MediDrink Neo

MEDIFOOD

PRODUCT MONOGRAPH

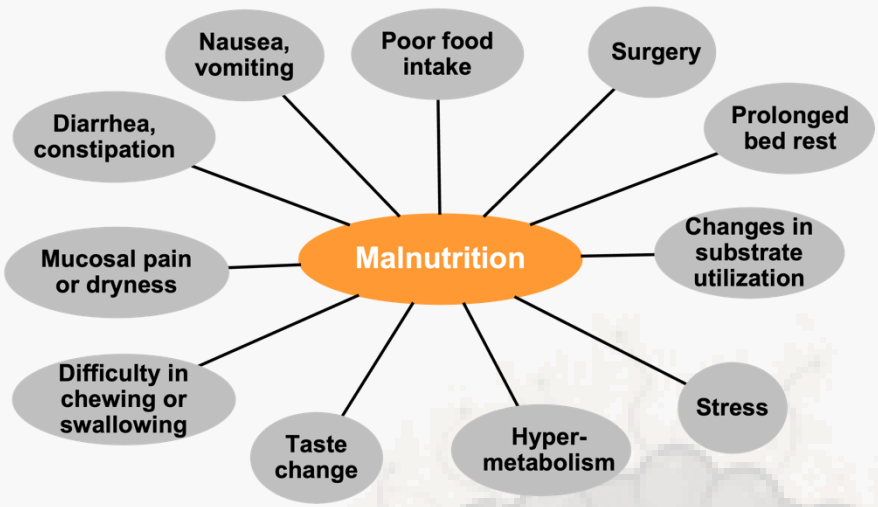
FOOD FOR SPECIAL MEDICAL PURPOSES FOR THE DIETARY MANAGEMENT OF CANCER-RELATED MALNUTRITION

1. Malnutrition

1. 1. Background

Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. One type of malnutrition is undernutrition, which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals). Malnutrition affects people in every country. Around 1.9 billion adults worldwide are overweight, while 462 million are underweight. An estimated 41 million children under the age of 5 years are overweight or obese, while some 159 million are stunted and 50 million are wasted (WHO 2016).

Malnutrition is as much a cause as a consequence of ill health: a poor food intake, especially for a prolonged period, makes patients more prone to illness and injury and illness and injury can lead to a reduced appetite through a wide variety of mechanisms – which results in poor food intake. Thus, it is a vicious cycle which often requires medical help to stop.



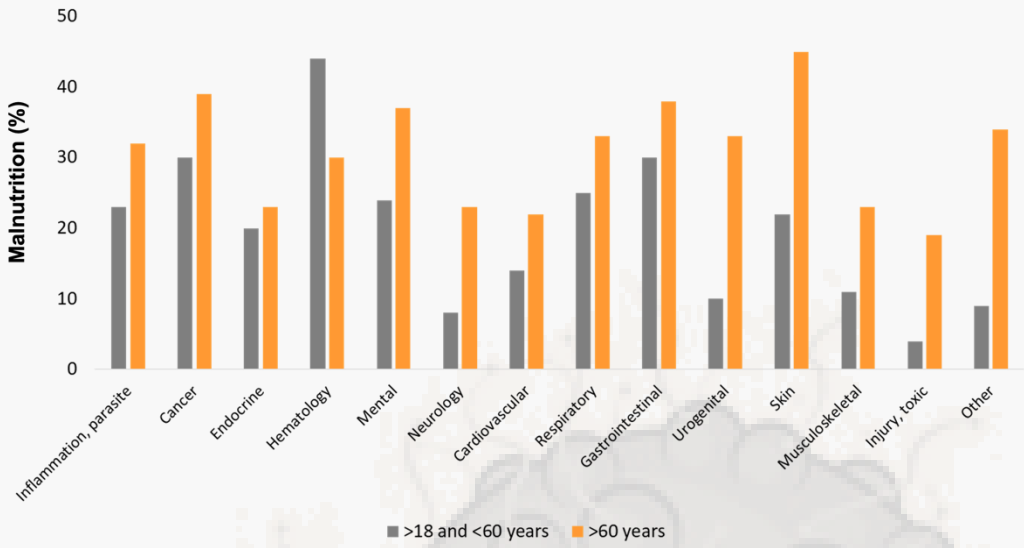
Factors contributing to the development of malnutrition

