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Review

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Nutrition for Brain Recovery After Ischemic Stroke: An Added Value to Rehabilitation

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In patients who undergo rehabilitation after ischemic stroke, nutrition strategies are adopted to provide tube-fed individuals with adequate nutrition and/or to avoid the body wasting responsible for poor functional outcome and prolonged stay in the hospital. Investigations have documented that nutrition interventions can enhance the recovery of neurocognitive function in individuals with ischemic stroke. Experimental studies have shown that protein synthesis is suppressed in the ischemic penumbra. In clinical studies on rehabilitation patients designed to study the effects of counteracting or limiting this reduction of protein synthesis by providing protein supplementation, patients receiving such supplementation had enhanced recovery of neurocognitive function. Cellular damage in cerebral ischemia is also partly caused by oxidative damage secondary to free radical formation and lipid peroxidation. Increased oxidative stress negatively affects a patient's life and functional prognosis. Some studies have documented that nutrition supplementation with B-group vitamins may mitigate oxidative damage after acute ischemic stroke. Experimental investigations have also shown that cerebral ischemia changes synaptic zinc release and that acute ischemia increases zinc release, aggravating neuronal injury. In clinical practice, patients with ischemic stroke were found to have a lower than recommended dietary intake of zinc. Patients in whom daily zinc intake was normalized had better recovery of neurological deficits than subjects given a placebo. The aim of this review is to highlight those brain metabolic alterations susceptible to nutrition correction in clinical practice. The mechanisms underlying the relationship between cerebral ischemia and nutrition metabolic conditions are discussed. (*Nutr Clin Pract.* 2011;26:339-345)

Keywords: stroke; rehabilitation; dietary supplements, proteins, zinc, oxidative stress

Stroke is currently the third leading cause of death in Western societies. In Italy, the general prevalence of stroke is 6.5%[1]; in 65% of cases the stroke is of an ischemic nature, whereas the other 35% have a hemorrhagic cause. The incidence of ischemic stroke in different age ranges varies from 0.85% (population 65-74 years of age) to 2.2% (population 75-84 years of age) and 3.2% (population ≥85 years of age).[2] The poststroke mortality rate is 20% during the acute period (within 30 days) and 30% at 1 year. Furthermore, stroke is one of most important causes of disability.[3,4] In Italy, about one-third of patients surviving 1 year after a stroke are totally dependent on other people,[5] creating an enormous socioeconomic burden.

These data should compel physicians dealing with rehabilitation of stroke sequelae to make every effort to obtain the best possible neurological and cognitive recovery of patients. To this aim, interventions planned to enhance the speed of recovery and functional outcome of stroke patients can have great medical importance.

In this context, it is our firm belief that nutrition interventions can enhance the efficacy of stroke rehabilitation. This belief is based on results from animal and human studies showing the existence of metabolic alterations in the brain following acute ischemia and reperfusion and the efficacy of specific nutrition interventions in reducing/reversing brain dysfunction.

In rehabilitation patients with ischemic stroke, nutrition strategies are adopted to provide tube-fed individuals adequate nutrition intakes and/or to avoid the body wasting

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responsible for poor functional outcome and excessively prolonged stay in hospital.[6-8] From 2000 to 2009, a focus on connections between nutrition and the brain developed with interventions planned to target some brain metabolic alterations primed by acute brain ischemia, such as impaired protein synthesis, excess free radical production, and deficiencies of minerals, including zinc.[7,8]

Investigations have documented that recovery of neurocognitive function in individuals with ischemic stroke may indeed be enhanced by nutrition interventions. This is particularly important in light of the following considerations.

- First, no drug acting on damaged brain structures is available in clinical practice for the rehabilitation of patients with ischemic stroke.
- Second, 80% of the recovery of neurological impairment occurs within the first 30 days after acute ischemia,[9,10] which suggests that every effort should be made to obtain the best functional outcomes during this period of rehabilitation.
- Third, a large proportion of patients with stroke may have a catabolic state.[11]
- Fourth, 30 to 35 days after a stroke, patients tend to have the same nutrition deficits as at the time of their admission to a rehabilitation center.[11]
- Fifth, important calorie-protein deficits have been found 6 months after an acute stroke.[12] ‘
- Sixth, patients with ischemic stroke have reduced plasma levels of tyrosine, the amino acid precursor of brain adrenergic neurotransmitters (epinephrine, norepinephrine, dopamine).[13]

A better understanding of brain metabolic alterations following cerebrovascular occlusion and the ways to limit them by nutrition would provide the information necessary to improve the functional outcome of stroke patients.

