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The effect of a hydrolyzed collagen-based supplement on wound healing in patients with burn: A randomized double-blind pilot clinical trial

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ABSTRACT

Introduction: Burn is among the most severe forms of critical illness, associated with extensive and prolonged physical, metabolic and mental disorders. The aim of this study was to assess the effect of an oral, low-cost, and accessible collagen-based supplement on wound healing in patients with burn.

Methods: In this randomized double-blind controlled pilot clinical trial, 31 men, 18–60 years, with 20–30% total body surface area burn were studied. Patients were randomly assigned to receive either a collagen-based supplement (1000 kcal) or an isocaloric placebo, for 4 weeks. Serum pre-albumin, rate of wound healing, length of hospital stay, and anthropometries were assessed at baseline, and the end of week 2 and 4.

Results: Serum pre-albumin was significantly higher at week 2 (29.7±13.6 vs. 17.8±7.5 mg/dL, P=0.006) and week 4 (35.1±7.6 vs. 28.3±8.2 mg/dL, P=0.023) in collagen than control group. Changes in pre-albumin concentration were also significantly higher in collagen group at week 2 (13.9±9.8 vs. −1.9±10.3 mg/dL, P<0.001) and week 4 (19.2±7.5 vs. 8.5±10.1 mg/dL, P=0.002). The Hazard ratio of wound healing was 3.7 times in collagen compared to control group (95% CI: 1.434–9.519, P=0.007). Hospital stay was clinically, but not statistically, lower in collagen than control group (9.4±4.6 vs. 13.5±7 days, P=0.063). There were no significant differences in weight, body mass index, dietary energy and protein intakes between the two groups.

Conclusion: The findings showed that a hydrolyzed collagen-based supplement could significantly improve wound healing and circulating pre-albumin, and clinically reduce hospital stay in patients with 20–30% burn.

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1. Introduction

Burns are among the major traumatic events that usually require intensive care, and long hospitalization and rehabilitation. Based on WHO reports, around 180,000 annual deaths are attributed to burns, with a considerable fraction in low and middle-income countries. In addition, in 2004, around 11 million people required medical care due to major burns and consequent morbidities [1]. The extensive tissue injury in burn could lead to serious wounds, pain, depressed immunity, infections, hypermetabolism, muscle wasting, and scars, which in turn could cause major physical and mental distresses [2,3]. Accelerating the rehabilitation phase and wound healing are of importance due to extensive physiological, psychological and social consequences of burn. Currently, wound dressings, different systemic and topical medications, wound excision and skin grafting, biological and synthetic skin substitutes, skin tissue engineering and surgical approaches are available in burn management [2]. Although recent advancements have substantially improved burn outcomes, there are still many challenges about their efficacy and these strategies are relatively costly and not attainable in all countries.

Nutritional support and dietary supplements are among the most essential interventions to comply the metabolic demands and alleviate persistent and profound hypermetabolism in burn [4]. Data from an international nutrition survey showed substantial energy and protein deficit in burn victims receiving enteral nutrition, which was dose-dependently associated with higher mortality, irrespective of disease severity [5]. Failure to supply sufficient energy and nutrients, especially protein, could interfere with wound healing and delay recovery [6]. Higher protein requirement is the result of urinary and wound protein losses, increased gluconeogenesis and tissue repair [7].

Collagen is the main structural component of bones, muscles, connective tissues and skin. Hydrolyzed collagen or gelatin is derived from partial hydrolysis of collagen [8]. Previous studies have confirmed the efficacy of hydrolyzed collagen on wound repair and improvement of skin and connective tissues [8]. It has been shown that an oral collagen supplement could improve the healing of pressure ulcers in residents of long-term-care facilities [9]. Experimental studies have reported the effect of oral collagen supplements on accelerating the healing of diabetic wounds [10], alleviating UV induced skin photo-aging [11], and reducing aging-related changes of the extracellular matrix [12]. A systematic review of studies in patients with diabetic foot ulcers showed the efficacy of collagen-based dressings on wound healing [13]. Collagen-based biological dressings are also widely applied for the management of burn wounds [14].