Disease-related malnutrition (malnutrition caused by the changes of the body metabolism which increases the daily nutritional needs due to illness) has been an important and under-recognized problem for many years, and it continues to be a growing major public health problem with an aging population (Correia et al. 2003, Meijers et al. 2009). Since disease-related malnutrition inversely affects different organs and systems of the body and leads to severe physical and psycho-social consequences, all health care settings need to develop ways for the early diagnosis and the treatment / prevention of this condition. Surveys from the United Kingdom (UK) suggest that the majority of persons affected by or at risk of malnutrition are not those being treated in the hospital. Of the estimated 3 million people affected by malnutrition in the UK only 2% are in hospitals, 93% live in the community, largely in their homes, 2-3% in sheltered housing, and 5% in care homes (Pryke et al. 2013). In the European Union countries, about 20 million patients are affected by disease-related malnutrition. This number is as high as 33 million patients when all countries of Europe are considered. Annual treatment costs of disease-related malnutrition reach € 120 billion in the European Union, and about € 170 billion in Europe (Ljungqvist et al. 2009, Ljungqvist et al. 2010). In Germany, UK, and Ireland, the annual costs of disease-related malnutrition on a national level have been calculated: € 9 billion in 2006, and € 15 billion in 2007 (Freijer et al. 2014a, Freijer et al. 2014b).

Nutritional depletion in Western countries is usually caused by the joint action of an underlying disease (e.g. cancer, chronic obstructive pulmonary disease [COPD], inflammatory bowel disease [IBD], cognitive impairment of the elderly, Alzheimer disease) and dietary deficiency (Naber et al. 1997). As a consequence, treatment should focus not only on the disease itself, but also on nutritional intervention. The most common diseases that can cause malnutrition include oncological diseases such as cancer, pulmonary diseases such as chronic obstructive pulmonary disease or cystic fibrosis and gastroenterological diseases such as inflammatory bowel disease. Certain treatments of these diseases, such as chemotherapy or radiation therapy, can also have a negative impact on nutrition.

2. Disease-related malnutrition

Disease-related malnutrition is present in a wide range of diseases, e.g. in infectious and parasitic diseases, oncologic, endocrine, gastrointestinal, pulmonary, hematologic, psychiatric, urogenital, and neurological disorders. The problem is known worldwide, affecting about 20 million patients with the cost of 120 billion Euros in the EU countries (Freijer et al. 2013).



Frequency of malnutrition in different diseases (Freijer et al. 2013)

For patients with a variety of diagnoses, reports indicate that up to 62% may be considered at risk of malnutrition or frankly malnourished on admission to hospital with rates of up to 12.5% in the community. Studies specifically in general medical patients indicate a possible prevalence rate of up to 56% on admission to hospital (Stratton et al. 2003).

The consequences of malnutrition, if left untreated, are serious, causing a marked decline in physical and psychological health and function. Malnutrition has a negative effect on recovery from disease / treatment efficacy, wound healing, frequency of complications (e.g. infection, decubitus), prognosis, mortality, tolerance of treatment, quality of life, and healthcare use (e.g. general practitioners visits, number and length of hospital stay) (Martyn et al. 1998, Löser C. 2010). Weight loss during an illness is a red flag for even the most inexperienced clinician, but malnutrition in the absence of manifest illness is rarely recognized as a modifiable risk factor for development of chronic diseases. The social determinants influencing food intake and hence malnutrition, e.g. loneliness and isolation, poverty, poorly fitting dentures, inaccessible food outlets, difficulty in cooking, or supporting oneself to eat and drink, may be in operation long before associated comorbidities appear. Moreover, treatment and amelioration of these factors may delay or even prevent the onset of disease (Pryke et al. 2013).

For such a widespread significant problem, malnutrition has so far attracted very little attention in primary care. One factor of this phenomenon may be nutrition's notable absence from most medical school curricula and postgraduate training, resulting in poor awareness, large knowledge gaps, and a deficit of nutrition-related competencies. Lack of ownership among clinicians is another factor, because malnutrition, like other processes such as pain, inflammation and obesity, cuts across traditional clinical specialty boundaries instead of falling neatly within one or other. Reflecting this collective uncertainty and patchy knowledge, a host of unhelpful nutritional myths have also propagated and stabilized within our culture and have normalized nutritional problems. It would be timely to debunk the perception that weight loss is an inevitable part of ageing or that lower energy "healthy foods" are appropriate for everyone (Pryke et al. 2013).