The aim of this review is, therefore, to highlight only those brain metabolic alterations susceptible to nutrition correction in clinical practice.

Suppression of Brain Protein Synthesis and Nutrition Interventions

Experimental studies have documented that acute ischemia induces early and profound alterations of brain protein synthesis. Indeed, protein synthesis is completely suppressed in the ischemic penumbra[14] (ie, in the region of tissue initially adjacent to the infarct that ultimately progresses to infarction). This suppression is not caused by energy failure or intracellular ion abnormalities, but by alterations of cellular homeostasis, including a reduction in the ratio of guanosine triphosphate to guanosine diphosphate[15] and a lowering of cellular pH before adenosine triphosphate (ATP) decreases.[16]

A decline in amino acid incorporation occurs at blood flow rates as high as 100 mL per 100 g per minute, which suggests that protein synthesis is dissociated from energy metabolism in regions of the brain with focally reduced blood flow. Reduction of protein synthesis begins at blood flow rates approximately 80% of normal,[14] and complete suppression occurs at a net blood flow <40 mL per 100 g per minute. The threshold for protein synthesis is, therefore, much higher than the threshold at which neuronal reduction of ATP formation occurs (<10 mL per 100 g per minute).[17] The consequence is that protein synthesis is inhibited at substantially higher flow values than energy metabolism, suggesting that selective neuronal injury will ensue even at high blood flow levels. There is also strong evidence that dysfunction of the endoplasmic reticulum is involved in the suppression of protein synthesis induced by cerebral ischemia.[18]

The suppression of protein synthesis is clinically relevant. First, if not reversed, inhibition of protein synthesis leads to cell death, and the restoration of protein synthesis may allow cells to repair ischemic damage and recover function.[18] Second, suppression of protein synthesis is paralleled by progression of the infarction zone. It has been found that suppression of protein synthesis leads to neuronal destruction in the ischemic penumbra.[11] Even an isolated blockade of protein synthesis is lethal to cells.[19] Furthermore, suppression of protein synthesis correlates with the final size of the area of ischemic injury much more closely than do energy state or other parameters, including DNA fragmentation.[9] Thus, the inhibition of protein synthesis represents the most reliable parameter heralding the expression of brain infarction.[9]

In humans, the importance of brain protein synthesis for neuronal survival was documented for the first time by an investigation showing the upregulation of growth arrest and DNA damage in the ischemic brain with consequent implications for the regulation of protein synthesis and DNA repair.[20] Alterations of brain protein synthesis can negatively affect brain function in otherwise normal individuals. This was highlighted in an epidemiological study showing neurological disorders in humans with low protein intake.[21]

Several studies on rehabilitation patients, designed to study the effects of counteracting or limiting a reduction of protein synthesis by providing protein supplementation, have shown that patients receiving such supplementation have better recovery of neurocognitive functions. For example, patients given an oral protein supplementation of 20 g/d for 21 days had better recovery of their neurological deficit compared with patients who received a placebo,[17] as determined by scores on the National Institutes of Health Stroke Scale (NIHSS), which quantifies 15 neurological deficits following acute stroke on a scale from 0 (normal neurological condition) to 36 (the most important neurological alterations). The average

