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Use of Ornithine α-Ketoglutarate in Clinical Nutrition of Elderly Patients

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Malnutrition affects 40% to 70% of elderly patients in hospitals and in institutional care and 5% to 10% of all persons older than 70 y. This phenomenon is a consequence not only of the aging process and reduced food intake but also of stress and disease.[1,2] Physiologic changes accompany malnutrition in the elderly, including a loss of muscle mass, a fall in protein synthesis, and impaired atrophy of the digestive mucosa.[3–5] Malnutrition in the elderly has important consequences on morbidity and mortality.[6] In particular, malnutrition favors the onset of infection and the occurrence of fractures. One characteristic of the elderly is their failure to regain weight and former nutrition status during the months after injury or disease. Correct management of nutrition status and early refeeding of the malnourished elderly is therefore of major importance and helps reduce complications. If protein-energy malnutrition is not rapidly corrected, bed sores and infectious complications can occur.[7] It then becomes difficult for such patients to ingest sufficient food orally, making enteral nutrition a necessity. However, intensive enteral nutrition in frail elderly patients can be a major source of iatrogenic disorders and is costly. Overall, the evidence indicates that an improvement in the nutrition status of elderly patients has important clinical and socioeconomic consequences.[8]

In addition to manipulating quantitative intake,[8] qualitative intake needs to be considered. Research on preventive measures using amino acids (AAs) and precursors has been conducted in recent years. Some AAs are important regulators of protein turnover and can counteract functional and metabolic disorders induced by trauma. Supplementation with these AAs brings us into the field of pharmacologic nutrition. Two of the best known of these are glutamine and arginine.

Glutamine is an important fuel for all rapidly dividing cells (including enterocytes and immune cells), a precursor of glutathione, pyrimidines, and purines, and it stimulates protein synthesis and inhibits protein catabolism. This justifies including (in parenteral products) or increasing (in oral and enteral products) glutamine in diets for injured patients.[9] Solano et al.[10] recently reported changes in nutrition status indicators of institutionalized elderly patients induced by addition of monosodium glutamate to food. However, it is difficult to determine whether the action of glutamate, the direct precursor of glutamine, in the improvement of nutrition status is mediated by its metabolic or its taste-enhancing effect. Because one of the metabolites or precursors of glutamine is α-ketoglutarate, administering this as a calcium salt to patients with chronic renal failure has been envisaged.[11] Another salt, ornithine α-ketoglutarate (OKG), was evaluated initially for the purpose of reducing ammonia levels in patients with terminal liver cirrhosis.[12] Although clinical investigations have confirmed lower ammonia levels in patients treated with OKG, there was no improvement in coma status. However, investigators noticed improvements in nutrition status in OKG-treated patients.[13]

This review covers the literature on the nutritional effects of OKG in the elderly.

OKG is a salt formed of two molecules of ornithine and one of α-ketoglutarate (10 g of OKG contains 1.30 g of nitrogen). For a full review, see Cynober.[13,14]

The effects of OKG on nutrition status were demonstrated 15y ago. Results showed that OKG is a potent nutritional modulator characterized by an anticatabolic activity, anabolic activity, or both, according to the tissue considered and the pathologic situation, and is an efficient immunomodulator and a key promotor of wound healing and tissue repair.

The mechanisms underlying the improved nutritional status resulting from OKG administration are not completely understood.[14] OKG action is probably multifactorial, linked to the stimulation of the secretion of anabolic hormones (insulin and growth factor), to the production of OKG metabolites, or both, such as glutamine, arginine, proline, and polyamines. All of these act in the control of protein anabolism and modulation of cell multiplication and differentiation and thus play a major role in the viability and function of the proximal intestine. All these effects result largely from the specific interaction between the two components of the molecule.[15]

In the elderly, OKG improves clinical outcome in chronic malnutrition by increasing appetite and body weight gain and improving healing (Table I) .[16–22]

The first study,[16] published in 1985, was conducted in hospitalized patients with chronic malnutrition (infection, cancer, lung, heart, neurologic, or digestive diseases). They received 0, 5, 10, or 20 g/d of OKG in the morning (20 to 22 patients in each group). Nutritional assessment was performed with the use of biological parameters. At day 30 increases in albumin and transferrin concentrations were observed as the major effects of 10 g of OKG.