There is ongoing debate in the literature about the merits of oral nutritional supplements (ONS) compared to first-line dietary advice ("food first": information on food fortification, snacks, food choices). Skepticism regarding ONS relate to its largely hospital-focused evidence base. Issues around palatability, taste fatigue (particularly in the chronically ill requiring long-term supplementation), patient preference for "normal food" and psychological factors were regarded as factors that might all impact the effectiveness of therapy. Thus, skeptics suggest to prefer dietary advice versus ONS. Conversely, superficial dietary advice runs the risk of at-risk patients simply increasing calories without addressing essential protein and micronutrient requirements, and it is unfeasible for a "food first" approach to address nutritional deficits in some patients, particularly those with anorexia and/or early satiety. Although dietary fortification and counselling can improve nutritional intake, the evidence base is weak for improved outcomes relative to the evidence for ONS, questioning whether "food first" can replicate the combination of nutrients found in ONS (Pryke et al. 2013). These results indicate that compared to dietary counseling, the use of ONS are based on more evidence in the treatment and prevention of malnutrition. Numerous clinical studies investigated the effect of nutritional therapy on disease-related malnutrition. Meta-analyses on treatment of disease-related malnutrition with medical nutrition show a reduction in complications and mortality, improvement of wound healing, and increase of quality of life (Elia et al. 2021, Elia et al. 2005, Stratton RJ. 2005).

2.1. Malnutrition in cancer

In cancer, more than 30% of patients die due to cachexia and more than 50% of patients with cancer die with cachexia being present. In other chronic illnesses, one can estimate that up to 30% of patients die with some degree of cachexia being present. Mortality rates of patients with cachexia range from 10% to 15% per year (COPD), to 20% to 30% per year (chronic heart failure / CHF, chronic kidney disease / CKD) to 80% in cancer (von Haehling & Anker. 2010).

The prevalence of malnutrition in patients with cancer has frequently been shown to be one of the highest of all hospital patient groups. Weight loss is a frequent manifestation of malnutrition in patients with cancer. Several large-scale studies over the last 35 years have reported that involuntary weight loss affects 50-80% of these patients with the degree of weight loss dependent on tumour site, type and stage of disease. Recent data suggest that losses as little as 2.4% predicts survival independent of disease, site, stage or performance score (Ryan et al. 2019).

Weight loss is also a major distress for cancer patients, partly because muscle wasting "makes the disease visible" and is taken as signifying the proximity of death (Aapro et al. 2014). A systematic review found a negative relationship between loss of weight and health-related quality of life in cancer patients. Median overall survival (OS) was also significantly shorter in patients with pre-chemotherapy weight loss compared to those who had maintained their weight. Weight loss was associated with poor prognosis in prostate, colorectal, and certain types of lung cancer. In patients with advanced breast cancer, response rates were lower among those who had lost weight before chemotherapy (Aapro et al. 2014).

In a retrospective analysis of 1,555 consecutive chemotherapy patients with gastrointestinal cancer, self-reported weight loss before treatment was associated with more frequent and severe toxicities despite being treated for a shorter period, with shorter failure-free and overall survival, decreased response rate, quality of life and performance status (Andreyev et al. 1998). In lung cancer, weight loss before chemotherapy was an independent predictor of OS (Ross et al. 2004). Both in resected and non-resected pancreatic cancer, cachexia is significantly associated with poorer survival (Bachmann et al. 2008). Older patients with cancer may have an increased risk of early discontinuation of active antitumor treatment, which results in poor outcome in curative or adjuvant setting. In a study of 96 patients older than 65 years receiving palliative first-line chemotherapy, early discontinuation was associated with shorter OS, and malnutrition was an independent predictive factor for early discontinuation of anticancer treatment (Kim et al. 2014).

2.2. Summary

Since cancer-related malnutrition and cachexia are closely related to prognosis and outcomes in patients with malignant diseases, early detection and treatment of these conditions are increasingly important in the hope that timely intervention improves both patient- centered and oncology outcomes.

