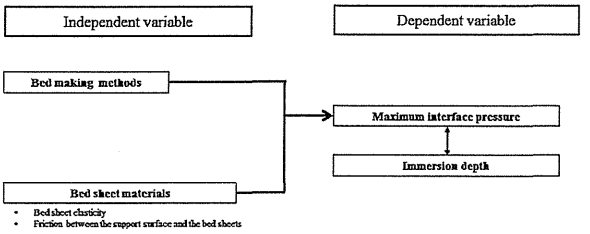

Figure 8 The conceptual model of this study.

Methods

The study was conducted at 24.3 °C ± 0.8 °C and 55.3% ± 4.8% humidity. The anatomical model was placed on the pressure mapping system and a load was applied. After stabilization for 3 min, the pressure distribution was measured. After 10 min, the immersion depth was measured, and the anatomical model, loading device, and bed sheets were subsequently removed from the support surface. For each method and bed sheet material, a total of three measurements were made at 10-min intervals. The bed sheets were changed, and the pressure mapping system was recalibrated between measurements (Fig. 7). We included a control consisting of only the support surface and its cover but no bed sheets. We assessed a total of 10 different scenarios. Bed sheet elasticity and friction were both measured three times, and the bed sheets were changed between measurements.

Statistical analyses

The conceptual model of this study is shown in Fig. 8. The average maximum interface pressure and immersion depth were normalized to the values of the control group (relative value = value of each group/average value of the control group). Comparisons were made using one-way analysis of variance (ANOVA) and Tukey's multi-comparison test to determine differences in maximum interface pressures. Multiple linear regression analysis was performed to evaluate the independent predictors of maximum interface pressure. Stepwise multiple regression analysis was used; the dependent variables were maximum interface pressure, and the independent variables were bed making method, bed sheet elasticity, static friction, and dynamic friction. Pearson's product–moment correlation coefficient (r) was used to examine the correlation between immersion depth and maximum interface pressure. Data were analyzed using SPSS v19 statistical software (IBM–SPSS, Inc. Chicago, IL, USA).

Results

The one-way ANOVA with Tukey's multi-comparison analyses revealed that the relative maximum interface pressure values were significantly higher than that of the control for the following conditions: cotton sheets with hospital corners ($p = 0.02$); polyester sheets with no corners ($p = 0.01$); cotton sheets with no corners ($p = 0.003$); and polyester fitted sheets ($p = 0.002$) (Fig. 9).

The results of the comparisons of bed sheet elasticity and friction comparisons are shown in Table 2. Stepwise multiple regression analysis revealed that the maximum interface pressure was negatively correlated with bed sheet elasticity (width and length; $R^2 = 0.74$ and $p < 0.01$). A

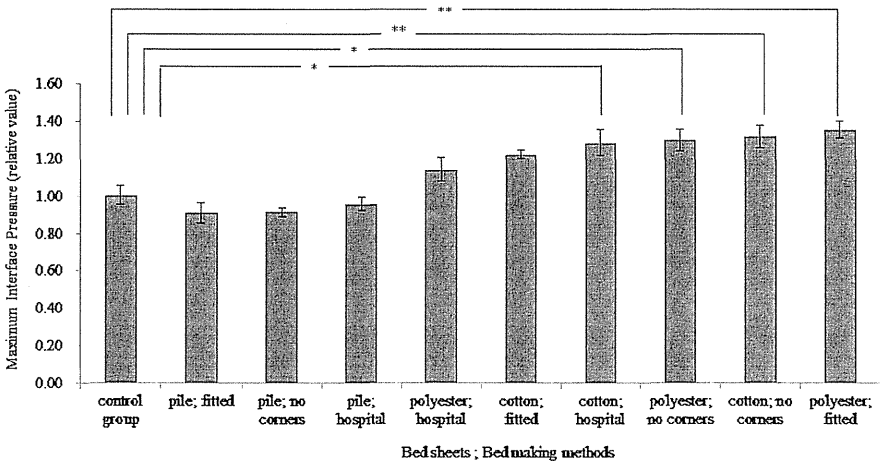

Figure 9 Difference in maximum interface pressure. Note. The average maximum interface pressure was normalized to the values of the control group (relative value = value of each group/average value of the control group). $^*p < 0.05, ^{**}p < 0.01$.

Table 2 The results of bed sheet elasticity and friction.

Bed making	Bed sheets	Bed sheet elasticity with test piece length cut parallel to		Coefficient of friction	
		Width (cm)	Length (cm)	Static	Dynamic
Hospital corners					
No corners	Cotton	0.33 ± 0.05	1.30 ± 0.08	0.53 ± 0.00	$0.06 \pm 96 \times 10^{-5}$
Fitted sheets corners	Cotton	0.37 ± 0.05	1.20 ± 0.08	0.53 ± 0.00	$0.06 \pm 96 \times 10^{-5}$
Hospital corners					
No corners	Polyester	0.73 ± 0.05	1.70 ± 0.08	$0.28 \pm 78 \times 10^{-4}$	$0.05 \pm 48 \times 10^{-5}$
Fitted sheets corners	Polyester	1.07 ± 0.09	2.37 ± 0.09	$0.28 \pm 78 \times 10^{-4}$	$0.05 \pm 48 \times 10^{-5}$
Hospital corners					
No corners	Pile	12.80 ± 0.43	17.17 ± 0.21	0.49 ± 0.00	$0.06 \pm 83 \times 10^{-5}$
Fitted sheets corners	Pile	15.87 ± 0.31	16.50 ± 0.33	0.49 ± 0.00	$0.06 \pm 83 \times 10^{-5}$

Note. Value is mean ± SD.
Bed sheet elasticity and friction were both measured three times.

statistically significant negative correlation was observed between immersion depth and maximum interface pressure (Pearson's correlation coefficient: $r = -0.40$ and $p = 0.04$; Fig. 10)

Discussion

Previous studies have suggested that bed making methods and bed sheet materials may influence pressure distribution [5–7]; however, until now, no study has compared the effects of different bed making methods and bed sheet materials on the support surface with the aim of reducing the hammock effect.

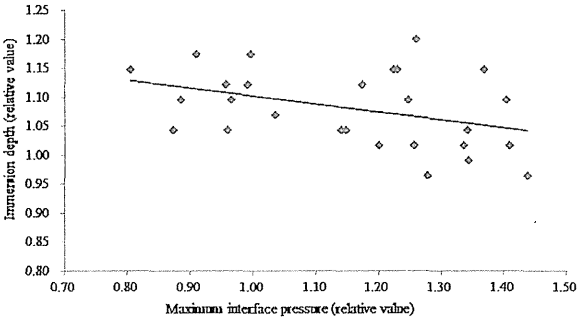

Figure 10 Relationship between maximum interface pressure and immersion depth. Note. The average maximum interface pressure and immersion depth were normalized to the values of the control group (relative value = value of each group/average value of the control group). The data was included all combinations of bed sheets and bed making methods. Pearson's correlation coefficient and the corresponding p-values for this correlation were $r = -0.40$, and $p = 0.04$, respectively.