Most of previous studies investigating the effects of collagen were performed in experimental models or as topical treatments in clinical conditions other than burn. Thus, the aim of this preliminary study was to investigate the effect of an oral, inexpensive, and accessible collagen-based supplement on wound healing in patients with burn.

2. Material and methods

2.1. Patients

In this randomized double-blind controlled pilot clinical trial, 34 men were enrolled. To have a power of 90% to detect a 10 difference of change in pre-albumin (also known as transthyretin) between two groups, with a standard deviation (SD) of 8 and type I error of 5%, a sample size of 14 in each group seemed to be enough. To compensate for a probable 20% drop out, 17 patients were recruited to each group. The inclusion criteria were (1) male, (2) age 18–60 years, (3) 20–30% total body surface area (TBSA) burn in body trunk, and (4) ability to oral intake of food within 24–48 h of admission. Patients with prohibition of high protein diets such as those with diabetes, kidney and liver failure, patients allergic or intolerant to dairy foods, and those who have consumed high protein or vitamin-mineral supplements within the past 6 months were not included. Participants with burn of sole of the foot were not included due to difficulty of measuring body weight. Besides, participants with respiratory, gastrointestinal and malabsorptive disorders, immune deficiencies such as HIV infection, and drug users were not eligible for this study.

Participants were included from those admitted to the emergency unit of Motahari burns hospital, within 24–48 h of admission, considering the inclusion and exclusion criteria. TBSA was screened using “Rule of Nines” by an emergency physician and then confirmed by an internist or a surgeon at admission. Patients were allocated to two groups to receive either hydrolyzed collagen or placebo supplements. Allocation was performed through simple randomization and using computer-generated random numbers, by a hospital staff blinded to the aim of the study. Patients and main researchers were blinded to randomization and allocation. Patients in both groups received standard treatments. The same wound treatment protocol was used for all patients. Wounds were washed every day with normal saline and dressings were changed. A topical bactericidal ointment and vaseline gauze were used for dressing. Wound excision and grafts were used to accelerate healing based on the surgeon’s decision. All participants or their surrogates signed an informed consent before the initiation of the intervention. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. This trial was registered at Iranian Registry of Clinical Trials (http://www.irct.ir:IRCT2017011015536N5).

2.2. Interventions

The total daily energy need of each patient was calculated by Curreri formula. Based on available recommendations, the diet should consist of 20–25% protein [7]. It has been decided to provide 1000 kcal of total energy requirement from the supplements and the rest from usual meals. Daily diet programs, same in content and source of nutrients between the two groups, was designed and prescribed by investigators for each patient individually throughout the study.

In the intervention group, participants received 1000 kcal per day supplement containing 45 g gelatin powder (36 g hydrolyzed bovine collagen) (Amutiya, Qom, IRAN) mixed with 100 g sugar

and 500 g 3.5% fat yogurt, divided in 4 meals, for 4 weeks. In the control group, patients received a supplement with the same calorie. For having a product with same physical characteristics, after heating the mixture of 84 g soy flour (35 g soy protein), 80 g sugar and 200 g water for 10 min, it has been mixed with 500 g 3.5% fat yogurt and consumed similar to collagen supplement. All ingredients were weighted by kitchen digital scale. Both products were prepared by a hospital staff not involved in the research and packed similarly and coded as A and B. The weight difference between supplement and control food was about 6 g, which was undetectable by the participants and researchers. The researchers and hospital staffs monitored and documented the complete intake of main meals and supplements. Supplements and detailed diet programs were given to the patients who were discharged before the end of 4 weeks, in wound dressing visits at hospital.

2.3. Assessments

2.3.1. Anthropometries

The patients' weight were assessed in light clothing at baseline, end of 2 week, and at the end of the study using a digital scale (Beurer, Germany). The height was measured without shoes using a wall-mounted tape (Seca, Germany). Body mass index (BMI) was calculated as weight (kg) divided by height square (m^2).

2.3.2. Wound area

Changes in wound area were assessed using a visual analogue scale based on photography at day 1, the end of week 2 and week 4. Wound healing was defined as the absence of a burn ulcer and the presence of a new layer of epithelium.

2.3.3. Length of hospital stay

Days of hospital stay were recorded. Some patients did not need further hospitalization but were instructed to refer to hospital for regular dressing up to complete wound healing.

