Poor Nutritional Status on Admission Predicts Poor Outcomes After Stroke
Observational Data From the FOOD Trial
FOOD Trial Collaboration

Background and Purpose—Previous studies suggest that undernourished patients with acute stroke do badly. The data, however, are not robust. We aimed to reliably assess the importance of baseline nutritional status as an independent predictor of long-term outcome after stroke in a large prospective cohort enrolled in the Feed Or Ordinary Diet (FOOD) trial, a multicenter randomized trial evaluating various feeding policies.

Methods—Patients admitted to hospital with a recent stroke were enrolled in the FOOD trial. Data on nutritional status and other clinical predictors of outcome were collected at trial entry. At 6 months, the coordinating center collected data on survival and functional status (modified Rankin Scale). Outcome assessment was done by researchers blinded to baseline assessments and treatment allocation.

Results—Between November 1996 and November 2001, 3012 patients were enrolled, and 2955 (98%) were followed up. Of the 275 undernourished patients, 102 (37%) were dead by final follow-up compared with only 445 (20%) of 2194 patients of normal nutritional status (odds ratio [OR], 2.32; 95% CI, 1.78 to 3.02). After adjustment for age, prestroke functional state, and stroke severity, this relationship, although weakened, still held (OR, 1.82; 95% CI, 1.34 to 2.47). Undernourished patients were more likely to develop pneumonia, other infections, and gastrointestinal bleeding during their hospital admission than other patients.

Conclusions—These data provide reliable evidence that nutritional status early after stroke is independently associated with long-term outcome. It supports the rationale for the FOOD trial, which continues to recruit and aims to estimate the effect of different feeding regimes on outcome after stroke and thus determine whether the association observed in this study is likely to be causal. (Stroke. 2003;34:1450-1456.)

Key Words: clinical trials • nutrition • prognosis • stroke outcome

Malnutrition in hospital patients is a common and often unrecognized problem, especially in the elderly and those who remain in hospital for prolonged periods.1 The reported frequency of malnutrition after stroke has varied from 8%2 to 34%.3 This variation is probably due to patient selection, the definitions of malnutrition, and the method and timing of assessments. In general, these studies included only small numbers of patients (n=494 to 2015), so the estimates of frequency were not only potentially biased but also imprecise. In routine clinical practice, it is not easy to assess stroke patients’ nutritional status for many reasons: A dietary and weight history may not be available if patients have communication problems; other sources of this information may not be available if, as is common, the patient lives alone; simple assessments of weight and height to estimate the body mass index (BMI) may be difficult or impossible in immobile stroke patients; specialized equipment such as weighing beds, hoists, or scales that accommodate wheelchairs may not be available in the stroke unit; and because stroke patients often cannot stand, height cannot be directly measured but must be estimated from the patient’s demi-span or heel-knee length. Fortunately, simpler clinical assessments (“bedside” estimates of the patient size and fat distribution) have been shown to be practical and reliable and can be used to identify most patients with low BMI and abnormal anthropometry.6

Despite these difficulties in assessing nutrition after stroke, there is widespread belief that it may influence recovery. We aimed to establish whether nutritional status early in a patient’s hospital stay is associated with long-term survival and functional status in survivors. Here, we report an analysis of a prospective cohort comprising the first 3012 patients randomized in the Feed Or Ordinary Food (FOOD) trial. This is an international multicenter randomized trial to evaluate different feeding policies in hospitalized stroke patients, which will continue to recruit patients until at least 2004.7

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The Appendix, which can be found online at http://stroke.ahajournals.org, lists all individuals’ contributions.
The views expressed in this article are those of the authors and do not necessarily represent those of the funding bodies.
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The FOOD trial comprises a family of 3 randomized controlled trials that share the same randomization, data collection, and follow-up systems. These trials aim to compare the outcomes of hospitalized stroke patients managed with different feeding policies (Table 1). The trial has broad eligibility criteria. Any patient who is admitted to a participating hospital with a recent (within 7 days) stroke (first ever or recurrent) can be enrolled if the responsible clinician is uncertain of the best feeding policy and the patient or a relative consents to enrollment. Patients with subarachnoid hemorrhage are not included. The national coordinating centers collect follow-up information 6 months after enrollment by researchers blinded to the treatment allocation and baseline data by means of a postal questionnaire or structured telephone interview. If patients were unable to complete these, then the information was collected from a caregiver or proxy. The follow-up aims to establish patient vital status, place of residence, and functional ability on the modified Rankin Scale.