3. Nutritional needs in cancer

3.1. Energy and protein intake

By population prevalence, one of the most frequent cachexia subtypes is cancer cachexia (von Haehling & Anker. 2010). Cachexia is a complex metabolic syndrome associated with underlying illness and is characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). From an energy point of view, an increased weight loss may be related to a decrease in thermodynamic efficiency. Variable thermodynamic efficiency in metabolic systems is related not only to differences in weight but also may confer metabolic advantages or drawbacks. At present, it is widely held that elevated resting energy expenditure (REE) is a major determinant in the development of malnutrition in cachectic patients. Resting energy metabolism represents the combustion of fuel sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs and for the mechanical processes involved in keeping the body alive. It is appropriate, therefore, to presume that abnormalities in carbohydrate, lipid and protein metabolism are major biochemical bases of elevated REE (Hyltander et al. 1991, Argiles et al. 2014).

Malnutrition, anorexia and cachexia are common findings in cancer patients. Though they become more evident with tumor growth and spread, the mechanisms by which they are sustained often arise early in the history of cancer. For malnutrition, these mechanisms involve damage caused by the primary tumor or by specific anticancer therapies (surgery, chemotherapy, radiotherapy). This damage may arise also in cancers that usually are not directly responsible for nutritional and metabolic status alterations. For anorexia, meal-related neural or hormonal signals and humoral signals related to body fat or energy storage and the interaction of these signals with the hypothalamus or the inappropriate hypothalamic response play a pathogenic role (Nicolini et al. 2013).

Patients with cancer cachexia frequently develop a chronic negative energy and protein balance driven by a combination of reduced food intake and metabolic change. Treatment for cachexia has concentrated on increasing food intake, although that alone is unable to reverse the metabolic changes (Tisdale et al. 2004). Due to the hypercatabolic state and increased protein breakdown seen in malnourished / cachectic patients, increased energy and protein intake is vital in slowing down / stabilizing or even reversing weight loss and lean body mass /muscle wasting in cachectic patients.

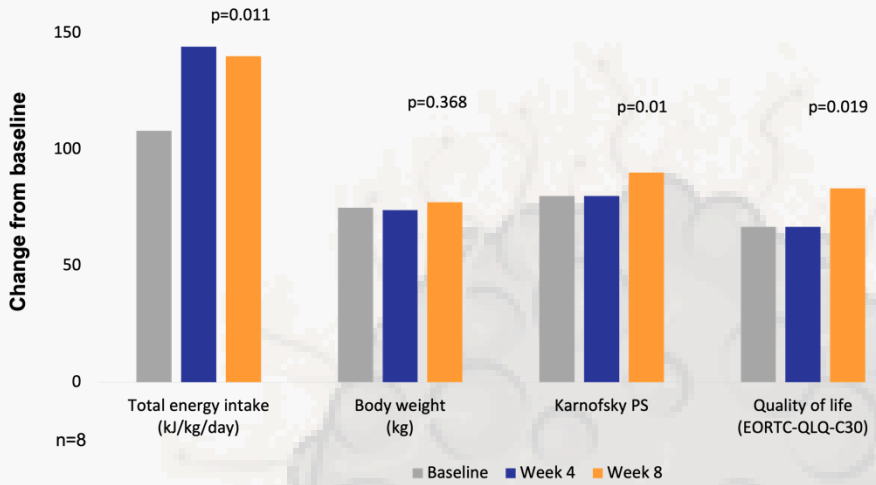
Higher energy intake attenuates the deterioration of the nutritional status (Laviano et al. 2005), significantly improves weight (Baldwin et al. 2012), decreases the rate of complications (Marin Caro et al. 2007), may influence the modulators of the catabolic response (Bosaeus et al. 2002), has a sparing effect on protein utilization in order to favor restauration of lean body mass (Jéquier E.), and can improve the cancer patients' status and consequently their quality of life (Marin Caro et al. 2007).

Sarcopenia (defined as having an appendicular skeletal muscle mass (kg/height in m^2) less than 2 standard deviations below the mean of a young reference group) is present in 20-70% of cancer patients depending on the tumor type and sarcopenia definition used. There are over 25 studies in the literature reporting rates of sarcopenia in different cancer populations. The majority of studies describing sarcopenia in oncology populations place cancer patients akin to those healthy elderly aged late 70s to early 80s. (Ryan et al. 2016).