Our findings showed that bed sheet elasticity influenced the pressure distribution on the support surface and that several of the combinations tested here produced greater maximum interface pressures than the control method (Fig. 9). Further, bed sheet material had a significantly greater influence on pressure distribution than did bed making method, and increasing bed sheet elasticity reduced the maximum interface pressure. These findings support our hypotheses that it is possible to reduce maximum interface pressure using stretchable bed sheets (e.g., pile). Statistical analyses showed that maximum interface pressure and immersion depth were significantly negatively correlated (Fig. 10), which indicates that bed sheets which can be stretched by the buttocks reduce maximum interface pressure.

The results of the present study showed that friction and bed making method do not significantly reduce maximum interface pressure, although the hammock effect can be reduced through the use of stretchable bed sheets on the support surface.

One limitation of this study is that the anatomical model and loading device were in the supine position; however, in the clinical setting, the patient's head is often raised. Second, the anatomical model employed in this study was created to mimic an elderly bedridden patient with extremely bony prominences; therefore, these results should be cautiously applied to other body types. Nonetheless, the results of the present study clearly showed that bed sheets with greater elasticity can better protect patients from the hammock effect.

Conclusions

Several combinations exhibited greater maximum interface pressures than the control method, which did not employ bed sheets and thereby inhibited the pressure distribution on the support surface. Bed sheet elasticity was shown to affect the pressure distribution on the support surface significantly; therefore, the use of stretchable bed sheets may effectively reduce maximum interface pressures.

Conflict of interest statement

All authors took part in design, data collection, analysis and drafting, and approved the submission. The authors state that no financial and/or personal relationships exist with other people or organizations that have inappropriately influenced our work.

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Nutrition-related status and granulation tissue colour of pressure ulcers evaluated by digital image analysis in older patients

- **Objective:** Granulation tissue colour may be an indicator for nutritional assessment in pressure ulcer (PU) care. This study evaluated the relationship between nutritional status, anaemia and diabetes, and granulation tissue colour of PUs by colour analysis of digital photographs in the clinical setting.
- **Method:** The cross-sectional study included 42 older patients with 51 full-thickness PUs from 10 institutions. Patient demographics, wound status, nutritional status and dietary intakes were obtained from medical charts. From a wound image, the granulation red index was processed by computer software and the proportion of pixels exceeding the threshold intensity of 80 for the granulation tissue surface (%GRI80) was calculated.
- **Results:** Haemoglobin levels were positively associated with %GRI80 levels (p=0.007) in the crude model, but not in the adjusted model (p=0.260). The interaction term between diabetes and protein intake was significantly associated with %GRI80 levels in the adjusted models (p=0.010). At protein intakes of 0.95 g/kg or higher, diabetic wounds exhibited lower %GRI80 levels than non-diabetic wounds (p=0.002). At protein intakes of less than 0.95 g/kg, %GRI80 levels did not differ between diabetic and non-diabetic patients (p=0.247). Protein intakes of 0.95 g/kg or higher were associated with higher %GRI80 levels in non-diabetic patients (p=0.015), but not in diabetic patients (p=0.127).
- **Conclusion:** Granulation tissue colour, evaluated by the objective and quantitative analysis of digital photography, is related to haemoglobin level, diabetes and dietary intakes in clinical settings.

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anaemia; diabetes; diet; nutritional assessment; granulation tissue colour; pressure ulcers

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Malnutrition and nutrition-related complications such as anaemia and diabetes are frequently observed in individuals within the frail older population with existing pressure ulcers,[1] and is attributed to the failure of wound treatment[2] and increased medical costs.[3] These complications are detrimental factors related to impaired PU healing both in experimental and clinical settings, in terms of prolonged inflammation and infection, increased wound area, poor granulation tissue formation and decreased neovascularisation.[4,5] Nutritional management including oral nutritional supplements containing high energy and protein is generally provided for malnourished patients to promote PU healing.[6,7]

One of the challenges in nutritional care for PUs is the methodology to assess directly the effects of nutritional support on PU healing. Current indicators, such as systemic nutritional status and wound characteristics,[6,7] may not be sensitive enough to monitor whether nutrients can be supplied to the wound site. Assessment of systemic nutritional status such as weight, serum protein level, clinical status and dietary intakes alone may be insufficient to manage wound healing because changes in nutritional status do not always correlate with wound healing.[7,8] Furthermore, nutritional requirements to maintain systemic metabolism, such as energy and protein intakes, differ by wound severity.[9] These results indicate that the adequacy of nutritional care should be evaluated by the degree that nutrients can be delivered and metabolised at the wound site in PU care. By contrast, the reduction of ulcer size and clinical severity using the structured tools may not have the adequate level of sensitivity needed to assess nutritional effects because various non-nutritional factors such as pressure, shear or infection also influence changes in PU status.[10] In addition, some wound indicators are subjective and require more time for changes to become apparent, especially in large PUs.[11,12] Therefore, a validated wound marker reflecting systemic nutritional status is needed.

Granulation tissue colour at the wound surface

may be a marker of nutritional status, as histological studies reported impaired granulation tissue formation or capillary formation with altered colour in malnourished rats.[13,14] Traditionally, granulation tissue colour has been used by practitioners to assess the quality of granulation tissue formation in clinical settings.[15] However, the effects of nutritional factors on granulation tissue colour remains unclear because of the lack of a validated method for colour evaluation. Granulation tissue colour has only thus far been evaluated subjectively, described using terms such as 'beefy red', 'pink' or 'pale' by clinicians, thus compromising its reliability. We have developed a novel method using digital photography to quantify the granulation tissue red colour of PUs, expressed as the granulation red index (GRI; Fig 1).[16,17] This method is reliable, objective and noninvasive for patients, and is easily available using general commercial software. It has been shown that the GRI is associated with blood haemoglobin levels, exudate hydroxyproline levels and wound healing.[16,17]

The purpose of this pilot study was to evaluate the relationship between nutrition-related status and granulation tissue colour for PUs by using the objective GRI method in the clinical setting. This study explores the nutrition-related factors including malnutrition, glycaemic control and anaemia status, which would be potentially associated with increased red colouration of granulation tissue.