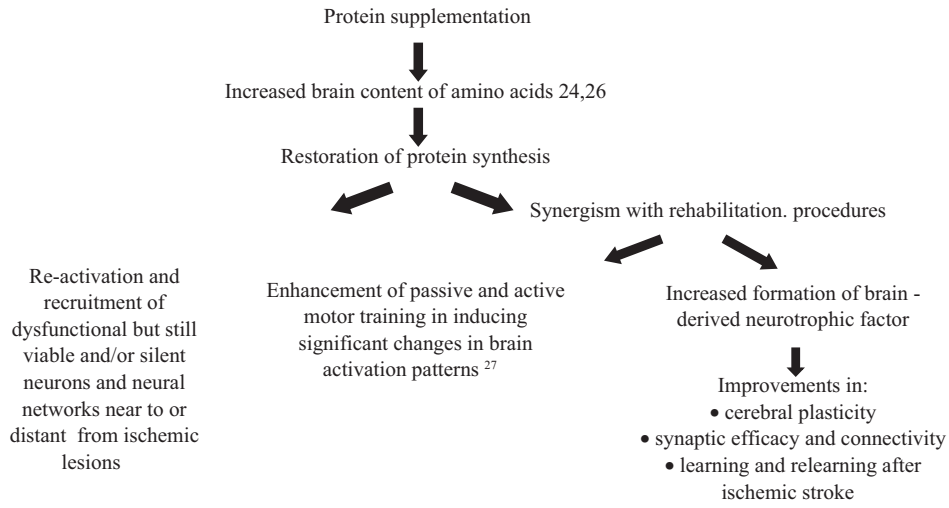

Figure 1. Plausible mechanisms for enhanced neurocognitive recovery as a result of protein supplementation in patients with subacute stroke (>14 days from acute event).

reduction of NIHSS score was 4.4 points in patients who received the protein supplementation and 3 points in the controls who did not ($P < .01$). Moreover, protein intake was significantly and positively correlated with improvement in NIHSS score; this was in contrast with the ratio of daily carbohydrate intake (g per day) to protein intake (grams per day). This ratio was positively linked to neurological deficit: at day 21 after starting the protocol, the dietary carbohydrate–protein ratio decreased significantly in the protein-supplemented patients from a baseline value of 3.2 to 2.3, whereas in patients on placebo, the ratio decreased from the baseline value of 3.2 to 2.9. We had previously found that the dietary carbohydrate–protein ratio in healthy subjects aged 40-75 years is 3.17 ± 0.8, independent of gender (unpublished data).

In another investigation of subacute stroke patients, 21 days of daily supplementation with a formula providing 20 g of protein and 250 kcal (carbohydrate 28.2 g, lipids 7 g in addition to the 20 g of protein) improved cognitive recovery (+3.9 points on the Mini Mental State Examination, MMSE), whereas the baseline MMSE score remained virtually unchanged in the control patients.[22] MMSE is a clinical test that evaluates the patient's cognitive state on a scale from 0 (the most compromised cognitive functions) to 30 (normal cognition).

In further support of these data, we recently documented a positive correlation between spontaneous improvement of neurocognitive deficits and dietary protein intake and a negative correlation with the dietary carbohydrate:protein ratio in patients with subacute stroke.[23]

When considering explanations for the positive influence of protein on brain function, the first point to keep in mind is that the types of cerebral proteins,[24] and hence the amino acid profile in the brain,[25] are influenced by

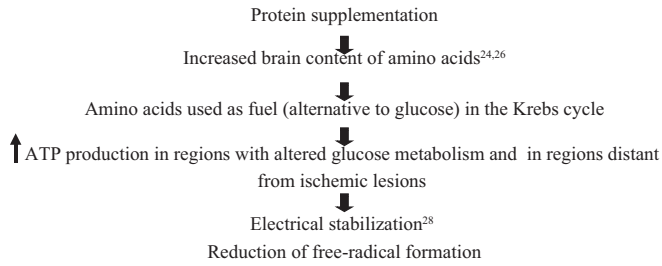

Figure 2. Improvement in neuronal energy formation by supplemental proteins explaining enhanced neurological recovery in subacute stroke.

the types of dietary proteins. We proposed[11,13,22,23] that multiple mechanisms may account for the efficacy of protein supplementation on brain function of patients with subacute stroke. These mechanisms, primed by increased cerebral availability of amino acids,[26] include a synergistic action between induced brain protein synthesis and rehabilitation procedures (Figure 1),[24,26,27] an improvement in neuron energy formation (Figure 2),[24,26,28] and better neurotransmitter synthesis (Figure 3).[24,26,27,29]

Our investigations pointed to the need to monitor the carbohydrate intake of stroke patients to prevent carbohydrate intake in excess of protein intake because this imbalance slowed neurocognitive recovery 2 weeks after the acute event. That an excess of carbohydrate ingestion can negatively affect recovery from brain dysfunction should not be surprising, given the alterations of brain glucose metabolism occurring in focal cerebral ischemia. Both hyperglycolysis in penumbra cells[30] and reduced aerobic glucose metabolism in cerebral regions remote from the primary ischemic lesion occur in the ischemic brain.[31] In this condition, an excess of carbohydrate

