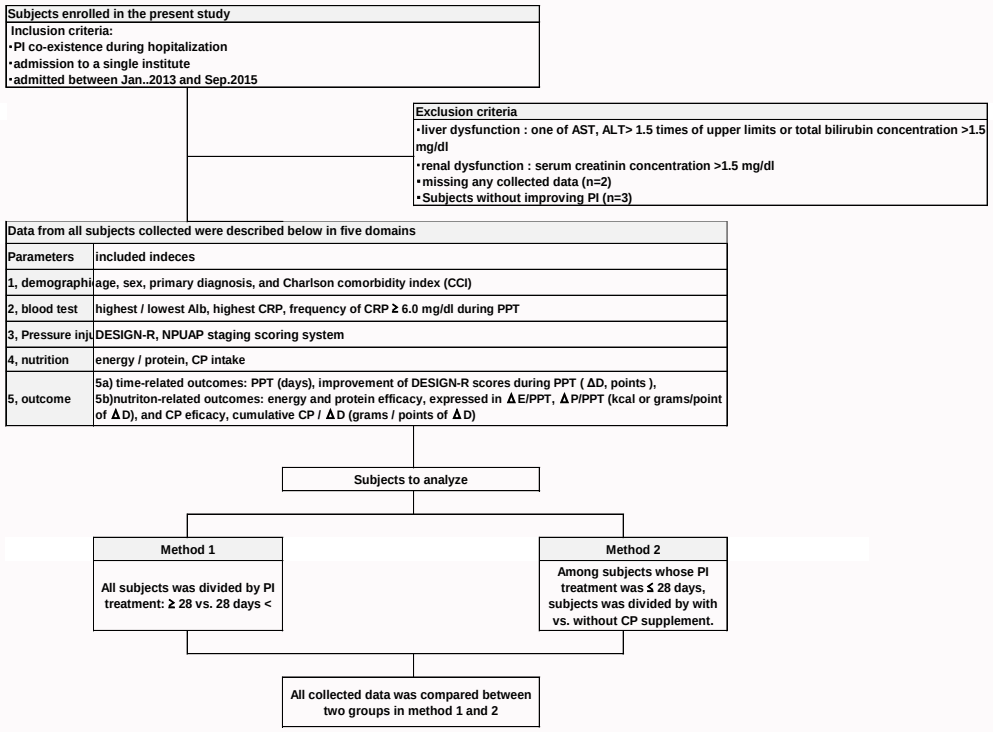

Figure 1: Comparison of all data in PI patients with PPT ≤ 28 *vs.* >28 days.
Abbrevations: Alb: Serum Albumin (mg/dl); AL T: Alanine Transaminase; AST: Asparagine Transaminase; CP: Collagen Peptide; CRP: C-reactive Protein; NPUAP: National Pressure Ulcer Advasatory Panel; PPT: Length of PI Treatment