Methods

Study design

This is a pooled analysis of cross-sectional surveys conducted between 2007–2008 and 2010–2011 at 10 institutions in total. All surveys were conducted based on the same protocol. All patients who had at least one full-thickness PU were recruited. Wounds were excluded if surfaces were completely covered by necrotic tissue or skin graft, were bleeding, or had a wound bed that was difficult to evaluate for reasons such as tunnelling. Also, patient records lacking data on age, sex and dietary intake were excluded. The institutions recruited by snowball sampling and included two university hospitals, six community hospitals, one long-term care hospital, and one nursing home. Patients received standard care for PUs based on the Japanese guidelines and received usual nutritional care planned by each local setting. The

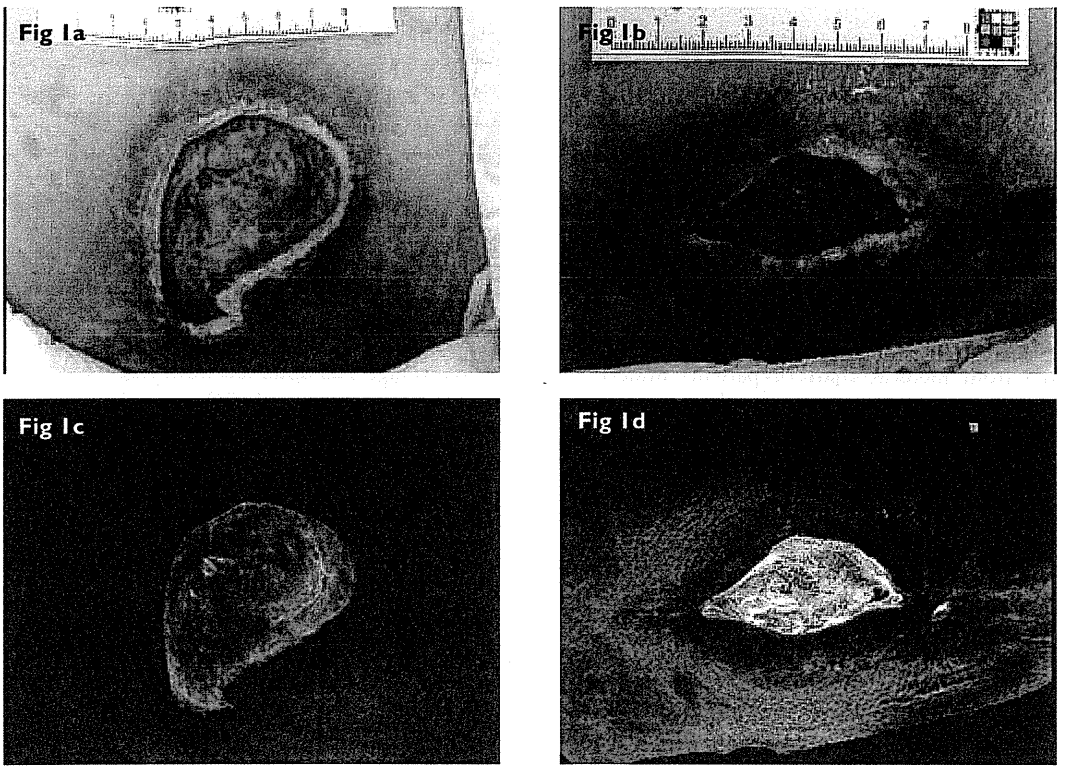

Fig 1. Representative cases of granulation red index (GRI) (a, b): Pressure ulcers with clinically poor and good granulation tissue. (c,d): Images representing the GRI for each wound. The %GRI80 was the proportion of pixels exceeding the threshold intensity of 80 on the granulation tissue. The %GRI80 levels were 47.3% (c) and 97.1% (d).

study protocol was approved by the Ethical Committee of the Graduate School of Medicine, University of Tokyo (#2691). Written informed consent was obtained from all patients.

Data collection

Patient demographics including age, sex and comorbidities were collected from medical charts. Comorbidities were evaluated by the Charlson comorbidity index.[18] The total score (range 0–30) also was calculated with higher value indicating increased degree of disease burden.

For wound assessment, wound, ostomy and continence nurses at each institution evaluated wound location and the total score of the DESIGN-R tool. The DESIGN-R tool was developed to evaluate PU severity and to monitor the wound healing process using seven parameters: depth, exudate, size, inflammation/infection, granulation tissue, necrotic tissue, and pocketing (undermining).[19] The total score (range 0–66) is calculated from six parameters, excluding depth, based on the healing time, and the score of >18 indicates severe PUs mostly taking more than 3 months to heal.[20] The depth score was assessed separately from the total score, and was ranked as follows: persistent redness (d1), dermal wounds (d2), wounds extending to the subcutaneous tissue (D3), wounds extending to muscle tissue (D4), wounds extending to bone (D5), and unstageable wounds (DU). The predictive validity and inter-rater reliability of the DESIGN-R tool have been confirmed by previous studies.[19,20]

Nutrition-related status was assessed by anaemia status, acute-phase proteins, glycaemic control, anthropometry and nutritional intake. Blood and biochemical data, including levels of haemoglobin, serum albumin, serum C-reactive protein, pre-albumin, plasma fasting glucose and HbA1c, were collected from medical charts if patients underwent blood sampling within a week. The height and weight within a month were assessed from a medical chart, and body mass index (BMI) was calculated.

Nutritional intakes were evaluated from nursing records for three consecutive days from the day of recruitment. Patient records contained data on the proportion of daily nutritional intake of hospital diets including each meal, nutritional supplements and infusions. In addition, data on the energy and protein contents of each meal were collected from the dietary menus of each hospital. For patients who received nutrients enterally and parenterally, the content and volume of all supplements and infusions were recorded. Daily energy and protein intakes were calculated and expressed per kg of body weight. In order to evaluate the adequacy of dietary intakes on wound status, intakes were classified by the average requirements as shown in previous studies: 30 kcal/kg of energy intake meeting total energy expenditure[21] and 0.95 g/kg of protein intake meeting nitrogen balance.[9]

Wound photography and digital image analysis

The detailed protocol of wound photography and the subsequent image analysis was described in the previous study.[16] Briefly, all PUs were photographed by one of two researchers (I.S. and S.J.) using a digital point-and-shoot camera (Lumix, Panasonic Co., Osaka, Japan). The camera was set to greater than 2048×1536 pixels using the macro mode, automated white balance and automated ISO sensitivity. A flash was not used except when in an extreme underexposure environment. A commercially available reference colour chart with nine calibrated colours (Casmatch, Bear Medic Co., Tokyo, Japan) was placed next to the surrounding skin. The settings of camera were the same as the previous study. During the procedure, patients lay down on their bed in lateral position. The distance between the wound and the camera was approximately 30cm, and may vary according to wound size.

The obtained photographs were processed by digital image analysis, which consisted of colour calibration and image calculation (Fig 1). The colour calibration can standardise the brightness and contrast of photographs taken under different conditions. Colour calibration was conducted according to the standard protocol of the colour chart by image-editing software (Photoshop 6; Adobe Systems Inc., San Jose, CA, USA). The dropper tool was used to set the level of three standard colour markers, including highlight, shadow and gamma.