Baes et al.[17] enrolled 52 patients with protein malnutrition mainly associated with cancer or lung disease or recovering from acute illnesses or surgery. These patients received various amount of OKG during two periods of 10 d. Evaluation criteria included anthropometric parameters (weight and brachial circumference) and subjective indices such as asthenia (score of 1 to 7) and appetite (mainly for meat; 100-point visual rating scale). Marked improvement for asthenia and appetite for meat (22 of the 52 patients) was noted in the OKG-treated group.

Mettetal et al.[18] studied 40 elderly hospitalized patients presenting anorexia and weight loss. They were included in a double-blind, randomized, placebo-controlled study. The patients presented vascular, respiratory, or bone diseases; patients with cancer or infectious diseases were excluded. OKG (10 g) or placebo was administered daily with meals in a glass of flavored water. An increase in protein and calorie intake (weight of patients' meal

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TABLE I.

EFFECT OF OKG IN ELDERLY PATIENTS

Reference	*n* Patients (men/women)	Population	*n* Control Subjects	Treated (*n* subjects)	Study duration	Mean ages (*y*) of control/treated subjects (range or SD)	Anthropometric data	Biological data	Appetite	Quality of life	Cost
16	84 (20/64)	Hospitalized with malnutrition	20	5 (22), 10 (22), 20 (20) g/d for 1 mo	1 mo	82 (63–97)*		Alb ↑ Trf ↑ 30 d for 10- and 20-g groups			
17	52 (25/27)	Hospitalized with malnutrition		4, 6, 10 g/d for 10 d, two periods	2 mo	†/72,5 (52–101)	Weight ↑ 60 d BC ↑ 60 d		↑ 60 d		
18	40 (7/33)	Hospitalized, anorexic	20 (MD)	10 g/d for 1 mo (20)	1 mo	85 ± 6/84 ± 6			↑ 15 and 30 d		
19	185	Ambulatory	93 (MD)	10 g/d for 2 mo (92)	4 mo	75 ± 6/74 ± 8	Weight ↑ 30 and 60 d		↑ 30 and 60 d	↑ 60 d	↓ 37% at 120 d
20	370 (113/257)	Free-living	167 (MD)	10 g/d for 2 mo (203)	2 mo	82 ± 0.5/80 ± 0.5	Weight ↑ 60 d	Alb ↑ 60 d TTR ↑ 60 d	↑ 60 d		

* Total population, control plus treated patients.
† No control group.
↓ or ↑, OKG-treated group versus the control group or basal level; Alb, albumin; BC, brachial circumference; MD, maltodextrin; OKG, ornithine α-ketoglutarate; Trf, transferrin; TTR, transthyretin.

trays) was observed after 15 and 30 d of treatment.

One of the two main studies was performed by Brocker et al.[19] They carried out a two-center, randomized, double-blind, placebo-controlled trial to evaluate the OKG treatment of elderly ambulatory patients recovering from acute illnesses. Patients were recruited from two hospitals in France and followed up over a 4-mo period. Eligible participants included patients older than 65 y who were able to live independently and eat without any assistance while recovering from acute respiratory infection, malignant disease, or surgery. Patients who were taking medication likely to affect nutrition status or who had undergone recent chemotherapy or radiation or oncologic surgery were excluded. One hundred eighty-five patients, recruited by 22 physicians, were included and blindly randomized to receive OKG (10 g/d) or maltodextrin as placebo. OKG and the placebo were taken at the end of the midday meal in a flavored solution or with a yoghurt, a milk-based dessert, or stewed fruit. Changes were observed over a 2-mo period. Evaluation criteria included subjective indices such as weakness and appetite (100-point visual rating scale), in addition to body weight and muscle circumference measurements. Nutrition status was assessed subjectively by each patient's practitioner as poor, average, or good. Medical costs were rated by various practical measures including number of days in the hospital, nursing care, number of medical visits, and number of prescriptions. The quality-of-life index was defined by several criteria appraising the patient's capacity for independent activity in addition to weakness and fever.