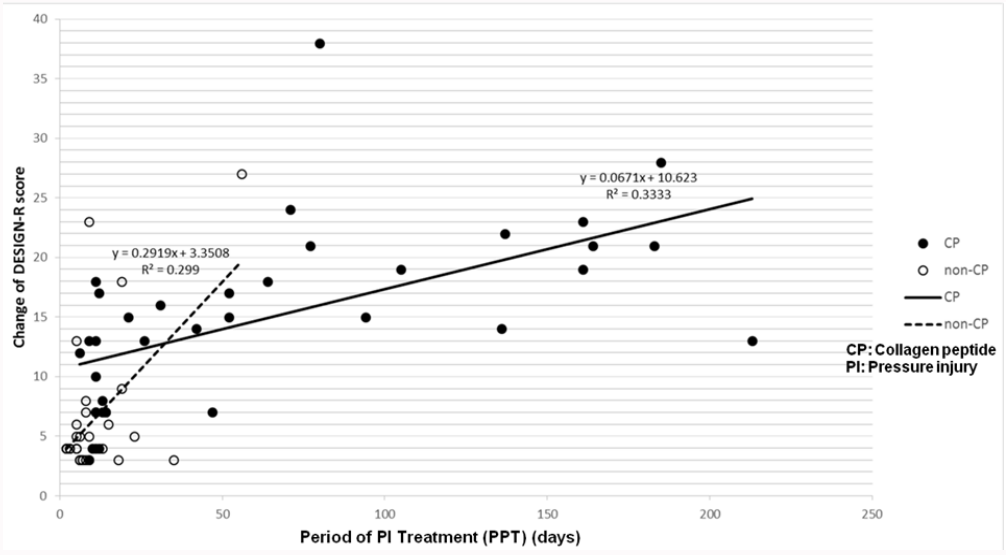

Figure 2: An association of PPT with the change of DESIGN-R scores in two groups, CP- and non-CP group.

(QRI), respectively (Table 1). During the study period, of the 2,245 patients admitted to this institute, 66 were PI inpatients of which 28 were Hospital-Acquired PI (HAPI) patients, who developed PI after admission. The prevalence of PI and incidence of HAPI were 2.93% and 1.69%, respectively.

Result 1

Result of Method 1: Comparison of all data in PI patients with PPT ≤ 28 days *vs.* >28 days

A comparison of all data between the two groups, showed that median age was, paradoxically, older for PPT ≤ 28 days than for >28 days (89 *vs.* 84, p=0.005, (Table 1). Similarly, serum albumin at baseline was significantly lower in the former group (3.1 *vs.* 3.6 mg/dL, p=0.012). PI severity shown by DESIGN-R score at baseline was significantly smaller (less severe) in the former group (5 *vs.* 19, p<0.001). From the aspect of nutritional efficacy, PPT/ΔD was significantly different in both groups (1.57 *vs.* 6.27, p<0.001 for PPT/ΔD; 0.636 *vs.* 0.160, p<0.001 for ΔD / PPT; Table 1).

Result 2

Result of Method 2: Comparison of subjects with PPT ≤ 28 days treated with CP *vs.* non-CP.

Table 1: Comparison of two groups - Group Healed within 28 days vs. over 28 days.

parameters			Total (n=66)	≤ 28 days (n=45)	28 days< (n=21)	P*
Demographics	Sex, male n (%)		26 (39)	16 (36)	10 (48)	
	Age (Year)		88 (82, 93)	89 (86, 94)	84 (75, 88)	0.005
	CCI		6 (5, 7)	6 (5, 8)	6 (5, 7)	0.55
Blood test	Hb, highest during PPT (g/dl)		9.9 (8.3, 11.5)	10 (8.6, 11.5)	9.8 (7.4, 11.6)	0.563
	Serum albumin, highest during PPT (g/dl)		3.3 (2.9, 3.7)	3.1 (2.7, 3.6)	3.6 (3.1, 4.0)	0.012
	Serum albumin, lowest during PPT (g/dl)		2.7 (2.6, 3.1)	2.9 (2.6, 3.2)	2.6 (2.3, 2.7)	0.042
Pressure injury	DESIGN-R score at baseline		8 (4, 17)	5 (4, 10)	19 (15, 23)	<0.001
	PI area (cm^2)		2.1 (0.5, 14.4)	1.1 (0.4, 7.0)	11.2 (1.5, 22.2)	0.005
Nutrition	Body weight at baseline (kg)*		40.4 (35.6, 47.2)	41.2 (35.2, 47.7)	41.0 (35.7, 45.8)	0.99
	Body weight at PI healing (kg)*		39.6 (34.5, 45.8)	38.7 (34.2, 47.3)	39.6 (34.7, 43.6)	0.654
	BMI at PI healing (kg/m^2)*		18.8 (17.4, 19.9)	18.8 (18.0, 20.3)	18.1 (16.2, 19.9)	0.2
	Body weight change between at PI development and healing (kg)		-0.1 (-1.1, 0.0)	0 (-1.0, 0.0)	-0.8 (-3.7, 1.1)	0.359
	Body weight change until PI healing (%)		-0.3 (-2.9, 0.0)	0 (-2.9, 0.0)	-1.9 (-7.6, 2.6)	0.425
	Cumulative intake / DESIGN-R score	Energy efficacy / ΔD (kcal / point)	2300 (782, 4113)	1018 (604, 2317)	5531 (3554, 8334)	<0.001
		Energy efficacy / ΔD / body weight (kcal/point / kg)	52 (20, 105)	25 (13, 55)	140 (94, 178)	<0.001
		Protein efficacy / ΔD (g / point)	85.3 (26.6, 164.6)	39.1 (23.2, 90.2)	226.4 (147.9, 312.9)	<0.001
		Protein efficacy / ΔD / body weight (g / point / kg)	2.1 (0.7, 4.1)	1 (0.5, 2.1)	5.6 (3.7, 7.4)	<0.001
Outcome	PPT		13 (8, 52)	9 (6, 13)	80 (52, 161)	<0.001
	Improvement of DESIGN-R score (ΔD)		7 (4, 14)	5 (4, 8)	15 (12, 21)	<0.001
	PPT / ΔD (days/ point)		2.20 (1.19, 4.83)	1.57 (0.84, 2.50)	6.27 (3.61, 9.21)	<0.001
	efficacy, ΔD/PPT (points/day)		0.455 (0.208, 0.844)	0.636 (0.400, 1.191)	0.160 (0.109, 0.277)	<0.001
	Length of hospitalization (days)		61 (14, 241)	33 (13, 181)	202 (102, 509)	<0.001