2.3.4. Blood sample

At baseline and at the end of week 2 and 4, blood samples were taken from all participants, and serum stored at −20°C. At the end of the study, serum pre-albumin concentrations were measured through turbidimetric method (BioSystems SA, Barcelona, Spain).

2.4. Statistical analysis

Mean±SD, mean difference, and confidence interval (CI) were used to present data. The normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Differences in pre-albumin between collagen and control groups were analysed using *t*-test at baseline, end of week 2 and 4. Paired *t*-test was used to assess within-group changes (changes in weeks 2 and 4 compared to baseline). To assess the difference in the rate of wound healing in the two groups Cox regression and Hazard ratio were used. A P-value less than 0.05 was considered as statistically significant. SPSS software (IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Armonk, NY, USA) was used to perform the statistical analysis.

3. Results

Thirty-one participants completed the study. One patient in the collagen and two patients in the placebo group were excluded (Fig. 1).

3.1. General characteristics

There were no baseline statistical differences in age (30.1±9.7 vs. 31.9±12.4 year, P=0.654), BMI (24.7±4.7 vs. 25.2±4.9 kg/m^2, P=0.778) and other anthropometries, TBSA % (24.7±4.27 vs. 24.4±4.54%, P=0.83), and cause of burn (P>0.99), between the collagen and control groups (Table 1). Depth of burn (Table 2), and distribution of patients who received wound excision and grafts were similar in two groups.

3.2. Pre-albumin concentration

Serum pre-albumin levels were significantly higher at the end of week 2 (29.7±13.6 vs. 17.8±7.5 mg/dL, P=0.006) and week 4 (35.1±7.6 vs. 28.3±8.2 mg/dL, P=0.023) in the collagen compared to the control group, respectively. Changes in pre-albumin concentration from baseline were significantly higher in the collagen compared to the control group at week 2 (13.9±9.8 vs. −1.9±10.3 mg/dL, P<0.001) and week 4 (19.2±7.5 vs. 8.5±10.1 mg/dL, P=0.002), respectively.

Pre-albumin concentration increased significantly at week 2 compared to baseline within the collagen group (P<0.001), but not within the control group (P=0.471). At the end of week 4, serum pre-albumin was significantly higher within each of the collagen and control groups compared to the initiation of the study (P<0.001 and P=0.006, respectively) (Table 3, Fig. 2)

3.3. Hospital stay

Duration of hospital stay was 9.4±4.6 days in the collagen and 13.5±7 days in the control group, which was not statistically significant between the two groups (P=0.063) (Table 2).

3.4. Wound healing

At week 2, wounds were completely healed in 8 (50%) patients of the collagen and 1 (6.7%) patient of the control groups (P=0.015). At the end of the study, wounds in all patients of the collagen and 6 (40%) patients of the control group were entirely healed (P<0.001) (Table 2). The Hazard ratio of wound healing was 3.7 times in the collagen compared to the control group (95% CI: 1.434–9.519, P=0.007).

3.5. Anthropometric parameters

There was no significant difference in body weight at the end of week 2 (74.5±13.5 vs. 73±14 kg, P=0.775) and week 4 (75±13.9 vs. 72.7±13.3 kg, P=0.639) between the collagen and control