Image calculation for the GRI, which reflected the degree of redness, was performed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). After the red (R) and green (G) channels of the digital colour images were transformed logarithmically, the image was obtained from (logR–logG) by the image calculator tool. Subsequently, another calibration was applied to the image, in which the intensity of the whole image was multiplied by a factor given by 150/(the mean intensity of the red colour marker). Through this process, the intensity of the red colour marker was further standardised and the intensity of any region in an GRI image was expressed as a relative value.

To calculate the colour indicators, a researcher manually selected the region of granulation tissue using a freehand tool. The areas of non-granulation tissue, defined as areas with localised slough, necrotic tissue, bleeding and exposed subcutaneous fat, fascia, or bone, were excluded. In the region of interest—i.e. the granulation tissue area—the %GRI80 was calculated, which represents the proportion of pixels exceeding the threshold intensity of 80 for the total number of pixels on the granula-

Table 1. Correlations between granulation tissue colour and continuous variables

			Model 1*		Model 2*	
Variables	**n**	**Mean (SD)**	**r†**	**p-value**	**r†**	**p-value**
Age (yrs)	42	81.3 (8.9)	0.094	0.554	−0.004	0.982
Charlson comorbidity score	42	3.2 (2.3)	−0.205	0.192	−0.156	0.324
Haemoglobin (g/dL)‡	40	9.9 (2)	0.392	0.013	0.247	0.125
Albumin (g/dL)	42	2.8 (0.5)	0.263	0.092	0.199	0.206
C-reactive protein (mg/dL)	42	2.7 (3)	−0.143	0.367	−0.058	0.717
Pre-albumin (mg/dL)‡	26	15.1 (6)	0.08	0.697	0.022	0.916
Plasma fasting glucose (g/dL)‡	37	124 (44.7)	−0.153	0.367	−0.211	0.211
HbA_1c (%)‡	14	5.8 (1.4)	−0.068	0.818	−0.119	0.685
Body mass index (kg/m^2)	42	18.6 (3.7)	−0.172	0.277	0.081	0.608
Energy intake (kcal)	42	1159.2 (367.7)	0.226	0.15	0.247	0.115
(kcal/kg)	42	29.5 (10.5)	0.185	0.24	0.011	0.944
Protein intake (g)	42	47.6 (17.7)	0.251	0.109	0.252	0.108
(g/kg)	42	1.2 (0.5)	0.228	0.146	0.048	0.762

*Model 1 included more severe pressure ulcers and Model 2 included less severe pressure ulcers for patients with multiple ulcers.
†Correlation coefficients between each variable and granulation tissue color by %GRI80. ‡Data are lacking because of no records in the medical charts.

tion tissue surface. The reliability, concurrent validity and predictive validity of %GRI80 and its cutoff points were reported in previous studies; inter-rater reliability for calculation of GRI value in the same photograph was almost optimal.[16] Moreover, the %GRI80 could predict PU healing indicated by the area under the receiver operating characteristics curve for wound healing of 0.68, which was greater than that of other cutoff points.[16,17]

Statistical analysis

Descriptive data are expressed as mean (±SD) for continuous variables or n (%) for categorical variables. Correlations were evaluated by Pearson's correlation coefficient. Differences in granulation tissue colour between categorical independent variables were evaluated by a t-test. If a patient had multiple ulcers, the analyses were separately performed by including more severe ulcers (model 1) or less severe ones (model 2) for a patient, defined by the DESIGN-R total score.

Multivariate analysis to evaluate relationships between granulation tissue colour and independent variables were then conducted by a linear mixed model that included multiple PUs as a repeated variable with an unstructured covariance (SAS PROC MIXED). All PUs from a patient were included into analysis in order to examine the relationships between tissue colour and variables of systemic status independently of wound status or locations. An interaction term between independent variables was also assessed. If an interaction term was significant, the stratified analyses were conducted with least square means among the levels of one variable in each strata of the other variable by CONTRAST statement. Covariates for the adjusted models included patient characteristics, wound location and severity because wound severity or healing process may inherently affect granulation tissue colour.[16] All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at $p<0.05$.

Results

All together, 59 patients with 68 full-thickness PUs met the inclusion criteria and participated in this study. Of these, 17 patients were excluded from the analysis because of wounds covered by necrotic tissue (n=7) or tunneling (n=10). A total of 42 patients with 51 PUs were eligible for analysis. Nine patients had two full-thickness PUs. Thirty patients (71.4%) were recruited from long-term care settings. All patients were immobile. The nutritional route was 31.0% oral feeding, 42.9% enteral nutrition and 26.2% parenteral nutrition. The mean age (±SD) was 81.3 (±8.9) years old and the mean Charlson comorbidity score was 3.2 (±2.3; Table 1). Mean serum albumin levels were 2.8 (±0.5) g/dL. Mean BMI was 18.6 (±3.7) kg/m^2 and 20 patients (±47.6%) showed BMI<18.5. Twenty-six patients (61.9%) were female and nine patients (21.4%) were diagnosed with diabetes (Table 2). The mean DESIGN-R total score was 29.0 (±11.2). The most frequent category of depth of wound was D4 (n=27, 52.9%), followed by D3 (n=18, 35.3%). The most frequent location of wounds was the sacrum (n=31, 60.8%), followed by the greater trochanter (n=11, 21.6%). The mean %GRI80 was 48.7 (±29.5). The mean (min–max) number of pixels for wound area in photographs

was 168824.9 (13905–1325543).Mean (±SD) level of %GRI80 was 48.7% (±29.5).

Univariate correlations between %GRI80 levels and independent variables are shown (Table 1). Haemoglobin levels (p=0.013) were positively associated with %GRI80 levels in model 1, but were not significant in model 2. Serum albumin levels and nutrient intakes per body weight were positively, but not significantly, associated with %GRI80, only in model 1. Energy intake was associated with protein intake (r=0.92, p<0.001). Patients with diabetes showed lower %GRI80 levels compared with non-diabetic patients in model 1 (p=0.006); model 2 showed a strong tendency for reduced %GRI80 levels in diabetic patients also (p=0.075, Table 2). When protein intake was dichotomised by the average requirement, %GRI80 levels tended to be higher at protein intakes >0.95g/kg in models 1 and 2 (p=0.072 and 0.094, respectively). When energy intake was dichotomised by 30 kcal/kg, there was no significant difference in the %GRI80 levels.

Before the multivariate analysis, the multicollinearity among variables was checked. Because serum albumin levels were closely associated with haemoglobin levels, only the latter variable was included, based on the previous results.[16] For the same reason, only protein intake, not energy intake, was included at first. In the multivariate analysis, haemoglobin levels were positively associated with %GRI80 levels (β=5.7, p=0.007) in the crude model (Table 3). This association was attenuated to a non-significant level in the adjusted model including other demographic and wound variables (β=3.5, p=0.260). Diabetes and protein intake were not independently associated with %GRI80 levels, but their interactions were significantly associated in the crude (p=0.002) and the adjusted models (p=0.010).