Abbreviations: Alb: albumin, BMI: body mass index, CCI: Charlson comorbidity index, CRP: C-reactive protein, DTI: Deep tissue injury, HAPI: Hospital-acquired pressure injury, HD: Hemoglobin, PPT; period of PI treatment (days)
*median (QRI)
**cumulative energy deficit defined as difference between target and real energy intake, where target energy amount was set at 25kcal / kg of present body weight /day
***cumulative protein deficit defined as difference between target and real protein intake, where target energy amount was set at 1.0 gram / kg of present body weight /day

A comparison of all data between the subjects treated within 28 days that were divided into two groups was conducted: treated with or without CP (CP- and non-CP groups, respectively). The CP-group had a more severe PI demonstrated by their DESIGN-R score at baseline (9 *vs.* 4 points, p=0.003, Table 2) and a significantly lower Alb and Hb and a significantly higher frequency of CRP ≥ 6.0 mg/dL at baseline. In addition, the correlation lines of PPT expressed on the x-axis and Δ D on the y-axis for the CP and non-CP groups intersected at day 46 (Figure 2).

Discussion

Is there an effective nutritional supplement for treating PI?

To date, one systematic review and two internationally available guidelines have analyzed the effectiveness of nutritional supplements for treating patients with PI [1-3]. The systematic review, reported by the Cochrane Library in 2014, found that nutritional intervention was effective in the treatment but not prevention of PI [3]. Since then, global PI guidelines have been developed by collaboration between the European Pressure Ulcer Advisory Panel (EPUAP), the National Pressure Ulcer Advisory Panel (NPUAP), and the Pan Pacific Pressure Injury Alliance (PPPIA) [1], and guidelines developed by the nutritional association have analyzed the nutritional management for adult patients with PI [2]. These guidelines and systematic reviews concluded that not protein but energy addition onto standard hospital diets might be effective for treatment but not prevention of PI as a nutritional intervention. Therefore, two questions should be raised before designing a nutritional strategy: 1) Is CP an effective treatment for PI? 2) What kinds of PIs are treated most effectively with CP? To answer them, our results must be analyzed further.

Is CP an effective treatment for PI?

To answer the first question above, Method 2 examined the efficacy of CP-enriched supplementation. The solid and dotted lines in (Figure 2) show the relationships between periods of PI treatment and PI improvement rate expressed as a change of DESIGN-R score for PI patients treated with CP and non-CP supplements. In this figure, a higher value on the y-axis means a faster healing of PI during the same period shown in the x-axis. From this understanding, patients with PI treated with CP seem to have improved more quickly. In other words, PI patients might have achieved an improvement in their PI with CP supplements more quickly than without CP. However, this

Table 2: Comparison of nutritional and outcome parameters between CP and non-CP group: treated within 28 days.