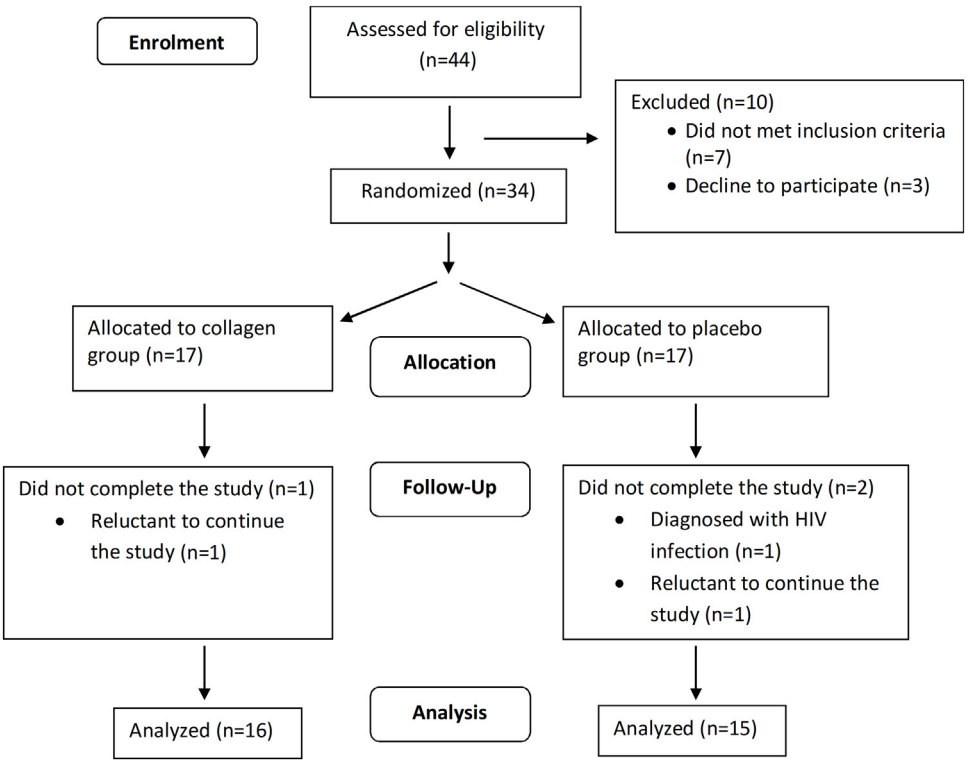

Fig. 1 – Flow diagram of the study based on CONSORT statement.

groups. Changes in body weight from baseline were not also considerable in the collagen compared to control group at week 2 (−1.5±4.6 vs. −1.2±5.9 kg, P=0.857) and week 4 (−0.9±4.6 vs. −1.5±7.5 kg, P=0.807), respectively (Fig. 3).

BMI was not significantly different at week 2 (24.2±4.1 vs. 24.9±3.8 kg/m^2, P=0.670) and week 4 (24.4±4.1 vs. 24.7±3.4 kg/m^2, P=0.819) between the intervention and control groups. In addition, changes in BMI from baseline were not significantly different between the collagen and control groups at week 2 (−0.5±1.5 vs. −0.4±2.1 kg/m^2, P=0.859) and week 4 (−0.3±1.6 vs. −0.5±2.5 kg/m^2, P=0.816), respectively.

Table 1 – Baseline characteristics of the study population.

		Placebo (n=15)	Collagen (n=16)	P
Age (years)		31.9±12.4	30.1±9.7	0.654*
Weight (kg)		74.2±17.4	75.9±15.2	0.764*
Height (cm)		171±6	175±7	0.115*
BMI (kg/m^2)		25.2±4.9	24.7±4.7	0.778*
TBSA (%)		24.4±4.54	24.7±4.27	0.83**
Cause	Petrol	6 (40)	6 (37.5)	>0.99***
	Gas	4 (26.7)	5 (31.3)	
	Explosives	2 (13.3)	2 (12.5)	
	Fire flame	1 (6.7)	2 (12.5)	
	Other	2 (13.3)	1 (6.3)	

Data presented as mean±SD or n (%).
* Based on *t*-test.
** Based on Mann–Whitney test.
*** Based on Fisher's exact test.

No within group changes were observed for body weight or BMI, neither in the collagen nor in the placebo group, at any time point.

3.6. *Dietary intake*

There were no significant differences in dietary intakes of energy and protein (%) between the collagen and control groups at baseline and following 4 weeks intervention (Table 4). Mean energy/kg body weight was 31±5.6 vs. 30.7±6.6 kcal/kg at baseline and 39.5±5.2 vs. 40.4±5.6 kcal/kg at the end of the study, in the collagen and control groups, respectively. Mean protein/kg body weight was 1.6±0.3 vs. 1.6±0.3 g/kg at baseline and 2.6±0.4 vs. 2.6±0.4 g/kg at the end of the study, in the collagen and control groups, respectively. All within group values (pre- to post-4 weeks intervention) of energy, protein percentage from energy (%), energy and protein per kg body weight were increased significantly (P<0.001).