Subsequently, we explored the relationship between diabetes, protein intake and %GRI80 levels (Fig 2). Diabetic patients with protein intake of 0.95g/kg or higher showed lower %GRI80 levels than non-diabetic patients (p=0.002). In diabetic patients with protein intake less than 0.95 g/kg, %GRI80 levels did not differ between diabetic and non-diabetic patients (p=0.247). On the other hand, protein intakes of 0.95 g/kg or higher were associated with higher %GRI80 levels in non-diabetic patients (p=0.015), but not in diabetic patients (p=0.127). If protein intake was replaced by energy intake (cutoff; 30 kcal/kg), there were similar associations of %GRI80 levels with haemoglobin levels (p=0.040) and the interaction term between diabetes and energy intake (p=0.049) in the crude model. There were no significant associations in the adjusted model (p=0.348 for haemoglobin levels and p=0.079 for the interaction between diabetes and energy intake).

Table 2. Differences in granulation tissue colour according to categorical variables

			Model 1*		Model 2*	
Variables	**Categories**	**n**	**Mean (SD)**	**p-value**	**Mean (SD)**	**p-value**
Sex	Male	16	56 (29.1)	0.277	56.5 (29.4)	0.201
	Female	26	45.4 (30.8)		44.1 (30.4)	
Congestive heart failure	without	30	47.4 (31.4)	0.615	45.9 (31)	0.331
	with	12	54.4 (27.8)		56.1 (28.4)	
Cerebral vascular accident	without	20	45.8 (25.2)	0.468	47.2 (23.7)	0.736
	with	22	52.7 (34.4)		50.4 (36.2)	
Dementia	without	31	51.5 (29.3)	0.463	51 (28.8)	0.444
	with	11	43.6 (33.4)		42.7 (34.8)	
Pulmonary disease	without	27	53.2 (28.7)	0.283	53.5 (29.5)	0.187
	with	15	42.6 (32.8)		40.5 (30.9)	
Diabetes	without	33	54.3 (31.6)	0.006	53.2 (31.2)	0.075
	with	9	31.6 (15.7)		32.9 (20.9)	
Paraplegia	without	31	49.7 (27.7)	0.916	48.9 (27.7)	0.974
	with	11	48.6 (38.1)		48.6 (38.1)	
Cancer	without	35	51.4 (28.8)	0.340	49.6 (29.3)	0.719
	with	7	39.3 (37.6)		45.0 (37.2)	
Energy intake (kcal/kg)	<30	25	47.9 (30)	0.698	50.8 (29.2)	0.615
	≥30	17	51.6 (31.4)		45.9 (32.4)	
Protein intake (g/kg)	≥0.95	15	38.2 (27.3)	0.072	38.3 (28)	0.094
	≥0.95	27	55.7 (30.4)		54.7 (30.4)	

*Model 1 included more severe pressure ulcers and Model 2 included less severe pressure ulcers for patients with multiple ulcers. SD; standard deviation.

Table 3. Multivariate analysis for granulation tissue colour and associated factors

Patient	**Crude model***		**Adjusted model†**	
Variables	**F**	**p-value**	**F**	**p-value**
Haemoglobin levels	8.17	0.007	1.31	0.260
Diabetes	1.57	0.219	0.4	0.529
Protein intake (<0.95 g/kg vs. ≥0.95 g/kg)	0.69	0.41	0.03	0.862
Interaction between diabetes and protein intake	10.6	0.002	7.33	0.01

*Multivariate linear mixed model included multiple pressure ulcers as the repeated variable.
†Adjusted model included age, sex, co-morbidity score, pressure ulcer location and severity.

Discussion

This pilot study using digital image analysis of granulation tissue colour found that three nutrition-related characteristics, including haemoglobin levels, diabetes and nutritional intake, closely influenced the degree of red colouration in the granulation tissue of PUs. Although clinicians generally regard granulation tissue formation as a target

for nutritional support in PU care,[4,22] the relationship has not been well established because of the lack of a validated assessment for granulation tissue. Digital image analysis of granulation tissue colour is a possible marker from nutritional perspective besides the established validity for collagen concentration and wound healing of PUs.[16,17]

Higher haemoglobin levels were related to a higher degree of red colouration of granulation tissue in the crude model. This result is consistent with the notion that red colouration of the skin is a reflection of the concentration of haemoglobin.[23,24] Our results may indicate that even blood haemoglobin affects the tissue colour of the wound. In granulation tissue, the red colouration can be derived from the angiogenesis of blood vessels penetrating into the wound site and oxygen saturation of the tissue.[23,25] Blood haemoglobin levels may affect oxygen delivery to tissue, though we did not directly measure tissue oxygen levels. Interestingly, the multivariate model including wound severity attenuated the influence of haemoglobin, indicating that haemoglobin's influence on tissue colour is partially through wound severity because of the cross-sectional design; patients with decreased haemoglobin levels or anaemia may develop more severe PUs,[26,27] resulting in poor granulation tissue. A prospective study is required to evaluate how much a nutritional intervention to improve systemic haemoglobin levels can contribute to the improvement of local granulation tissue colour.

Diabetes and nutrient intake in combination were related to granulation tissue colour; the association of one factor is dependent on the level of the other factor. If protein intake met the requirement (0.95g/kg for Japanese patients),[9] diabetes was associated with decreased levels of granulation tissue colour. On the other hand, diabetes did not affect tissue colour if the protein intake requirement was not met. These findings suggest that diabetes has a marked effect on granulation tissue under adequate nutritional support, while poor nutritional support may mask the effects of diabetes on granulation tissue formation. Diabetes compromises various aspects of wound healing, including decreased levels of angiogenesis, nitric oxide synthesis, extracellular matrix formation, expression of several growth factors, increased glycation endproducts, susceptibility to colonisation or infection of bacteria, and latent biofilm covering the tissue surface.[28-30] The effects of such factors may appear on granulation tissue and alter the colour of the wound surface. Conversely, other biochemical markers of diabetes, such as plasma glucose levels or HbA1c, are not associated with granulation tissue colour. Besides the different duration that each marker reflects, oth-