PPT			<= 28 days			
			Total	CP	non-CP	P*
Parameters			(n=45)	(n=16)	(n=29)	
Demographics	Sex, male n (%)		16 (36)	3 (19)	13 (45)	0.08
	Age (years)		89 (86, 94)	93 (88, 94)	88 (83, 93)	0.091
	CCI		6 (5, 8)	5 (5, 6)	7 (5, 8)	0.004
Blood test	Hb, highest during treatment period* (g/dl)		10.0 (8.6, 11.5)	9.5 (8.4, 9.5)	10.4 (8.6, 11.9)	0.031
	Serum Alb, highest during PPT (g/dl)		3.1 (2.7, 3.6)	2.7 (2.6, 3.3)	3.3 (3.1, 3.7)	0.01
	Serum Alb, lowest during PPT (g/dl)		2.9 (2.6, 3.2)	2.6 (2.6, 2.8)	3.0 (2.8, 3.3)	0.004
Pressure injury	PI severity at baseline	DESIGN-R	5 (4, 10)	9 (7, 13)	4 (4, 7)	0.003
		PI area* (cm^2)	1.1 (0.4, 7.0)	5.5 (0.9, 23.5)	0.6 (0.4, 2.3)	0.029
Nutrition	Body weight at healing (kg)		38.7 (34.2, 47.3)	34.7 (33.1, 43.3)	42.0 (37.4, 48.2)	0.042
	Body weight change between at PI development and healing (kg)		0.0 (-1.1, 0.0)	-1.0 (-1.1, -0.1)	0.0 (-0.3, 0.0)	0.014
	Daily body weight change during PPT (kg/day)		0.000 (-0.091, 0.000)	-0.088 (-0.106, -0.006)	0.000 (-0.028, 0.000)	0.048
	Body weight change until PI healing (%)		0.0 (-2.9, 0.0)	-2.9 (-2.9, -0.3)	0.0 (-0.6, 0.0)	0.008
	Total intake of collagen peptide (g)		110 (68, 120)	110 (100, 128)	10 (3, 25)	0.002
	Cumulative energy / protein intake	Cumulative energy intake / day (kcal/day)	897 (544, 1068)	568 (534, 948)	999 (711, 1100)	0.041
		Cumulative energy deficit (kcal)	-1161 (-3393, 178)	-3393 (-3701, -425)	-324 (-2943, 515)	0.031
		Cumulative protein deficit (g)	-46.6 (-178.2, 13.7)	-175.3 (-201.5, 11.3)	-18.8 (-113.0, 23.6)	0.107
	Nutritional efficacies' parameters	Collagen peptide / ΔD (g/point)	11.2 (5.3, 19.1)	14.7 (7.2, 19.8)	2.3 (0.3, 4.6)	0.003
		Cumulative energy / ΔD (kcal/point)	1018 (604, 2317)	774 (602, 1536)	1179 (634, 2492)	0.129
		Cumulative energy / body weight / ΔD (kcal/kg/point)	25 (13, 55)	22 (12, 45)	25 (13, 64)	0.226
		Cumulative protein /ΔD (g/point)	39.1 (23.2, 90.2)	25.7 (23.0, 61.5)	55.2 (27.7, 92.4)	0.118
		Cumulative protein/body weight / ΔD (g/kg/point)	1.0 (0.5, 2.1)	0.7 (0.5, 1.8)	1.0 (0.6, 2.3)	0.131
Outcome	Length of hospitalization (days)		33 (13, 181)	38 (13, 196)	30 (13, 99)	0.682
	Improvement of DESIGN-R score (ΔD)		5 (4, 8)	9 (7, 13)	4 (3, 6)	<0.001
	Length of PPT (days)		9 (6, 13)	11 (10, 13)	7 (5, 12)	0.006
	PPT / Δ D (days/ point)		1.57 (0.84, 2.50)	1.57 (0.74, 2.00)	1.80 (0.92, 2.71)	0.476
	efficacy, ΔD / PPT (points/day)		0.636 (0.400,1.191)	0.636 (0.500, 1.358)	0.556 (0.369, 1.100)	0.476
	Frequency of CRP >= 6.0 mg/dl, n (%)		18 (40)	11 (69)	7 (24)	0.003