Both low muscle mass and low muscle attenuation have been associated with poorer tolerance to chemotherapy; increased risk of postoperative complications; significant deterioration in a patients' performance status, and poorer psychological well-being, overall quality of life, and survival (Ryan et al. 2019).

In a cross-sectional study of 630 cancer patients, a significant discrepancy was reported between body surface area (BSA) and body composition with more than 30% of patients differing considerably from the established mean of their respective BSA category. In the subcohort of patients receiving chemotherapy, absolute fat-free mass [HR=0.970, p=0.026] as well as being allocated to the low fat-free mass group (HR=1.644, p=0.025) emerged as predictors of increased 1-yr mortality (Stobäus et al. 2013).

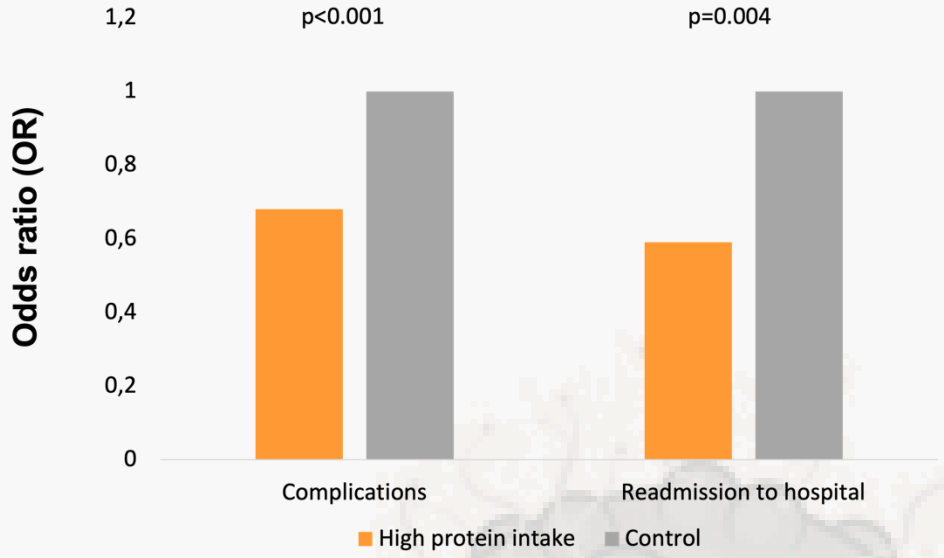
Higher protein intake ameliorates the immune functions and thus decrease the therapy-related immune suppression and the frequency of complications, facilitates wound healing after surgical treatments and radiotherapy, and facilitates the preservation of albumin level (Bauer & Capra 2005).



Energy- and protein-dense oral nutritional supplement improved dietary intake, nutritional status, and quality of life in cancer patients (Bauer & Capra 2005)

In a cross-sectional, observational study including 106 patients with gastrointestinal tract tumors, patients were divided into two groups: a low-protein diet group (≤ 1.2 g/kg/day, 65% of patients) and a high-protein diet group (> 1.2 g/kg/day, 35% of patients). Logistic regression after adjusting for sex and caloric and carbohydrate consumption showed an association between skeletal muscle mass index and high-protein diet (OR=4.19, 95% CI [1.06–16.56], p<0.001), but not with branched chain amino acids (BCAA). Daily total protein intake, but not isolated BCAA or leucine, was able to predict an increase in skeletal muscle mass index in 43% of patients (p=0.006). Thus, high-protein diet was associated with skeletal muscle mass index, and total protein intake was a better predictor of skeletal muscle mass index than BCAAs (Soares et al. 2020).