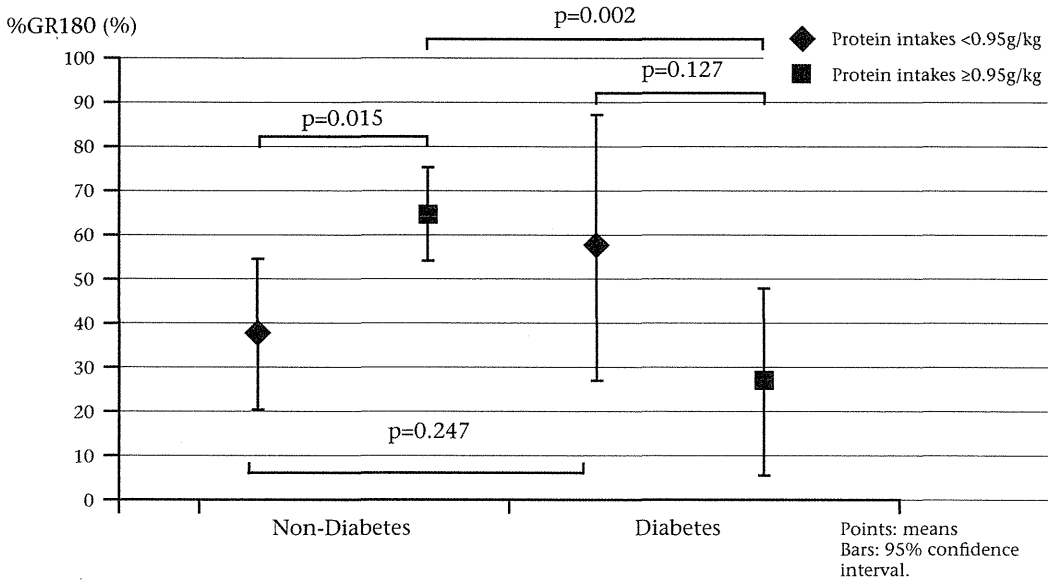

Fig 2. The %GRI80 levels according to diabetes and protein intakes in the adjusted linear mixed model. P values for each pair were obtained by the CONTRAST statement of the model. The points represent mean values and the bars indicate the 95% confidence intervals. Protein intakes were dichotomised by the requirement (0.95g/kg).

er mechanisms, except for hyperglycaemia, may influence the results. In addition, the small sample size decreased statistical power of the results related to HbA1C, which was not regularly measured for some non-diabetic patients in long-term care settings. Future studies investigating detailed aspects of the above hypothesised mechanism will be required to explore the specific care for diabetic PUs.

In non-diabetic patients, meeting the average protein requirement was associated with a higher degree of granulation tissue colour. In animal studies, malnutrition, especially protein deficiency, impaired wound healing through delayed wound healing process, poor collagen synthesis, and impaired angiogenesis.[13,31] Nutritional support has the potential to reverse the impaired wound healing process,[7,14] enhancing granulation tissue colour during the proliferative phase. Our data show that protein intake may have a certain threshold for increased granulation tissue colour because the continuous form of the variable showed weaker univariate correlations. Therefore, the priority in nutritional care for the granulated wound may be the attainment of 0.95g/kg of protein. The %GRI80 may be a useful marker to monitor nutritional effects of enhanced protein intake in wound care for non-diabetic patients.

By contrast, protein intake was not related to granulation tissue colour for diabetic patients. Granulation tissue colour may have limited usage in nutritional assessment for diabetic patients. One possible explanation is that the impaired microcirculation associated by diabetes may inhibit the flow of nutrients into the wound site.[32] Also, nutrient usage may be lowered by metabolic changes in proliferating cells. This hypothesis is supported partly by a previous study reporting that the metabolic cycle to produce energy was impaired by altered enzyme activity in diabetic granulation tissue and muscle.[33] Nutritional management for diabetic PU is challenging because high energy and protein supplementation, which were generally recommended for wound healing, should be restricted for maintaining glycaemic control or renal function. A research study reported that oral nutritional supplementation for diabetic patients failed to improve wound status.[34] It is necessary to reveal detailed nutrient metabolism and requirements in granulation tissue formation for diabetic PUs.

Energy intake is another important nutritional factor for PU healing.[4] Because energy and protein intake were highly correlated with each other in this cross-sectional study, the different roles of protein or energy for granulation tissue were not fully revealed. A similar but weaker association with tissue colour was obtained for energy requirement than the protein requirement in the multivariate analysis. Because participants were almost immobile with low physical activity levels, the validity of energy requirement may be lowered in this population compared with the protein requirement.

The results of univariate correlations differed by wound severity within a patient. This result indicated that besides nutritional variables, granulation tissue colour would be affected concurrently by non-nutritional factors such as wound severity or biofilm. Granulation tissue colour will be strongly affected by such factors at the early stage of wound healing such as during the inflammatory phase whereas it may also be lowered by re-epithelialisation or diminished blood vessels during maturation periods.[25] In other words, the influence of nutritional factors will appear strongly on granulation tissue colour during a suitable period of wound healing. Further studies will be required to monitor longitudinal change of granulation tissue colour and nutritional status along with wound healing process.

The GRI has several advantages in nutritional assessment for PU management. Firstly, it can quantitatively and reliably evaluate the quality of granulation tissue colour in clinical settings.[16] Traditional colour evaluations based on visual assessment by each clinician may result in low inter-rater reliability.[11] One reason for the low reliability may be misinterpretation of the ambiguous colour of granulation tissue under different luminance levels. Clinical settings will produce considerable variations in brightness levels because of differences in the locations of beds, rooms and/or weather, unlike in the contained laboratory setting. Under this condition, it is difficult to fully standardise environmental factors. Using the GRI, clinicians in a multidisciplinary PU team can perform nutritional management based on a common assessment for granulation tissue. Secondly, the GRI enables clinicians to evaluate the whole area of the wound surface as a two dimensional image. In dermatology, objective and quantitative methods for evaluating skin colour using reflectance spectrophotometer or tristimulus colourimeter are widely used, especially for the evaluation of skin erythema.[24] Such devices, however, can evaluate only a limited narrow area of the broad and heterogeneous wound surface. The GRI can distinguish the influence of systemic factors including nutritional status on wound from that of other local ones such as interface pressure because the effect of systemic nutritional status may appear over the whole wound surface.

Study limitations

A limitation of this study was the relatively small number of eligible patients. Besides the low prevalence of full-thickness PUs in Japan, the strict inclusion criteria about wound status to accurately assess and take pictures for granulation tissue may affect the statistical power. Our results may also be affected

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by incomplete data collection or measurement errors in some variables because the majority of data was collected from medical charts in each setting. Furthermore, the majority of patients was recruited from a long-term care setting and was severely malnourished. Because malnourished patients with severe PUs might have received enhanced nutritional support, the reverse causal relationships may affect the results in the observational study. By similar reasoning, the local treatment for wounds, which was determined by wound severity, could not be included as covariates in the multivariate analysis. Because this is the cross-sectional design study, the causal relationships were not verified. For example, severe PUs may impair granulation tissue colour caused by edema or inflammation, which can affect dietary intake or nutritional status.[9] A prospective multicenter cohort study or an intervention study with nutritional management including a larger number of participants will be necessary to further reveal the contribution of nutritional determinants for the granulation tissue colour of PUs. Finally, the results of this study should be carefully applied to other populations because our study participants consisted only of Japanese people with similar skin tones. However, the results might not largely differ between different skin tones because granulation tissue is not covered by skin itself and does not contain melanin.