4. Discussion

Pre-albumin concentration and its improvement during the current study was considerably higher in the collagen compared to the control group. The wound healing rate was significantly higher (Hazard ratio: 3.7) following supplementation with a hydrolyzed collagen-based supplement. Hospital stay was not statistically different between the two groups, however, this difference seems to be clinically important. No significant changes were seen in weight and BMI throughout the study.

Table 2 – Details of burn characteristics and wound healing in the study population.

Patients	Age (year)	TBSA (%)	Degree	Hospital stay (day)	Healing at week 2	Healing at week 4
1	26	25	2 & 3	11	No	Yes
2	33	30	2 & 3	13	No	Yes
3	20	30	2 & 3	8	Yes	Yes
4	49	20	2	6	Yes	Yes
5	35	30	2 & 3	8	No	Yes
6	30	20	2	5	Yes	Yes
7	52	20	2 & 3	5	Yes	Yes
8	27	20	2 & 3	8	Yes	Yes
9	24	25	2 & 3	4	Yes	Yes
10	20	20	2 & 3	12	No	Yes
11	33	30	2 & 3	15	No	Yes
12	20	25	2 & 3	21	No	Yes
13	31	20	2 & 3	8	No	Yes
14	25	30	2 & 3	10	Yes	Yes
15	37	25	2	4	Yes	Yes
16	20	25	2 & 3	13	No	Yes
17	19	25	2 & 3	32	No	No
18	35	29	2 & 3	10	No	Yes
19	45	30	2 & 3	10	No	No
20	28	30	2 & 3	14	No	No
21	33	27	2	6	No	No
22	25	20	2 & 3	9	No	Yes
23	21	20	2 & 3	21	No	No
24	53	20	2	9	No	Yes
25	23	30	2 & 3	19	No	No
26	50	20	2 & 3	12	No	No
27	20	30	2 & 3	19	No	No
28	27	20	2 & 3	16	No	No
29	20	20	2	6	Yes	Yes
30	27	20	2 & 3	7	No	Yes
31	53	25	2 & 3	13	No	Yes

Table 3 – Pre-albumin concentration (mg/dL) at baseline and following 4 weeks of collagen intervention in patients with burn.

	Control (n=15)	Collagen (n=16)	95% CI			P*
	Mean±SD	Mean±SD	Diff	Lower	Upper	
Baseline	19.8±8.8	15.9±9.5	−3.89	−10.64	2.86	0.248
Week 2	17.8±7.5	29.7±13.6	11.93	3.86	20	0.006
Change week 2 from baseline	−1.9±10.3	13.9±9.8	15.82	8.44	23.2	<0.001
P** (week 2 vs. baseline)	0.471	<0.001				
Week 4	28.3±8.2	35.1±7.6	6.78	0.99	12.57	0.023
Change week 4 from baseline	8.5±10.1	19.2±7.5	10.67	4.16	17.18	0.002
P** (week 4 vs. baseline)	0.006	<0.001				

* Based on *t*-test.
** Based on paired samples test.

Based on our knowledge, there is no study investigating the effect of an oral hydrolyzed collagen-based supplement on wound healing in burn. Low serum pre-albumin levels are associated with poor nutritional status, longer hospital stay, delayed wound healing and recovery, and higher mortality both in chronic diseases and critically ill patients. The assessment of pre-albumin is recommended due to its short half-life that reflects rapid responses to both metabolic stresses and treatments, and also its cost-effectiveness [15,16]. The current study showed a considerable improvement in pre-albumin concentration following 2 and 4 weeks consumption of a hydrolyzed collagen-based supplement compared to the control group in 20–30% TBSA burn. Serum pre-albumin has been considered as a marker of improvement of nutritional status in patients with 25–95% TBSA burn [17]. Pre-albumin concentration was correlated with graft healing, and is a sensitive and considerable marker determining graft success in burn [18,19]. There was no clinical report on the efficacy of oral collagen supplement on pre-albumin levels in burn. However, it has been shown that comparable interventions consisting daily 0.5 g/kg glutamine for 14 days, with oral or artificial feeding, could improve circulating pre-