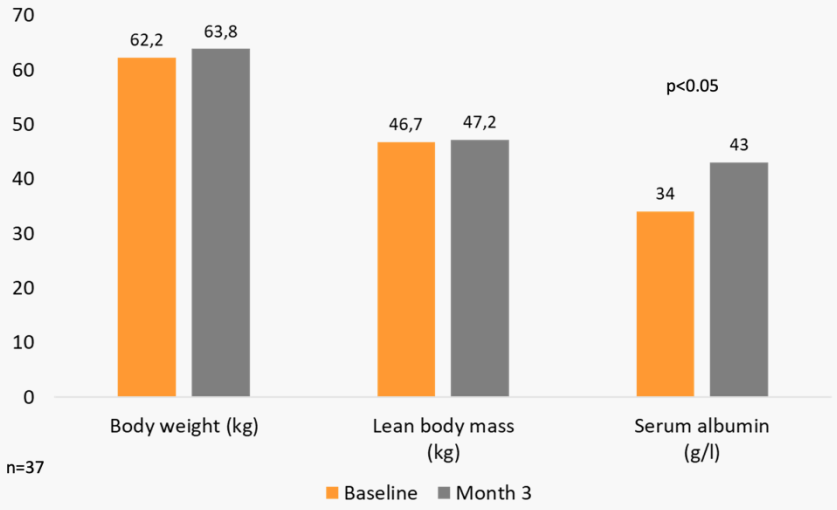
A systematic review involving 36 randomized controlled trials of 3,790 patients (mean age 74 years; 83% of trials in patients >65 years) and a series of meta-analyses of high protein ONS studies demonstrated a range of effects across settings and patient groups in favor of the high protein ONS group. The review and meta-analysis provided evidence that high protein supplements produce clinical benefits and favorable economic implications (Cawood et al. 2012).



High protein intake decreases the risk of complications and rehospitalization in cachectic patients (Cawood et al. 2012)

In a study of 32 patients with elective colorectal surgery and 21 patients operated on for acute obstruction or severe peritonitis, dietary advice and protein supplements administered for 4 months after discharge substantially increased protein intake, gain in body weight and lean body mass, especially in the legs as shown by dual-energy X-ray absorptiometry (Jensen and Hessov. 1997).

In 37 ambulatory head-and-neck cancer patients who did or did not receive concomitant chemotherapy, a 12-week postoperative nutritional therapy with a high-energy and high-protein, ω-3 fatty acids-enriched oral nutritional supplement improved weight, and fat-free mass, and significantly improved serum albumin level (de Luis et al. 2015).



High-energy, high-protein, and ω-3 fatty acids-enriched clinical nutrition improves body weight, fat-free mass and serum albumin level in postoperative ambulatory head-and-neck cancer patients (de Luis et al. 2015)

3.2. Tailored composition of enteral nutrition

Though increased energy intake is very important in treating malnutrition / cachexia of patients with chronic diseases, the source of this extra energy also plays an important role in the therapy of the primary disease (cancer, COPD, etc.). It is already well-known that most malignant cells depend on steady glucose availability in the blood for their energy and biomass generating demands and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction. Moreover, high insulin and insulin-like growth factor 1 (IGF1) levels resulting from chronic ingestion of carbohydrate-rich Western diet meals can directly promote tumor cell proliferation via the insulin / IGF1 signaling pathway. In addition, ketone bodies that are elevated when blood glucose and insulin levels are low, have been found to negatively affect proliferation of different malignant cells. Last but not least, many cancer patients exhibit an altered glucose metabolism characterized by insulin resistance. Thus, cancer patients may profit from a decreased carbohydrate and an increased protein and fat intake (Klement & Kämmerer 2011).

3.2.1. Cancer-specific signaling pathways

Hyperinsulinaemia (a hallmark of insulin resistance) and the increase in bioavailable IGFR1 seem to have a role in tumor initiation and progression in insulin-resistant patients. One of the reasons of the increased risk of cancer among insulin-resistant patients can be the overproduction of reactive oxygen species that can damage DNA contributing to mutagenesis and carcinogenesis. On the other hand, it is possible that the abundance of inflammatory cells in adipose tissue of obese and diabetic patients may promote systemic inflammation which can result in a protumorigenic environment (Arcidiacono et al. 2012).

Chronic activation of the IGFR1-insulin receptor (IR)/PI3K/Akt survival pathway through high blood glucose, insulin and inflammatory cytokines has been proposed as a cause of carcinogenesis and switch towards aerobic glycolysis. In this theory, hyperactivation of the IGFR1-IR signaling pathway does not occur primarily through somatic gene mutations, but rather through elevated concentrations