The FOOD trial has been approved by the multicenter research ethics committee in the United Kingdom and the local research committee at each center.

### Methods

The FOOD trial collaboration poor nutrition predicts poor stroke outcomes. The associations between baseline nutritional status, other baseline prognostic factors, survival, and functional status at final follow-up were explored. First, whether patients were alive at 6 months was used as the dependent variable in a logistic regression analysis, with nutritional status and other baseline prognostic factors as independent variables. Whether pa-

#### TABLE 1. Possible Treatment Allocations in FOOD Trials 1, 2, and 3 and the Numbers of Patients Allocated to Each Treatment Group

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Patients who are able to swallow within 30 d of admission are randomised between normal hospital diet until discharge (n = 1155) and normal hospital diet plus oral nutritional supplements until discharge (n = 1165) (3 × 120 mL of 1.5 Kcal/mL supplement per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 2</td>
<td>Patients who are unable to swallow within first 7 days of admission are randomised between early enteral tube feeding (n = 292) (started as soon after enrollment as possible) and delay any enteral tube feeding for at least 7 days (n = 291) (and hydrate using parenteral fluids as required)</td>
</tr>
<tr>
<td>Trial 3</td>
<td>Patients who cannot swallow within the first 30 days of admission, in whom a decision to tube feed has been made (or allocated in Trial 2) are randomised between tube feeding via an NG tube (n = 115) and tube feeding via a PEG tube (n = 117)</td>
</tr>
</tbody>
</table>

Total number allocated in the 3 trials is greater than the number of patients enrolled (n = 3012) because some patients were co-enrolled in >1 trial.

### Statistical Analysis

We plotted Kaplan-Meier survival curves for patients in each baseline nutritional status category. The associations between baseline nutritional status, other baseline prognostic factors, survival, and functional status at final follow-up were explored. First, whether patients were alive at 6 months was used as the dependent variable in a logistic regression analysis, with nutritional status and other baseline prognostic factors as independent variables. Whether pa-
patients were alive and independent at 6 months was modeled similarly. Survival was also modeled with Cox proportional-hazards method, but the results are not shown for brevity. The normal weight group was used as the reference group for comparisons with the undernourished and overweight groups. Age was analyzed as a continuous variable. All other prognostic variables were analyzed as binary variables. No adjustments were made for multiple comparisons.

Results

Between November 1996 and February 28, 2001, 112 hospitals in 16 countries had enrolled 3012 patients; by November 2001, 6-month survival and modified Rankin scores were available for 2955 (98%). The patients’ baseline characteristics are shown in Table 2. Patients were enrolled a median of 5 days (interquartile range [IQR], 2 to 8 days) after stroke onset and 4 days (IQR, 2 to 7 days) after hospital admission. Of the 3012 patients, 279 (9%) were judged as undernourished and 495 (16%) as overweight. The undernourished patients were older and more often lived alone before the stroke than the other groups. The method of nutritional assessment was collected only after the first 664 patients had been enrolled in the pilot phase. It was available in 2295 of 3012 (76%). In total, 1388 patients (60%) had their nutritional status assessed informally (ie, based on simple observation), whereas the remainder were assessed either individually or in combination: 448 (20%) were weighed or had their BMI calculated, 372 (16%) were assessed by a dietitian, 251 (11%) had blood indices, and 48 (2%) had anthropometry. Follow-up data were collected a median of 196 days (IQR, 177 to 224 days) after enrollment.

Table 3 shows the number and proportions of patients in each nutritional group who were reported to have developed a poststroke complication after randomization and before hospital discharge or in-hospital death. Interestingly, the undernourished patients had more pneumonia, other infections, and gastrointestinal bleeds than the others. Those of normal nutritional status were less likely to develop pressure sores than those who were undernourished or overweight.

Of the 3012 patients enrolled, 632 (21%) died before their final follow-up. At final follow-up, 856 (37%) of 2323 survivors (28% of all patients) had a modified Rankin score of 0 to 2 (ie, independent in everyday activities), whereas the remainder were dependent. Of survivors, 1782 (77%; 59% of all patients) were living in their own or a relative’s home.