Marked improvement in several measurements was noticed in the OKG-treated group as opposed to the placebo group after 30 d, including increased appetite for meat, overall appetite score, and greater weight gain (+149%; 1.23 kg ± 1.66 kg versus 0.493 kg ± 1.119 kg, $P < 0.001$). Changes in albumin concentrations could not be evaluated due to incomplete data. After 2 mo, patients receiving OKG showed a significant improvement in nutrition status, general appetite, appetite for meat, weight gain, and quality-of-life index (51.2 ± 28.8 versus 32.5 ± 37.9, $P < 0.001$). There was no difference in the medical-cost index during the first 2 mo of treatment. After 4 mo, however, patients receiving OKG had shorter convalescence periods, fewer home visits by physicians and nurses, and fewer prescriptions for medication. These effects resulted in substantially lower total medical costs accrued by the OKG-treated group (overall cost saving of 37%, i.e., 394 versus 623 euros/4 mo). The most marked saving was in nursing care, possibly due to improved healing of bed sores, fewer infectious complications, and greater independence. This study demonstrated improved

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clinical outcomes, and OKG therapy seemed to be effective in reducing malnutrition and shortening the convalescence period in this population of independent elderly patients.

A similar study was performed by Debry et al.[20] in 370 free-living non-hospitalized elderly patients. It was a multicentric (n = 11 centers), double-blind, controlled study. The subjects had recently recovered from various illnesses (poor general state, infection, lung disease, heart disease, neurologic disease, miscellaneous). The population was divided into two groups receiving an isocaloric placebo (maltodextrin) or OKG for 60 d. OKG or the placebo was administered once daily at the dose of 10 g at each midday meal with a glass of water, yoghurt, or a milk-based dessert.

Nutritional assessment was performed with the use of anthropometric indices (weight and body mass index) and biological indices (albumin and transthyretin concentrations). Appetite was evaluated with a simple visual rating scale (0 to 100). At day 60, relative to those who received the placebo, patients who received OKG showed significant improvements in body weight gain, albumin, transthyretin, and appetite. Like the previous one, this study was flawed by the use of a non-isonitrogenous placebo. Even so, the difference in nitrogen (1–3 g) is unlikely to be responsible for the differences observed according to treatment group.

Lastly, a review and analysis of four controlled clinical trials including 116 elderly patients, performed to evaluate the effects of OKG in the treatment of pressure ulcers, was performed by Meaume and Piette.[21,22] In all the studies there was a statistically significant increase in wound healing in the patients treated with OKG (10 g/d for 6 wk). The decrease in wound surface was two to three times greater with OKG than without.

Overall, the studies evaluating OKG in elderly patients older than 75 y demonstrated its beneficial effects whatever the situation (free-living, hospitalized, or institutionalized), initial nutrition status, and illnesses. The OKG dose tested was mostly 10 g. At higher levels hyperosmolar effects can occur, with diarrhea.[16] No hypoglycemia was reported by Varanasi and Saltzman.[23]

The nutritional assessment was performed with parameters that are well-recognized in elderly patients.[3,24] The effects on appetite were subjectively assessed except in one study[18] in which patients' meal trays were weighed and calorie and protein inputs were measured.

Only three studies were placebo controlled,[18–20] and only two were isocaloric.[19,20] In these latter studies, beneficial effects of OKG were observed promptly, from 1 mo, on appetite and anthropometric and biological data. There also was a long-term effect as shown by the reduced cost of medical care during the 2 mo that followed the 2-mo treatment period.[19]

Improvement in the clinical outcome of OKG-treated patients has important socioeconomic implications. However, although OKG supplementation is recognized as an efficient nutritional therapy, more studies are needed to evaluate clinical benefit in terms of infectious complications, length of hospital stay, efficacy:cost ratio, and mortality. But there is no doubt that OKG has a place in the "new" area of pharmaconutrition.

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