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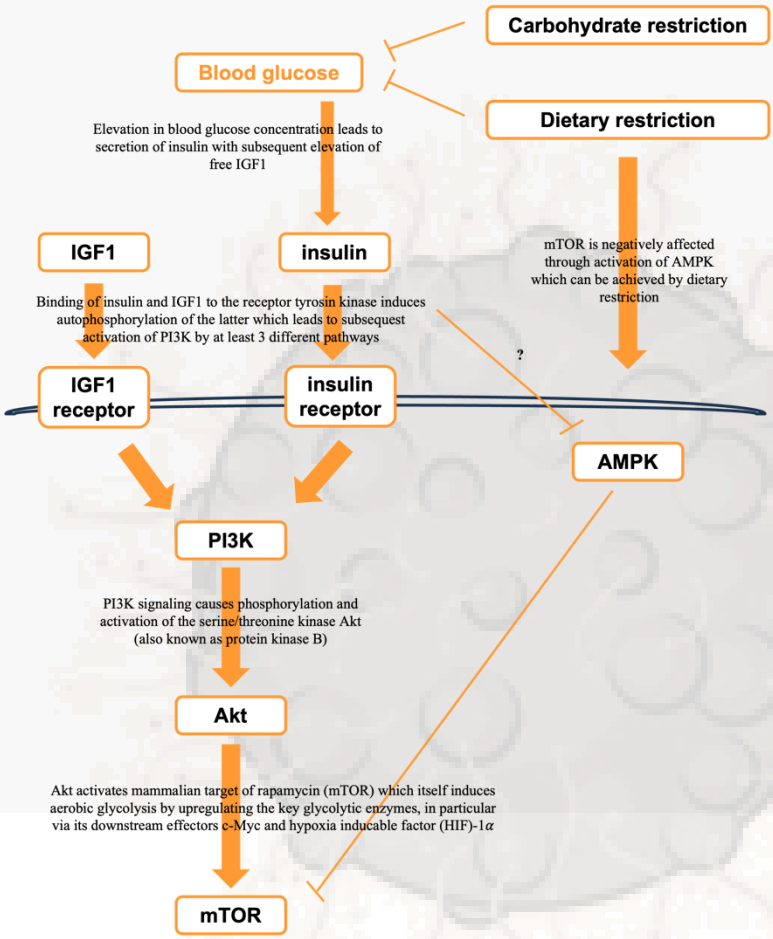
of insulin and IGF1, allowing for more ligands binding to their receptors. Interestingly, gain-of-function mutations resulting in ligand-independent overactivation of both IGFR1 and IR are uncommon. Furthermore, loss-of-function of the tumor suppressor PTEN may result in hypersensitivity to insulin/IGF1-mediated activation of the IGFR1-IR pathway rather than constitutive downstream activation. Thus, it seems possible that high levels of insulin and IGF1 in the microenvironment favor cell survival and evolution towards malignancy instead of apoptosis in DNA-damaged cells. Indeed, both hyperglycemia and hyperinsulinemia are predictors of cancer occurrence and cancer-related mortality. This highlights the link between the metabolic syndrome and cancer on the one hand and cancer and lifestyle factors like nutrition on the other. Restriction of dietary carbohydrates would counteract this signaling cascade by normalizing glucose and insulin levels in subjects with metabolic syndrome, in this way acting similarly to calorie restriction/fasting. Indeed, it has been shown in healthy subjects that carbohydrates restriction induces hormonal and metabolic adaptions very similar to fasting. Dietary restriction is able to inhibit mTOR signaling through a second, energy-sensing pathway by stimulating phosphorylation of AMP-activated protein kinase (AMPK). *In vitro*, AMPK phosphorylation is sensitive to the ratio of AMP/ATP within the cell; *in vivo*, however, concentrations of glucose and other nutrients are kept fairly stable throughout calorie restriction, suggesting that hormones such as insulin and glucagon might play a more dominant role in regulating AMPK and thus mTOR activation. This may open a second route to mimic the positive effects of calorie restriction through carbohydrate restriction (Klement & Kämmerer, 2011).



