Nutrition in cachexia: from bench to bedside

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Abstract

As malnutrition is often present in cachexia, nutritional intervention has been one of the widely accepted strategies. A literature review of cachexia models with dietary interventions in the present issue of this journal pointed out that the majority of nutrient intervention studies were of n-3 fatty acid, mainly eicosapentaenoic acid and docosahexaenoic acid. Effect on protein catabolism and anti-inflammation are most pronounced benefits of n-3 fatty acid. The effectiveness of n-3 fatty acid may depend on control diet or even be attributed to the polyunsaturated fatty acid deficiency inadvertently produced in control group. However, there is not enough clinical evidence to support a benefit of n-3 fatty acid substitution in patients with cachexia. The second important result from this review is that the majority of studies did not provide information about dietary design or did not standardize design, content, source, and overall composition. To guide dietary design for researchers in preclinical studies, a model has been proposed in this review, which may be useful to predict the efficacy of new dietary intervention in cachexia science. From a clinical point of view, the limited effectiveness of nutritional support in cachexia may partly be explained by the multifactorial nature of this condition. Cachexia differs from malnutrition inasmuch as malnutrition can be reversed by adequate nutrition and/or by overcoming problems of absorption or utilization of nutrients, but cachexia cannot be successfully treated by nutrition alone. Multidisciplinary approach including the assessment and intervention in feeding, appetite, swallowing, exercise, psychosocial, and psychological issue may be needed to improve nutrition in patients with cachexia.

Keywords   Cachexia; Nutrition; Models; Diet; Cancer

Introduction

As malnutrition is often present in cachexia,[1] nutritional intervention has been one of the widely accepted strategies recommended by guidelines.[2–4] The role of nutritional support in patients with cancer and cachexia has been examined in detail by previous reviews.[5,6] However, the findings suggest that nutritional interventions have limited effect on survival and that the influence on body weight is inconsistent, partially because it seems difficult to achieve high-quality evidence from clinical trials. Recruitment problems because of unwillingness or frailty of the patients in such a serious condition (i.e. cachexia) are major obstacles for an enrolment of patients, while a large number of participants are needed to achieve adequate power to analyse a widely heterogeneous population. Such difficulties in clinical cachexia studies underline the importance of well-characterized animal models. There are several recent reviews of cachexia animal models.[7–9] However, the number of reviews with a focus on nutrition is rather limited.[7] In the present issue of this journal, Giles et al.[10] successfully reviewed the role of the diet composition in experimental animal models of cancer cachexia. The authors have performed a literature review of scientific studies using animal models of cancer cachexia with dietary interventions.

n-3 fatty acid in animal study

The first main result is that the majority of nutrient intervention studies were of n-3 fatty acid, which was examined in 16 papers of 44 reviewed articles. The effects of n-3 fatty acid, mainly eicosapentaenoic acid and docosahexaenoic acid, are also broadly studied in humans.[11] In animal studies, the effect on protein catabolism[12] and its anti-inflammatory action[13] are most pronounced benefits of n-3 fatty acid. These actions are thought to be transmitted by attenuating NF-κB signalling, the ubiquitin proteasome pathway, and antagonizing superoxide dismutase.[2] However, although many

animal studies have been successful, there is not enough clinical evidence to support a benefit of n-3 fatty acid substitution in patients with cachexia.[6,11] Fearon *et al.* enrolled a total of 200 patients with cancer cachexia and demonstrated that enrichment with n-3 fatty acids did not provide an advantage in weight loss.[14] Jatoi *et al.* randomized 421 patients with cancer-associated wasting to an eicosapentaenoic acid, megestrol acetate, or both. Survival was not different among arms, and they concluded that eicosapentaenoic acid supplement does not improve weight or appetite compared with megestrol acetate alone.[15] In their review in the present issue,[10] Giles *et al.* pointed out that the effectiveness of n-3 fatty acid for antineoplastic actions depended on the levels of polyunsaturated fatty acids in control diet. In addition, the results of studies on n-3 fatty acid could be attributed to the polyunsaturated fatty acid deficiency inadvertently produced in control group, because n-6 and n-3 fatty acids are essential dietary nutrients. As n-3 fatty acid has received a lot of attention in recent years because of its broad-spectrum effect, these finding are important in view of designing clinical trials.

What is needed in an ideal animal study of dietary interventions?

The second important result from this review is that the majority of studies did not provide information about dietary design or did not standardize design, content, source, and overall composition. Many studies even failed to report food intake, or total energy and protein content of the diet. The lack of detailed dietary information may prevent correct interpretation of outcomes. Based on these results, the authors claimed that diet content and composition should be reported and food intake assessed during the experiments. In addition, they proposed a model to guide dietary design for researchers in preclinical studies. The first criteria in dietary design proposed by Gile *et al.* is that treatment and control diets should be isocaloric and isonitrogenous. The second criteria is making proportions of macronutrients and microniutrients similar to human intakes; carbohydrates should account for 45–65%, fat 20–35%, and protein 10–35% of total energy. In the field of drug discovery, high attrition rate in translating the results of experimental studies to clinical trials is problematic.[16] As the major cause of attrition are lack of efficacy and safety,[16] both of which account for 30% of failures, this type of guidance given by Giles *et al.* may be useful to predict the efficacy of new dietary intervention in the cachexia field.

Clinical perspective

From a clinical point of view, the limited effectiveness of nutritional support in cachexia may partly be explained by the multifactorial nature of this condition.[3,17] Although malnutrition is often present in cachexia, cachexia is distinguished from malnutrition by definition.[1,3] Cachexia differs from malnutrition inasmuch as malnutrition can be reversed by adequate nutrition and/or by overcoming problems of absorption or utilization of nutrients, while cachexia cannot be successfully treated by nutrition alone. Multidisciplinary approaches including the assessment and intervention in feeding, appetite, swallowing, exercise,[18,19] psychosocial,[20] and psychological issue may be needed to improve nutrition of patients with cachexia. Although some of these aspects can also be assessed in animal models,[21,22] others may be difficult to be monitored or intervened in animal models and vice versa. For example, Dwarkasing *et al.* demonstrated changes in orexigenic peptide (neuropeptide Y and agouti-related protein), anorexigenic gene (pro-opiomelanocortin and cholecystokinin), and serotonin/dopamine signalling in hypothalamus of cachectic mice,[22] and Peter *et al.* showed anti-anorexic effects of an anti-melanocortin-4 receptor in lipopolysaccharide-induced cachexia rats.[21] Needless to say, a psychosocial approach could not be recapitulated in animal models, but there has been a wealth of clinical studies addressing the potential of psychosocial effects.[23] Lastly, here we consider that there may be distinct mechanisms in cachexia associated with the underlying disease other than cancer such as heart failure, pulmonary disease, and kidney disease. Regarding nutrition, heart failure is second most studied underlying disease of cachexia next to cancer.[24] It would be most helpful to assess common endpoints and agree on standard operating procedures to increase the comparability of animal studies. This would be particularly helpful to interpret intervention efficacy in cachexia animal studies studying different underlying diseases.

Acknowledgements

Conflicts of interest

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