Figure 1 shows the Kaplan-Meier survival curves for patients in each of the 3 baseline nutritional categories. The patients who were undernourished at baseline appeared to have a poorer survival than those who were normal or overweight; the curves diverge early and continue to diverge throughout the follow-up period. The final outcomes of patients judged to be undernourished, normal, or overweight at baseline are shown in Figure 2. From the logistic regression (see Table 4), the undernourished patients were significantly more likely to die during follow-up than patients of normal weight (odds ratio [OR], 2.32; 95% CI, 1.78 to 3.02).
Although adjusting for patient age, prestroke function, living conditions, and stroke severity (including ability to swallow) weakened this relationship (OR for undernourished compared with normal, 1.82; 95% CI, 1.34 to 2.47), it remained significant (P<0.0001). The overweight patients were not significantly different from the normal-weight patients (OR, 0.83; 95% CI, 0.65 to 1.08; adjusted OR, 0.87; 95% CI, 0.65 to 1.15). Results of the Cox proportional-hazards modeling were similar (results available on request).

Undernourished patients were much more likely to be dead or dependent (ie, a modified Rankin score of 3 to 5) than those who were of normal weight (OR, 2.08; 95% CI, 1.50 to 2.88). Although adjusting for patient age, sex, prestroke function, living conditions, and stroke severity (including ability to swallow) weakened this relationship (OR, 1.52; 95% CI, 1.05 to 2.21), it remained statistically significant (P=0.03). Overweight patients were not significantly different from normal-weight patients (OR, 0.95; 95% CI, 0.77 to 1.18; adjusted OR, 0.91; 95% CI, 0.71 to 1.17). The association between being undernourished at baseline and being dead or dependent at final follow-up was similar in those in whom baseline nutritional status was measured informally and those whose status was formally measured, although even this large study did not have the power to establish whether any differences between these groups were statistically significant. Differences in survival and functional outcomes are

**Figure 2.** Survival and functional status (top) and living circumstances (bottom) of patients at 6 months who were undernourished, normal, or overweight at baseline in the FOOD trials. Bar height corresponds to percentage of patients in each nutritional category with the outcome; actual numbers of patients with each outcome are superimposed on the bars.

**Table 4.** Results of Logistic Regression Showing Relationships Between Baseline Variables, Including Nutritional Status, and 6-Month Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive at 6 mo</th>
<th>Alive and Independent at 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>Wald χ² P</td>
</tr>
<tr>
<td>Model with nutritional status alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undernourished</td>
<td>2.32 1.78–3.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.83 0.65–1.08</td>
<td>0.16</td>
</tr>
<tr>
<td>Model adjusted for other prognostic factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.06 1.05–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Before stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>1.00 0.81–1.24</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Independent in everyday activities</td>
<td>0.64 0.48–0.85</td>
<td>0.0021</td>
</tr>
<tr>
<td>After stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Able to talk and oriented in time, place, and person</td>
<td>0.58 0.46–0.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Able to lift both arms off the bed</td>
<td>0.61 0.48–0.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Able to walk without help from another person</td>
<td>0.71 0.47–1.07</td>
<td>0.10</td>
</tr>
<tr>
<td>Able to swallow</td>
<td>0.28 0.22–0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undernourished</td>
<td>1.82 1.34–2.47</td>
<td>0.0001</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.87 0.65–1.15</td>
<td>0.33</td>
</tr>
</tbody>
</table>
reflected in the different living circumstances of patients who were undernourished at final follow-up compared with the rest of the patients (Figure 2b).

We investigated which of the other prognostic factors that we adjusted for were the main causes of the decreased strength of the association between being undernourished and outcome. The most important factor was the relationship between undernourishment and greater age. The second was the relationship between being undernourished and the inability to walk.

Discussion

We have shown that being undernourished immediately after stroke is associated with reduced survival, functional ability, and living circumstances 6 months later. The relationship, although weakened when adjusted for other prognostic factors, remains statistically significant and raises the possibility that the relationship is causal.

The strengths of this study include the large sample size; recruitment from a wide range of hospitals in many countries, which increases its generalizability; collection of other robust predictive factors, which have been shown to be valid and reliable in several independent cohorts; assessment of outcome by researchers blinded to baseline factors; and virtually complete follow-up at 6 months. Study weaknesses include an inability to establish a dose-response relationship between degree of undernutrition and outcome and lack of standardization of assessment of nutritional status. However, a simple clinical judgment of nutritional status may be both valid and reliable. Nevertheless, the bedside assessment of nutrition used to assess most patients in FOOD may have been influenced by some aspect of patient frailty or comorbidity (such as malignancy) rather than just their nutritional status. However, any such bias might be reduced because other factors that we took into account—ie, age and prestroke dependency—probably reflect patient frailty and comorbidity. In developing our predictive model, we tested whether inclusion of specific comorbidities (diabetes mellitus, ischemic heart disease, cardiac failure, known malignancy, renal impairment, anemia) significantly improved its accuracy; they did not. Thus, one might conclude that our prediction model takes reasonable account of such comorbidities.