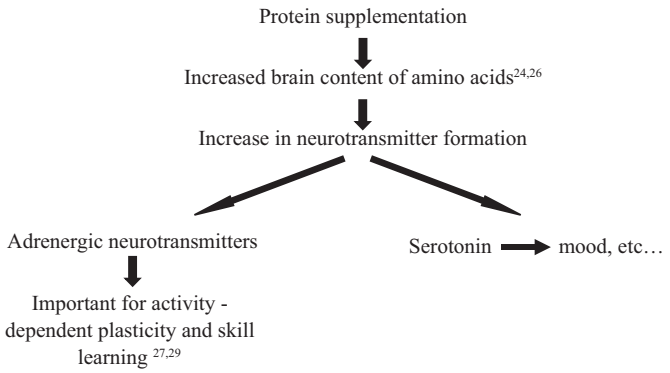

Figure 3. Increased brain neurotransmitter production by supplemental proteins potentially explains recovery in subacute stroke.

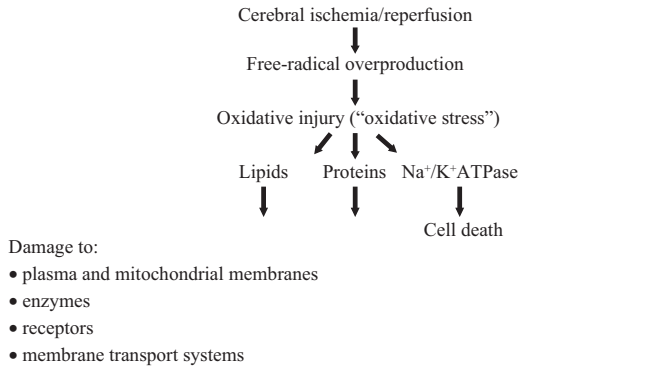

Figure 4. Some types of damage that can be caused by free radical overproduction following cerebral ischemia–reperfusion.

ingestion may increase lactate production, resulting in may damage to brain structures.

The reduction in both the efficiency and efficacy of glucose utilization in brain neurons once again highlights the role of amino acids as an alternative fuel for the aerobic production of energy (ATP) in patients with subacute stroke (Figure 2).[24,26,28]

Brain Oxidative Damage and Nutrition Interventions

Clinical and experimental data have documented that cellular damage in cerebral ischemia is partly caused by oxidative damage secondary to free radical formation and lipid peroxidation.[32] Sources of free radicals include inflammatory cells, xanthine oxidase, cyclooxygenases, mitochondria, glutamate, and aspartate excitotoxic activity.[33]

Free radical overproduction causes oxidative injury to macromolecules, particularly lipids (lipid peroxidation) and proteins. Lipid peroxidation is self-propagating and irreversibly damages both plasma membranes and mitochondrial membranes.[32] Moreover, lipid peroxidation breakdown products, including malondialdehyde, irreversibly damage enzymes, receptors, and membrane transport systems.[34] The Na^+/K^+–ATPase pump appears to be particularly vulnerable, with consequent increased cell death[35] (Figure 4).

Because products of brain lipid peroxidation are transported in the serum, lipid peroxide levels in the serum reflect those present in the brain. Thus, brain damage from free radical overproduction has been documented in humans by measuring plasma concentrations of lipid peroxidation products. Plasma levels of cholesteryl ester hydroperoxide, a specific marker of lipid peroxidation, were found to be higher in patients with cortical stroke than in patients with lacunar stroke or in normal controls, in whom this analyte was undetectable.[32]

Brain damage from oxidative stress is also inferred from reduced plasma levels of antioxidants, suggesting their increased consumption. This is the case of vitamins E and C, both potent antioxidants, whose levels were decreased in patients with stroke.[36] Moreover, plasma levels of vitamins A and E in patients with acute ischemic stroke were found to be lower than those in healthy controls.[37] Total antioxidant capacity was reduced in patients with acute stroke, and serum vitamin C concentrations deteriorated significantly during the study period.[38]