Abbreviations: Alb: albumin, BMI: body mass index, CCI: Charlson comorbidity index, CRP: C-reactive protein, DTI: Deep tissue injury, HAPI: Hospital-acquired pressure injury, Hb: Hemoglobin, PPT: Period of Pressure Injury Treatment (days).

trend seems to have switched inversely at day 46, as shown be the intersection of the two lines in (Figure 2). To sum up these results, indicators for the effectiveness of nutritional intervention for PI inpatients showed that CP seems to be more effective in terms of a larger energy deficit than treatment with non-CP (Table 2). From these observations, it could be concluded that CP supplementation seems to be more effective than non-CP in achieving better outcomes for PI patients.

What kinds of PIs are treated most effectively with CP?

To answer the second question above, compared with PI patients treated with non-CP in Method 2, subjects treated with CP had the following characteristics: ≥ 89 years old, a lower hemoglobin and serum albumin concentration, a lighter body weight, a more severe PI expressed as a DESIGN-R score ≥ 10, and a larger PI area, all evaluated at baseline (Table 2). These results might mean that PI patients who fulfill the above criteria may be candidates for PI treatment followed by healing within 28 days.

At this moment, the reason why CP might show its efficacy especially in PI patient's ≥ 89 years old must be considered. The answer might be that older adult's ≥ 89 years old might have a subclinical CP deficiency, which is discussed later. However, PI patients whose period of PI healing was within 28 days must be limited to those with a less severe PI, as expressed by a DESIGN-R score <10 at baseline. This could be interpreted as meaning that severe PI seems to be out of the range of treatment with CP because of extensive inflammation that cannot be handled with a nutritional strategy alone and that older PI patients with a DESIGN-R score <10 could be candidates for CP treatment. In other words, PI patients with a DESIGN-R score <10 at baseline and a PI area ≤ 5.5 cm^2 (Table 2) might be good candidates for PI treatment with CP. However, the reason for these results is not fully understood. One explanation might be that CP shows its effectiveness only in PI patients who are collagen deficient in the dermis. With increasing age, collagen density and the ability of fibroblasts to produce collagen decrease in the dermis [10]. Older adults seem to have a collagen deficiency in general. This deficiency

Table 3: Comparison of the contents of CP and non-CP formulae.

	CP	non-CP
volume, ml	125	125
Energy, kcal	80	100
Protein, gram	12	5
Fat, gram	0	0
Carbohydrate, gram	8	20
Collagen peptide, gram	10	0
Arginine, gram	0	2.5

has been demonstrated in a human study that resolved the deficiency by CP ingestion [10]. In addition, another explanation is that the number of PI patients treated with non-CP was too small, so that the reliability of the relationship (shown by the dotted line in Figure 2) would be limited. To confirm the efficacy of CP for PI treatment, patients whose PI treatment is predicted to be longer than 46 days must be collected.

What indicators show the effectiveness of CP for treatment of PI?

The present study used novel indicators of the determinants of PI healing, including the efficacy of energy and protein intake, and the time to heal a PI (Table 1 and 2). A previous, prospective study with random allocation of patients reported that patients with PI treated with a CP-enriched nutritional supplement showed a significant improvement in PUSH score after 8 weeks of treatment compared with PI patients receiving a control diet [11].