Conclusion

The GRI method is a relatively simple, non-invasive, objective and quantitative evaluation of granulation tissue colour using digital photography. The current study using this method, though it was a cross-sectional study with several limitations, revealed that granulation tissue colour in PUs was partly influenced by nutrition-related factors, including haemoglobin levels and the combination of diabetes and protein intake. Nutritional management to increase dietary intakes or improve anaemia might be beneficial to promote granulation tissue formation in a non-diabetic population. On the other hand, the factors influencing granulation tissue colour for diabetic PU requires further consideration. It is suggested that the GRI method will be a novel marker to assess nutrition-related status of PU especially in patients without diabetes from the perspective of wound healing. ■

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Guidance statement on appropriate medical services for the elderly

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Preface: need for guidance statement

With the increase in the elderly population, particularly those aged over 75 years,[1] there is an increasing demand for geriatric medicine services. However, providing proper medical care for the elderly remains difficult for care providers. There are several reasons: compared with their younger counterparts, elderly patients tend to have different clinical symptoms of diseases and different responses to treatment as a result of underlying physiological changes associated with aging; elderly patients may have multiple chronic conditions[2–4] and require a higher number of medications, which increases the risk of unexpected drug interactions and adverse drug reactions;[5–8] clinical guidelines specifically developed for elderly patients are still scarce,[9] and the application of clinical guidelines intended for younger patients may not necessarily result in better outcomes for the elderly.[10–12] This guidance statement is aimed at helping care providers understand the basic concepts of geriatric medicine and provide proper medical care for the elderly, avoiding either over- or undertreatment.[13]

How to apply the guidance statement

The guidance statement outlines points to be considered on providing medical care to the elderly and the required basic competencies for care providers. Although the guidance statement was initially developed for physician use, other professions involved in the care of the elderly may utilize the guidance statement. The guidance statement is not intended to replace existing clinical guidelines for specific conditions, but to impart the basic principles underlying geriatric medical care in actual medical settings. We recommend applying the principles set out in this guidance statement when making treatment decisions, particularly when clinical guidelines are not aimed at elderly patients or guidelines are contradictory to each other.

1. Multiple morbidity and heterogeneity of the aged

- Care providers should understand biological, physical and social function, and the living environment.

1.1. There is considerable interindividual heterogeneity in the aging process, and the effects of aging on physical, mental and social function also vary greatly from person to person (aged heterogeneity).[14] The prevalence of many chronic conditions including lifestyle-related diseases increases with aging, and hence elderly persons may have multiple chronic conditions, or "multimorbidity".[2–4] Therefore, in providing medical care to elderly persons, care providers should focus more on their role as a primary care provider to offer comprehensive management, taking into account all relevant medical conditions.

1.2. The elderly have substantial individual differences in physical, mental and social functions, and may present with atypical signs and symptoms when they fall ill.[14–16] It is imperative to keep such heterogeneity in mind and carry out comprehensive geriatric assessment to evaluate physical, mental and social aspects individually.[17–20] In addition, medical and biological factors, as well as social-environmental factors, affect the course of medical conditions in the elderly, which highlights the importance of understanding the living environment, customs, financial situation, family and social relationships in order to weigh such factors and individualize medical care.[21–25]

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1.3. Elderly patients are at high risk of receiving fragmented and redundant medical care from multiple care providers because of multimorbidity.[10,26–28] Conversely, elderly patients are also at high risk of undertreatment because care provision, including admission to facilities and surgical treatment, tends to be limited for reasons of age, and decreased physical, mental and social function.[29–33] Care providers should keep in mind that there exist medical treatments for which beneficial effects in the elderly have been established in clinical trials, and make efforts to provide medical care balancing the benefit against the risk.[34,35]

2. Care towards maintenance and improvement of quality of life

- Care providers should try to maintain and improve quality of life (QOL) by preserving the remaining daily living functions and alleviating symptoms.

2.1. The decline in physiological reserve with aging makes elderly patients vulnerable. Conditions that are usually temporary and do not result in any long-term sequelae in younger patients, such as back pain or pneumonia, can cause long-term adverse outcomes, such as a decline in activities of daily living (ADL) in elderly patients, leading to poor QOL.[36–38] Because complete recovery is hard to achieve once ADL decline,[39,40] it is imperative to prevent diseases that can trigger ADL decline by measures such as fall prevention intervention,[41–44] vaccination programs[45–48] and oral hygiene.[49–51] It is also important to preserve ADL by early mobilization and rehabilitation to restore physical function when the patient has an illness.[52,53]

2.2. Geriatric syndromes;[54] that is, common medical conditions in the elderly, such as dementia, delirium, depression, frailty, sarcopenia, malnutrition, dysphagia, falls, urinary incontinence, constipation, decubitus ulcer and dehydration, frequently cause decreased ADL and poor QOL.[55–57] Comprehensive screening and assessment are required for prevention of these geriatric syndromes, and early detection and treatment are required once they occur. Dementia requires special attention and broad screening for early detection, diagnostic workup at specialized facilities if indicated, and early intervention is crucial.

2.3. Many conditions commonly observed in the elderly are chronic and unlikely to be cured completely.[3] In managing such chronic conditions, it is vital to focus on the alleviation of symptoms rather than futile, intensive treatment aiming towards a complete cure. To preserve and improve QOL, through integrated medical, public health and social welfare services, care providers should provide healthcare including environmental modification, mental health services, nutrition management and oral care in addition to palliative care, in order to alleviate symptoms that could worsen QOL.

3. Healthcare provision in daily life setting

- Care providers should understand the importance of where elderly patients spend their daily life in maintaining their QOL, and should provide support to enable elderly patients and their families to choose an appropriate place to live and receive healthcare.
- Care providers should understand issues that may occur during the transition between different healthcare settings and take appropriate preventive measures.

3.1. Care providers should provide comprehensive care in cooperation with Community General Support (*chiiki hokatsu shien*), integrating medical, nursing, long-term care and welfare services, so that an elderly patient can live in a place where they feel comfortable and are able to maintain their QOL.[58] In cases where elderly patients require admission to acute care medical facilities, care providers should initiate discharge support early, to help facilitate their return to their place of residence. Care providers should closely communicate with patients and their family members, and provide support to enable them to choose an appropriate setting where they receive healthcare, when the current healthcare setting is no longer appropriate.[59,60]

3.2. The quality of care may be compromised during patients' transition between different healthcare settings as a result of poor communication between care providers.[61,62] In addition, transition across sites of care is associated with an increased risk of psychological symptoms, such as delirium[63] and disuse syndrome, and subsequent functional decline.[36–38] Care providers should understand these risks associated with healthcare transition, promote communication between healthcare settings and take appropriate preventive measures.[64]

3.3. Care providers should consider medical care provision at long-term care facilities or at home, utilizing medical resources in the community, such as Home-visit Nursing Services (*houmonkango*) and Dementia Support Doctors (*nintishosapo-to i*), as a valid alternative to inpatient or outpatient care.