The association between baseline nutritional status and outcome that we have observed in this study may actually underestimate the importance of nutrition. First, if our simple classification of nutritional status leads to a proportion of patients being misclassified, then this would lead to an underestimation of the strength of the association between baseline nutritional status and outcome. Second, some of our patients may have become malnourished during hospital admission despite their allocated feeding regime and had poor outcomes. Our finding that inability to swallow was independently associated with poor outcomes (Table 4) would be consistent with this. Several studies have shown that stroke patients’ nutritional status may worsen during hospital admission despite reasonable efforts to provide adequate nutrition. If we had serially measured nutritional status during admission, we may have found an even stronger relationship with outcome.

Previous studies of the association between baseline nutritional status after stroke and outcome have been hampered by small sample sizes, which limit their power to detect an association that is independent of other prognostic factors. Dávalos et al, in a study of 104 patients, showed that malnutrition (serum albumin <35 g/L or triceps skin-fold thickness or mid-arm muscle circumference <10th percentile) was present in 16.3% on admission and 26.4% after 1 week. Malnutrition at 1 week was associated with poorer outcome (dead or Barthel Index score ≤50) at 1 month, more infections and pressure sores, and longer length of stay, but these associations were not statistically significant after adjustment for age, sex, swallowing ability, urinary cortisol, and stroke severity categorized with the Canadian Stroke Scale. Gariballa et al, in a cohort of 201 patients, investigated the association of age, sex, smoking history, modified Rankin score, previous illness, drug use, and serum albumin on admission with 3-month survival. They established that low serum albumin but not BMI, anthropometry, serum iron, and transferrin was significantly associated with decreased survival at 3 months (hazard ratio per 1 g/L, 0.91; 95% CI, 0.84 to 0.99). One can argue to what extent low albumin reflects a patients’ nutritional status rather than the presence of any comorbidity.

Our data showing that pneumonia, other infections, gastrointestinal hemorrhage, and pressure sores are more common in undernourished patients are consistent with previous work and with our understanding of the effects of poor nutrition on the immune system and wound healing. The excess of gastrointestinal hemorrhage in undernourished patients might have several explanations: preexisting gastrointestinal disease (eg, peptic ulceration) that predisposes to undernutrition and hemorrhage, impaired healing of potential bleeding lesions, and adverse effects of enteral tubes inserted to improve nutrition. The excess of complications may help explain some of the observed difference in mortality at 6 months. However, these data on complications need to be interpreted with caution because of our lack of explicit blinding to baseline nutritional status and the lack of uniform definitions of complications with no central verification. The latter point might influence the absolute rates of complications but is less likely to influence the relative rates in different nutritional groups. In addition, the data are potentially confounded by variation in observation period arising from differential lengths of hospital stay, but because the differences in mean length of stay between nutritional groups are small, this is unlikely to be a major confounder.

Definitive evidence that any association between malnutrition and poor outcome is causal must come from randomized controlled trials that establish whether improving nutrition leads to better outcomes. Although a systematic review of randomized controlled trials evaluating nutritional supplementation has suggested that its use may improve survival, there are very few trials in stroke patients. Additionally, the review comprised large numbers of very small single-center trials, many of which were of poor quality. It is quite possible that any estimates of effect size were exaggerated by publication and other biases. One small randomized trial (n=42) has suggested that oral supplementation after stroke improves nutritional parameters,
but it was far too small to demonstrate any effect on survival or functional status.18 Dávalos et al12 argued for the need to establish in a randomized controlled trial whether early enteral feeding improves outcome after stroke, but no completed studies have been reported. Trial 2 of the FOOD family addresses this issue directly. A systematic review of randomized controlled trials comparing the outcomes of dysphagic stroke patients fed via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube included only 2 completed trials.17 Eight of 26 PEG patients (31%) died compared with 14 of 23 control patients (61%). This review provided an implausibly large estimate of the effect of PEG tube feeding (OR for death, 0.28; 95% CI, 0.09 to 0.89; absolute difference, 30%).