DESIGN-R to evaluate the severity of PI

Because DESIGN-R has been used in limited areas, it must be clarified what it is and whether it has been validated in clinical settings. In a multicenter prospective cohort study, the total score under this system showed a close, linear correlation with the total amount of medical resources required for treatment, with a higher score indicating a greater severity [12]. For example, a two times score indicates a doubling of the number of days required to use medical resources, such as human resources or medications; to stay in the hospital; or to make PI healing completely. In the present study, we collected DESIGN-R scores at least at the start and the end of PPT, and the following difference was calculated and abbreviated as ΔD, in all subjects:

ΔD = [DESIGN-R score at the end]-[DESIGN-R score at the start]

Alongside the ΔD calculation, PI severity was also evaluated with the newly introduced NPUAP staging scoring system proposed by the National Pressure Ulcer Advisory Panel.

Definition of CP

To follow our discussion for CP effectiveness, we would like to clarify the definition of CP. Collagen is the most abundant protein in the human body, accounting for approximately 30% of total protein [13,14]. It exists in various tissues, including the dermis, cartilage, bone [15], and skin tendons [16]. Its hydrolysate is often termed CP [17]. The constituent amino acids of CP appear in the blood after one or two hours of oral ingestion in humans [17]: negligible Proline-hydroxyproline (Pro-Hyp) levels before oral ingestion were increased in serum or plasma following ingestion. However, the bioavailability of Pro-Hyp remains unclear and it has not been proved whether it is transported directly to the wounded site or to other sites, such as a central neural site to stimulate to produce wound-healing molecules, such as arginine dose stimulate hypothalamus to produce growth hormone for growth and wound healing.

Biodynamics of ingested CP in the human body

Regarding CP dynamics after ingestion by human subjects, before conducting the present study, three points were raised as follows: (1) whether or not orally ingested CP, which is digested at brush borders, might not necessary be converted to the same peptide after it is absorbed?; (2) even so, is the absorbed CP necessarily be transported to the wounded site, such as PI?; and (3) even so, is CP transported to the PI necessarily be used for building collagen by fibroblasts in the dermis at PI? To address to our first and second points, a previously reported work showed that ingested CP appeared in the serum followed by the skin within 30 min. In this study, CP was in the form of di- and tripeptides. From these observations, it might be concluded that di or tripeptides involved in CP seem to be transported by transporters directly existing in the intestinal mucosa without enzymatic hydrolysis processes similar to those of other di and tripeptides [18-20]. To address the third point, an animal and human study successfully showed that dermal fibroblasts and collagen fibril density were significantly increased in the CP group compared with a control group in piglets and humans [13]. In summary, orally ingested CP could be transported by the intestinal mucosa followed by relocation to the skin and is associated with an increase of fibroblasts and collagen fibrils in the dermis. These observations might be interpreted as meaning that orally ingested CP could be absorbed and transported within 30 min to the skin to increase the number of fibroblasts and collagen fibrils in the dermis.

Study limitations

This study had several limitations. First, the subjects were not prospectively allocated, and CP was allocated to patients with a more severe PI, as shown by the DESIGN-R scores in Table 2 ($p=0.003$). As shown in Figure 2, patients treated with CP formula varied widely in PI severity, so a prospective study design is warranted. Second, the number of subjects for CP and non-CP treatment was 16 and 29, respectively. This subjects' number is the result of retrospective study fashion. So random allocation will be necessary to draw a definitive conclusion to improve the clinical outcomes for PI patients.

Conclusion

For all 2,245 included patients admitted during the study period, PI incidence was 1.69%. From our results, two conclusions were drawn: (1) PI inpatients healed within 28 days, were ≥ 89 years old, had a lower Alb, had better outcomes expressed by a significantly shorter PPT/ΔD. (2) PI inpatients treated with CP, who had a more severe PI and, paradoxically, a significantly lower Alb and Hb at baseline, healed within 28 days. In conclusion, CP could be a strategic agent for treatment of PI inpatients who are ≥ 89 years old, have a lower Alb and Hb, and have a DESIGN-R score <10 at baseline.

Acknowledgement

The authors would like to thank Mr. Kazunari Miyako (Head, General Affairs Division, Kikai Tokushukai Hospital) for kindly providing raw data for this report in 2018.