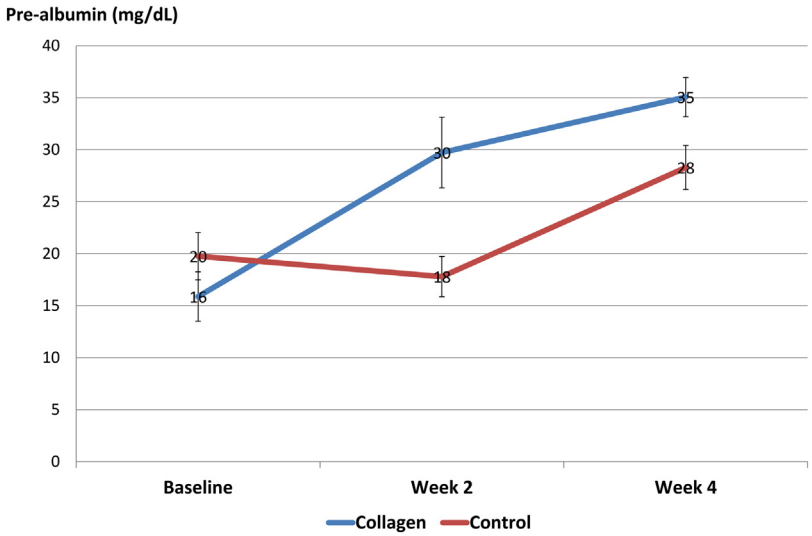

Fig. 2 – Changes in pre-albumin concentration from baseline to the end of 4 weeks supplementation with collagen in patients with burn.

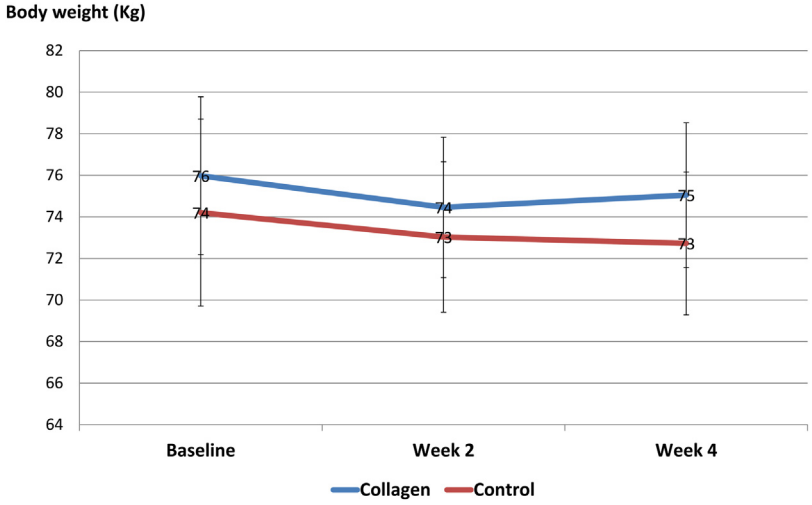

Fig. 3 – Changes in weight from baseline to the end of 4 weeks supplementation with collagen in patients with burn.

Table 4 – Dietary intakes at baseline and following 4 weeks of collagen intervention in patients with burn.

		Group		P*
		Control (n=15)	Collagen (n=16)	
Energy (kcal)	Baseline	2199±277	2286±230	0.349
	Week 4	2881±287	2911±312	0.783
Protein (%)	Baseline	21.2±1.4	21.2±1.6	0.917
	Week 4	25.5±2.2	25.9±2.6	0.731
Energy (kcal/kg)	Baseline	30.7±6.6	31±5.6	0.922
	Week 4	40.4±5.6	39.5±5.2	0.664
Protein (g/kg)	Baseline	1.6±0.3	1.6±0.3	0.945
	Week 4	2.6±0.4	2.6±0.4	0.880

* Based on *t*-test.

albumin, accelerate wound healing, and reduce hospital stay days in 30–75% TBSA burn [20].