The FOOD trial aims to establish whether more intensive feeding regimes (ie, oral supplements, earlier tube feeding, and greater use of PEG tube feeding) improve survival and functional outcomes after stroke. More than 4500 patients have been enrolled so far, but many more are required to show whether improving nutritional state after stroke actually improves patient outcomes and thus conclusively establish that the observed association between nutritional status and outcome is actually causal.

Acknowledgments

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References


Editorial Comment

Protein-Energy Undernutrition and Acute Stroke Outcome

Stroke is a common and devastating event that often results in death or major loss of independence with immense human and financial costs. Approximately 125 000 and 500 000 new or recurrent strokes occur each year in the United Kingdom and United States, respectively. The majority of strokes are not fatal, and the major burden is long-term disability. It is therefore the most important single cause of severe disability among Western people living in their own homes.1 Stroke in the developing world is less well documented. A statement from the Asia-Pacific Consensus Forum on Stroke Management predicts that ‘in the next 30 years or so the burden of stroke will grow most in developing countries rather than in the developed world.’

Stroke produces an almost infinite range of possible combinations of loss of function such as difficulties in swallowing, hemiplegia, impaired consciousness, perceptual deficits, visual fields defects, cognitive impairment, and motor apraxia or paralysis. These deficits will have an obvious and variable impact on the stroke patient’s nutritional demands and actual intake. Many studies have shown that a significant number of stroke patients were undernourished on admission and their nutritional status deteriorated further while in hospital. Undernutrition was associated with increasing morbidity and mortality.3,5 However, most of these studies suffered from methodological limitations.

In this issue of Stroke, Dennis et al6 report the results of an observational multicenter study of the relationship between baseline nutritional status and 6-month clinical outcome in 2955 hospitalized stroke patients. Their results indicate that baseline nutritional status was independently associated with clinical outcome.
The authors were able to study and follow a large sample of stroke patients recruited from a wide range of hospitals around the world, which does increase the external validity of the results. They used a simple bedside method performed by the randomizing clinician to categorize patients as “undernourished, normal, or overweight” (60% of patients) or, where practical, a fuller assessment of nutritional status. The findings indicate that 9% of those enrolled were judged undernourished and 16% overweight and that undernutrition was associated with poor outcome. This is an important result and a welcome advance in knowledge.

All studies have their limitations, and in very large multicenter studies like this one, the essential simplicity of the assessment method may lead to concerns over the reliability and validity of the nutritional status assessments. The authors are well aware of this and have performed assessments of interobserver reliability among a range of healthcare professionals. As of yet there is no “gold standard” for determining nutritional status because there is no universally accepted definition of undernutrition and all current assessment parameters are affected by age-related changes, disability, illness, and injury.7

Another important issue in this report is distinguishing underlying comorbidity from undernutrition, and to separate their effects on the stroke patient’s outcome. This is, however, one of the principal challenges that have always faced modern old people medicine. The authors have acknowledged this weakness, but more importantly they have adjusted for a number of poor prognostic factors such as age, prestroke dependency, and stroke severity, which together may, to some extent, reflect the patient’s frailty and comorbidity.

Elderly patients including strokes are likely to have poor nutritional status prior to hospital admission, which may be associated with impaired immune defensive responses.8 Their nutritional status is likely to deteriorate further as the result of the catabolism associated with the acute illness.9 During the stroke patient’s rehabilitation, nutritional depletion, however, may be more serious than during acute illness, given that rehabilitation periods may extend over weeks and months, and deterioration in nutritional status, although less marked than in the early catabolic phase, may be greater overall.10 A number of recent reports have indicated that poor nutritional status following acute illness in aging patients including strokes may be of more prognostic significance and amenable to therapy later on during the convalescent phase.5,11–13

This important study highlights 2 of the main challenges in understanding the interaction of nutrition, aging, and disease. The first is to find a valid, reliable, and practical way of measuring aging patients’ nutritional status in routine clinical practice. The authors of this article have “validated” an approach to meeting this challenge. The second is to determine the optimal timing, route, and composition of nutritional therapy relative to a patient’s metabolic stress, age, and specific illness.

Whether the relationship between undernutrition and poor stroke outcome reported in this issue of Stroke is a causal one or a mere association needs to be determined. Nevertheless, the authors of this report have provided us with the strongest evidence yet that this may indeed be the case. Confirmation of this relationship must await results of the interventional arm of their study.

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