In brief, brain oxidative damage in ischemic stroke can be inferred from the increased plasma levels of lipid peroxides and/or reduced concentrations and activities of antioxidants. Increased oxidative stress negatively affects a patient's life and functional prognosis. The reduction of total antioxidant activity of plasma is associated with the volume of ischemic cerebral infarction and with the degree of neurological impairment.[39] Moreover, a reduced plasma antioxidant profile is linked to poor early outcome including death or functional decline.[37]

Some studies have documented that nutrition supplementation with B-group vitamins may mitigate oxidative damage after acute ischemic stroke. For example, in a study in which patients were randomized within 12 hours after a brain infarct to receive (n = 24 patients) or not receive (n = 24 patients) 2 weeks of daily supplementation with B-group vitamins, including folate (5 mg), B_2 (5 mg), B_6 (50 mg), and B_{12} (0.4 mg), those who received the vitamin supplementation not only had a reduction in plasma levels of malondialdehyde over 90 days, but also had lower levels of plasma C-reactive protein, a marker of tissue inflammation, than the controls.[40] Interestingly, the antioxidant and anti-inflammatory effects of the

group B vitamins were independent of their homocysteine-lowering effect.[40] The patients' antioxidant capacity was measured as plasma total antioxidant capacity, whereas plasma malondialdehyde was determined as a marker of lipid peroxidation.

Another study documented the positive effects of supplementary antioxidants (oral vitamin E and vitamin C) on antioxidant capacity of patients with acute ischemic stroke.[41] In this study, 96 patients with acute ischemic stroke admitted within 12 hours of symptom onset were randomly allocated to oral vitamin E (800 international units) and vitamin C (500 mg) (n = 24), to B-group vitamins (5 mg of folic acid, 5 mg of vitamin B_2, 50 mg of vitamin B_6, 0.4 mg of vitamin B_{12}) (n = 24), to both types of supplementation (n = 24), or to the control group (n = 24). Antioxidant capacity was measured as plasma total antioxidant capacity, and plasma malondialdehyde was also measured.

Total antioxidant capacity improved significantly over 7 and 14 days in the antioxidant-only group, whereas capacity declined in the control group. Changes were less marked in subjects who received B-group vitamins with or without antioxidants. There was a significant reduction in plasma malondialdehyde in the 3 treatment groups, in contrast to the increase observed in the control group. The study demonstrated that antioxidant supplementation with or without B-group vitamins enhanced antioxidant capacity, mitigated oxidative damage, and exerted an anti-inflammatory effect immediately after the index event.

The reduction of ischemia-induced oxidative stress in the brain induces rapid defense immune responses and increases antiapoptotic factors, including nuclear factor-κB activity.[42]

Although experimental and human data on brain damage attributed to free-radical overproduction have been collected in acute cerebral ischemia, antioxidant capacity could be expected to decline in rehabilitation patients with stroke because of the acute event and the high frequency of inadequate diet over the first week after a stroke.[11] In the case of low antioxidant capacity, it is important to investigate neurocognitive recovery during nutrition supplementation with antioxidant agents.

Low Zinc Intake and Nutrition Intervention

Zinc plays an important role in brain functioning because it acts as a mediator of central neuronal signaling, with large amounts being released by synapses during membrane depolarization. This specific neuronal role should be added to the well-known catalytic and structural properties of zinc.[43]

Brain function is affected by both zinc deficiency and excess amounts of zinc. During rapid brain growth, severe zinc deficiency leads to changes in emotions, lethargy, and deficits of learning, attention, and memory. Elevated brain levels of zinc are neurotoxic because they enhance and prolong the firing rate of neurons and inhibit the calcium-dependent release of transmitters.[44] Experimental investigations have shown that cerebral ischemia changes synaptic zinc release and that acute ischemia increases zinc release, aggravating neuronal injury.[44] Even mild and transient focal ischemia induces abnormal zinc accumulation in cortical neurons within 3 hours, thus accelerating the development of cerebral infarction.[10]

It has been documented that zinc chelators reduce infarct volume and increase survival rate in rat models of cerebral ischemia.[45] In a clinical study, zinc chelators were associated with a 90-day improvement in post–stroke recovery in patients with acute ischemic stroke.[46]

In contrast to the reports of zinc neurotoxicity in ischemia, various studies found that administration of the mineral provided neuroprotection by reducing ischemic brain edema[47] and attenuating infarct volume after both transient focal and global ischemia.[48] Systemic administration of zinc was also found to have positive effects on the hippocampus during reperfusion in a rat model of transient cerebral ischemia.[49]

These conflicting data about zinc neurotoxicity and neuroinfarction may be explained by differences in methodological designs.