References

1. National Pressure Ulcer Advisory Panel, European Pressure Ulcer

Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Emily Haesler (Ed.). Cambridge Media: Perth, Australia; 2014.

2. Volkert D, Berner YN, Berry E, Cederholm T, Coti Bertrand P, Milne A, et al. ESPEN Guidelines on Enteral Nutrition: Geriatrics. Clin Nutr. 2006;25(2):330-60.

3. Langer G, Fink A. Nutritional interventions for preventing and treating pressure ulcers. Cochrane Database Syst Rev. 2014;12(6):CD003216.

4. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

5. Liu A, Bui T, Van Nguyen H, Ong B, Shen Q, Kamalasena D. Serum C-reactive protein as a biomarker for early detection of bacterial infection in the older patients. Age Aging. 2010;39(5):559-65.

6. Jpn Soc of Presure Ulcers: DESIGN-R scoring manual (English version).

7. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159-211.

8. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33(6):929-36.

9. Coleman S, Gorecki C, Nelson EA, Closs SJ, Defloor T, Halfens R, et al. Patients risk factors for pressure ulcer development: Systematic review. Int J Nursing Stud. 2013;50(7):974-1003.

10. Asserin J, Lati E, Shioya T, Prawitt J. The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: evidence from an ex vivo model and randomized, placebo-controlled clinical trials. J Cosmet Dermatol. 2015;14(4):291-301.

11. Lee SK, Posthauer ME, Dorner B, Redovian V, Maloney MJ. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. Adv Skin Wound Care. 2006;19(2):92-6.

12. Sanada H, Iizaka S, Matsui Y, Furue M, Tachibana T, Nakayama T, et al. Clinical wound assessment using DESIGN-R total score can predict pressure injury healing: pooled analysis from two multicenter cohort studies. Wound Repair Regen. 2011;19(5):559-67.

13. Matsuda N, Koyama Y, Hosaka Y, Ueda H, Watanabe T, Araya T, et al. Effects of ingestion of collagen peptide on collagen fibrils and glycosaminoglycans in the dermis. J Nutr Sci Vitaminol. 2006;52(3):211-5.

14. Tanaka M, Koyama Y, Nomura Y: Effects of collagen peptide ingestion on UV-B-induced skin damage. Biosci Biotechnol Biochem. 2009;73(4):930-2.

15. Nomura Y, Oohashi K, Watanabe M, Kasugai S. Increase in bone mineral density through oral administration of shark gelatin to ovariectomized rats. Nutrition. 2005;21(11-12):1120-6.

16. Minaguchi J, Koyama Y, Meguri N, Hosaka Y, Ueda H, Kusubata M, et al. Effects of ingestion of collagen peptide on collagen fibrils and glycosaminoglycans in Achilles tendon. J Nutr Sci Vitaminol. 2005;51(3):169-74.

17. Iwai K, Hasegawa T, Taguchi Y, Morimatsu F, Sato K, Nakamura Y, et al. Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates. J Agric Food Chem. 2005;53(16):6531-6.

18. Yazaki M, Ito Y, Yamada M, Goulas S, Teramoto S, Nakaya MA, et al. Oral Ingestion of Collagen Hydrolysate Leads to the Transportation of Highly Concentrated Gly-Pro-Hyp and Its Hydrolyzed Form of Pro-Hyp into the Bloodstream and Skin. J Agric Food Chem. 2017;65(11):2315-22.

19. Zhang M, Xu J, Wang T, Wan X, Zhang F, Wang L, et al. The Dipeptide Pro-Gly Promotes IGF-1 Expression and Secretion in HepG2 and Female Mice via PepT1-JAK2/STAT5 Pathway. Front Endocrinol (Lausanne). 2018;9:424.

20. Martinez Molledo M, Quistgaard EM, Löw C. Tripeptide binding in a proton-dependent oligopeptide transporter. FEBS Lett. 2018;592(19):3239-47.