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Research Proposal: Treating Cancer-Related Anorexia-Cachexia  
with a Methionine Restricted Diet

Anorexia and cachexia are frequent concomitants of the later stages of cancer, and contribute significantly to poor quality of life (QOL). Moreover, family members and friends of cancer patients with anorexia and cachexia are often very distressed by the apathy, wasting, and hopelessness manifested by their loved ones. Caregivers are affected also.

Dietary methionine restriction (MR) has been found to be effective at treating certain cancers. In addition, in experimental animals it has been found to be as effective as caloric restriction (CR) in increasing healthy lifespan (1). Paradoxically, MR increases appetite and food intake (2), together with an increase in energy expenditure (EE) (3). The exact mechanisms involved remain to be elucidated.

Because the essential amino acid (EAA) methionine is found in low concentrations in fruits and vegetables, MR typically involves a vegan-type diet. In fact, it has been proposed that the beneficial effects of vegetarian diets on health may be due to their inherent methionine restriction (4).

As an EAA, methionine is necessary for young animals to grow and reproduce (5). Once the reproductive phase is over, however, the same dietary component may contribute to the aging process (6). Thus, restricting its intake may help to slow down

aging and aging-related diseases (7) including cancer, cardiovascular disease, diabetes, and dementia. The mechanism(s) involved may have to do with reduced insulin and insulin-like growth factor signalling (1).

The aim of the proposed research is to study whether MR can be helpful in treating anorexia and cachexia in patients with advanced cancer. Patients in palliative care units or in long term care units offering palliative care services, in which meal preparation and consumption can be controlled and monitored, will be recruited to participate in an open-label pilot study to look at the feasibility of providing MR diets in such units, their palatability for patients, acceptance by caregivers, and their effects on food intake, weight, muscle wasting, and QOL measures.

1. Perrone CE, Malloy VL, Orentreich DS, Orentreich N. Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents. *Exp Gerontol*. 2012
2. Orentreich N, Matias JR, DeFelice A, Zimmerman JA. Low methionine ingestion by rats extends life span. *J Nutr*. 1993;123:269-274.
3. Plaisance EP, Greenway FL, Boudreau A et al. Dietary methionine restriction increases fat oxidation in obese adults with metabolic syndrome. *J Clin Endocrinol Metab*. 2011;96:E836-E840.
4. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses*. 2009;72:125-128.

5. Narita K, Nagao K, Bannai M et al. Dietary deficiency of essential amino acids rapidly induces cessation of the rat estrous cycle. *PLoS One*. 2011;6:e28136.
6. Grandison RC, Piper MD, Partridge L. Amino-acid imbalance explains extension of lifespan by dietary restriction in *Drosophila*. *Nature*. 2009;462:1061-1064.
7. Spindler SR. Caloric restriction: from soup to nuts. *Ageing Res Rev*. 2010;9:324-353.