Oral collagen administration has improved wound healing in the current trial. Previous studies have shown the efficacy of collagen-based dressings on wound healing in diabetic foot ulcer [13], and burn [14]. Collagen dressings were suggested to modify bacterial burden, support growth factors against proteases, reduce matrix metalloproteinases, promote cell proliferation and tissue synthesis, and neutralize free radicals [21,22]. In addition, 15 g hydrolyzed collagen protein, 3 times daily, for 8 weeks improved pressure ulcer healing in residents of long-term-care facilities [9]. Experimental studies have also shown the promising effect of 2 g/kg body weight ingestion of hydrolyzed collagen on wound repair in diabetic ulcers [10]. Potential mechanisms include an increase in capillary density, vascular endothelial growth factor (VEGF), hydroxyproline and nitric oxide content of wounds, which all contribute to lower inflammation and faster tissue repair [12]. Experimental studies in conditions other than wound healing have also confirmed the efficacy of oral collagen administration on reduction of matrix metalloproteinase 13, apoptosis, and production of pro-inflammatory mediators, interleukin-1, nitric oxide, tumor necrosis factor, and malondialdehyde [23,24].

Moreover, it has been shown that oral collagen administration could inhibit UV radiation-induced skin injury (photoaging) by increase in the expression of pro-collagen, decrease matrix metalloproteinase 1, prevent oxidative stress and inactivation of endogenous antioxidant enzymes like catalase and glutathione peroxidase, and suppress the expression of nuclear factor kappa B and its consequent pro-inflammatory cytokines. Collagen inhibited down-regulation of transforming growth factor-β1 (TGF-β1) expression and up-regulated the expression of type II receptor of TGF-β1; the mediators that control the production of pro-collagen and are involved in the synthesis of matrix collagen [11,25].

Little is known about the role of soy protein in burns. Soy protein has good quality and amino acid profile compared to other plant-based proteins. It has been shown that soy protein could decrease inflammation, increase transferrin, and improve wound healing in patients with 20–50% TBSA burn [26]. The soy isoflavone genistein could also accelerate cutaneous wound healing predominantly through estrogen receptor independent mechanisms [27]. Genistein has improved diabetic wounds healing through decreasing oxidative stress, inhibiting inducible nitric oxide synthase (iNOS) activity and cutaneous forkhead box O transcription factor 1 (FoxO1) levels [28]. However, the current study showed that this collagen-based supplement could be even more effective in improving the outcomes than the control supplement containing the same amount of soy protein.

Adequate assessment and provision of calorie and protein needs are of vital importance in patients with burn. Longitudinal studies have reported that inadequate energy delivery (<30 kcal/kg) was associated with greater weight loss, and lower pre-albumin concentration [29]. Burn injuries could be associated with weight loss and prolonged body composition changes including catabolism of lean body mass and decrease in total and subcutaneous body fat [30,31]. Modifying these changes could improve immune responses, rate of wound healing and recovery. In the current study, we supplied almost total dietary requirements of energy and protein for each patient in both groups. There was no considerable weight loss in none of the collagen or control groups. Both groups received the same amounts of protein and the source of protein was the only difference between the two groups, which could be responsible for the observed differences of pre-albumin concentration, rate of wound healing and duration of hospital stay.

Length of hospital stay was not statistically different between collagen (9.5 days) and control (13.5 days) groups; however, it was clinically considerable. Earlier discharge could be associated with faster wound healing and better improvement in nutritional status. Lengthy hospitalization could be associated with more pathophysiological and psychosocial disorders. Each day of hospitalization also impose high costs to patients and health systems [32].

Providing adequate metabolic needs of the patients is one of the strengths of this study, which overcome the challenge of preventing significant weight loss. However, the major strength was to formulate and apply a beneficial low-cost oral supplement. This collagen-based supplement could be an excellent choice both in regular care and in emergencies and disasters.

This study had also some limitations that should be considered. We did not include women, which could restrict the generalizability of the findings. The efficacy of this intervention in women with burn and potential sex differences in outcomes should be addressed in future studies. In addition, as a preliminary study, our focus was on practical and clinical outcomes and clarifying a part of biochemical pathways; nevertheless, investigating more underlying mechanisms could strengthen the understanding of the findings, and should be considered in future studies.

5. Conclusion

The current findings showed that 4 weeks consumption of a hydrolyzed collagen-based supplement could significantly improve wound healing rate and serum pre-albumin concentration in men with 20–30% burn. The reduction in duration of hospital stay was also clinically of importance.

Conflict of interest

None.

Acknowledgements

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