In clinical practice, dietary zinc intake by patients with ischemic stroke was found to be lower than the recommended 10 mg/d. In confirmation of this, in a recent investigation on subacute ischemic stroke, our group found that zinc intake by patients averaged about 50% of the recommended amount.[50] When patients were randomized to receive either 10 mg of zinc supplementation per day for 30 days to normalize daily zinc intake, or placebo, subjects who received supplementation had a better recovery of neurological deficit (as determined by the NIHSS score) than did placebo subjects. Indeed, the average reduction in NIHSS score was 4.7 in the supplemented subjects and 3.3 in the placebo group,[50] with this difference between the 2 groups of patients being statistically significant ($P < .02$). We explained the positive influence of normalized zinc intake on neurological recovery by mechanisms such as brain reactivation of protein synthesis, improved chemical neurotransmission, and repair of cerebral damage (Figure 5).[11,22,50]

Conclusions

There are 2 practical implications of this report regarding the relationship between nutrition and cerebral function in subjects undergoing rehabilitation after stroke.

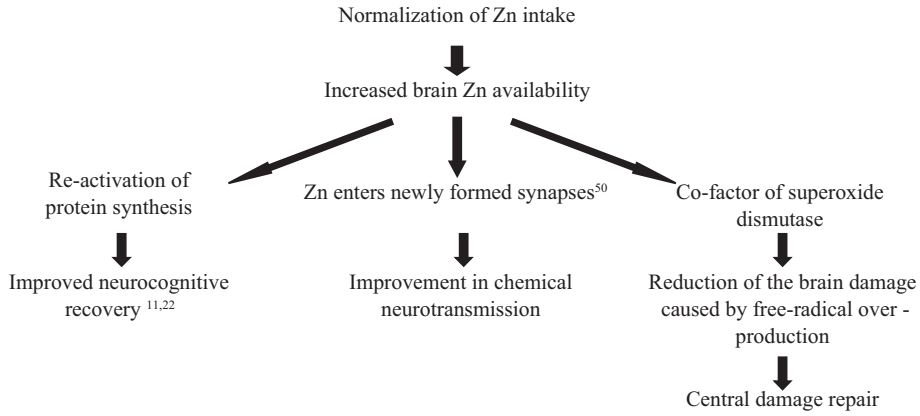

Figure 5. Potential effects of normalized zinc intake on improving brain function.

First, inadequate protein intake, low zinc intake, and low antioxidant capacity are all associated with expansion of ischemia-induced brain damage. Second, this brain damage can be reversed by specific nutrition interventions. In certain cases, nutrition interventions can be beneficial to rehabilitation of patients with ischemic stroke. This appears to be even more important when considering that nutrition interventions consist of providing natural substances and that in clinical practice there are no known drugs that modulate brain recovery.

While awaiting larger trials addressing the effects of nutrition and nutrition interventions on the recovery of brain function in ischemic stroke patients, some indications useful in clinical practice and derived from existing investigations can be provided:

1. In both acute and postacute (>7-14 days from event) stroke, it is preferable to determine the patient's plasma antioxidant capacity. If this is not feasible, the antioxidant vitamins E and C can be supplied.
2. In the subacute period, the following daily nutrition intakes might be recommended in clinically stable patients with normal renal function:
   a. Energy: ≥25 kcal/kg in nonobese subjects to maintain body weight; in the case of overweight/obese subjects given energy <25 kcal/kg, it is recommended to maintain a carbohydrate–protein ratio <2.5.
   b. Protein: >1 g/kg in order to achieve carbohydrate (g)–protein (g) ratio <2.5. For example, for a patient weighing 70 kg, an appropriate nutrition intake might be kcal 1,750, protein 1.5 g/kg (=24% energy), carbohydrate 3.12 g/kg (=50% energy), carbohydrate–protein ratio 2.08, lipids 0.72 g/kg (= 26% energy).
   c. Self-feeding subjects should eat a portion of lean meat or poultry or fish at least once a day to achieve a total zinc intake of 12-15 mg.

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