4. Basic concepts of pharmacotherapy for elderly patients

- Care providers should understand the principles of pharmacotherapy, which require consideration of

risk of adverse drug reactions, medication adherence and patients' priorities of healthcare outcomes, and put the principles into practice.

4.1. Elderly patients are at increased risk of adverse drug reactions.[65,66] Care providers should understand age-related changes in pharmacokinetics and pharmacodynamics,[67,68] and, as a general rule, start medication at the lowest feasible dose and titrate the dose upward slowly and gradually, monitoring the treatment response and adverse reactions to medication.[69,70] Polypharmacy, or use of multiple medications, should be avoided as much as possible, because polypharmacy, particularly when the number of medications is six or more, is associated with an increased risk of unexpected drug–drug reactions and adverse drug reactions.[6,71–76] In addition, several medications are known for their tendency to cause adverse drug reactions in elderly patients,[77,78] and particular attention should be paid to the indication and management of these medications.[79]

4.2. Various factors contribute to poor medication adherence, including cognitive impairment, fine motor impairment, dysphagia, limited access to pharmacy services, financial problems and polypharmacy.[80] Care providers should collect detailed information on medication adherence from patients as well as their family members and caregivers on a regular basis, and screen for factors that could lead to poor adherence in order to intervene and modify such factors, and prevent poor adherence.[81,82] Care providers should simplify medication regimens by use of combination drugs, single-dose packaging or changes in dosage forms.[83]

4.3. Although elderly patients often have multiple chronic conditions and geriatric syndromes, clinical guidelines for such elderly patients are still scarce.[9] However, application of clinical guidelines intended for younger patients may not necessarily result in good outcomes in the elderly.[10–12] It may also be inappropriate to consider pharmacological treatment separately for each medical condition and symptom. Care providers should evaluate the indications for medications and decide the priority of each medication depending on the therapeutic goals for patients and their family, comprehensively taking into consideration individual patients' medical conditions, their severity, organ function, physical, cognitive and daily function, and the family situation. Care providers should choose high-priority medications,[84] and consider discontinuing medications with low priority.[66,85,86]

4.4. Care providers should try non-pharmacological treatment first and avoid pharmacological treatment as long as alternative measures are available.[69,70] Care providers should regularly review medication using patients' medication records to identify all the medications patients take including vitamins, Chinese herbal medicines and over-the-counter drugs.[87,88] Care providers should avoid prescribing new medications if possible when a complete list of medications and dosages is not available. Care providers should understand that the absolute need for medications could alter over time as a result of age-related changes in pharmacokinetics and pharmacodynamics[67,68] or changes in healthcare settings, and should be re-evaluated regularly.[66,89–92]

5. Support for decision making

- Care providers should understand the importance of supporting the decision-making process and achieve a consensus on the treatment plan.

5.1. In geriatric medicine, the therapeutic goals may differ depending on the person's position and values. For example, a study on health outcome prioritization in geriatric medicine showed that the elderly considered effective treatment of diseases and improvement of physical function as the most important goals of care, whereas physicians prioritized improvement in QOL.[93] Therefore, it is essential to support the decision-making process by providing evidence regarding the treatment options and information on prognosis, and help build a consensus on the goals of care in line with values of both patients and their families.[94]

5.2. Care providers should respect and put the highest priority on the patient's personal wishes and values in the process of achieving a consensus on the treatment plan. Even if the patient is not able to express their wishes and values because of cognitive impairment or terminal illness, their family and the medical team should make an attempt to presume the patient's values and reach a decision on the treatment goals that best serve the patient's interests.

6. Providing support for caregivers, such as family members, as well

- Care providers should acknowledge the burden and distress experienced by caregivers, such as family members, and provide appropriate support for them from early on.

6.1. Caregivers experience mental and physical distress in care provision, and are at increased risk of developing depression and experiencing low QOL.[95–98] Therefore, care providers should actively provide information to help caregivers access social resources, such as long-term care services, and

propose interventions, such as respite care, to reduce their burden.[25,99-102] Caregivers should consider making a recommendation for caregivers to receive medical attention if they experience significant mental or physical distress.

6.2. Because of the low birth rate, the rapid aging population and the trend towards a nuclear family, the phenomena called "elderly living alone" in which an elderly person lives alone, "elderly-to-elderly care (*rou-rou kaigo*)" in which an elderly person provides care for another elderly person (usually a spouse) at home and "dementia-to-dementia care (*nin-nin kaigo*)" in which an elderly patient with dementia provides care to another patient with more severe dementia at home, are increasing in number and have become a public concern.[103] Such family situations warrant particular attention, and should prompt care providers to assess the caregiver's ability to provide care and initiate interventions, such as implementing long-term care insurance services.

7. Patient-centered team medicine

- Care providers should recognize that a patient is a part of the care team and provide patient-centered multidisciplinary care.

7.1. Team medicine is defined as "a care delivery system in which medical staff from diverse professional backgrounds work closely together and provide health services appropriate to the needs of patients, utilizing the expertise of each team member, while sharing common goals and information".[104] Team medicine in the care of elderly patients is effective in improving quality of care and safety, and reducing the burden on medical staff.[105-112] Care providers should understand and acknowledge the expertise of other team members from medical, nursing, long-term care and welfare fields, and engage in multidisciplinary team medicine.[113]

7.2. Team medicine should be patient-centered.[113] Care providers should encourage patients and their family members to participate in team meetings in addition to providing counsel and information. The active participation of patients and their family members in the care planning process may improve the quality of care,[114] and subsequently prevent functional decline and admission to acute care facilities.[59,60,115]

Conclusion

As society is facing the challenges of a "super-aged society", healthcare for the elderly is assuming greater importance, but is nonetheless fraught with problems. Inflating healthcare costs threaten to collapse the healthcare system. Opinions from care providers working in clinical settings will be increasingly considered important in order to establish a sustainable healthcare system for the elderly. Close collaboration between care providers, the local community and local government is crucial to foster a life environment conducive to the elderly population. In addition, evidence regarding the efficacy and safety of therapeutic interventions for elderly patients remains scarce, and only basic principles underlying geriatric medical care are presented in this guidance statement. It is paramount to promote clinical research, leading to establishment of evidence-based clinical guidelines.

In the practice of geriatric medicine, advanced medical skills are required to care for elderly patients with multimorbidity and heterogeneous nature in various care settings through multidisciplinary care teams while taking into account patients' values. Ideally, geriatricians with adequate experience and extensive knowledge in the field of geriatrics should provide care for elderly patients. However, the current number of geriatricians will not meet the continuous surge in demand for geriatric care. It is critical to improve the education system to produce more geriatricians, and create a framework to enlighten primary care physicians on the knowledge and skills of geriatric medicine.

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