Blood glucose, insulin and IGF1 in oncogenesis (Klement & Kämmerer, 2011)

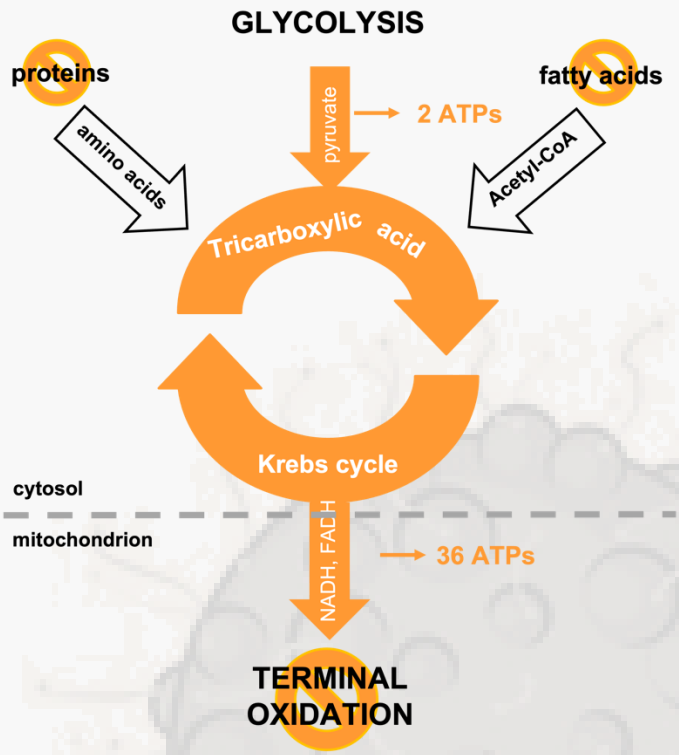
The Akt signaling pathway plays a vital role in cell survival. Aberrant activation of this signaling cascade has been detected in various types of malignancies and is associated with tumorigenesis. Akt functions as a pro-survival factor by inhibiting apoptotic signal cascades and activating pro-survival signaling pathways. Upon activation, Akt phosphorylates and inhibits a number of pro-apoptotic Bcl-2 family members, while, through direct inhibition and exclusion of pro-apoptotic transcription factor FOXO3a (Forkhead box O3), suppresses the expressions of pro-apoptotic factors. Another key pro-survival pathway targeted by Akt is the mTOR signaling pathway. Akt phosphorylates and activates mTOR kinase, leading to the phosphorylation/activation of anti-apoptotic protein Mcl-1. Furthermore, Akt negatively regulates hypoxia-induced apoptosis (Hein et al. 2014). mTOR is a component of the PI3K cell survival pathway that monitors the availability of nutrients, mitogenic signals and cellular energy and oxygen levels, and therefore is significant in the regulation of cell growth and proliferation. Abnormal activation of the PI3K pathway is considered involved in numerous cancers, and increased activation of this pathway is often associated with resistance to cancer therapies. mTOR acts upstream and downstream of Akt, operating at a key junction in the PI3K pathway. mTOR can form two different multiprotein complexes, mTORC1 and mTORC2, that regulate the protein synthesis necessary for cell growth and proliferation (Zarogoulidis et al. 2014).

Several lines of evidence implicate IGFs and their receptor, IGF-1R, in many human malignancies, including carcinomas of the lung. Two distinct signal transduction pathways have been identified for IGF-1R. One pathway activates Ras, Raf, and MAPK, the main mitogen-conducting pathway, and the other pathway involves PI3K, which is responsible for antiapoptotic signal transduction. In a tumor-bearing nude mice model, IGFs, especially IGF-I, stimulated the growth of NSCLC cells. IGF-binding protein 3 under the control of the cytomegalovirus promoter (Ad5CMV-BP3) inhibited the growth of NSCLC cells *in vitro* and *in vivo* by inducing apoptosis. IGF-binding protein-3 was also a potent inhibitor of the PI3K/Akt/PKB and MAPK signaling pathways, which are important mediators of cell survival (Lee et al. 2002). In a phase 3, double-blind, randomized, international trial comparing the mTOR inhibitor everolimus (10 mg/day) plus exemestane (25 mg/day) versus placebo plus exemestane in postmenopausal women with hormone receptor positive advanced breast cancer with recurrence/progression during or after nonsteroidal aromatase inhibitors, the addition of everolimus to exemestane markedly prolonged progression-free survival and was generally well tolerated (Yardley et al. 2013, Pritchard et al. 2013).

While anorexia may also be present, the energy deficit alone does not explain the pathogenesis of cachexia seen in about half of all cancer patients. The presence of an acute phase response (APR) has been linked to accelerated weight loss and a shortened survival time. The APR is thought to be initiated by cytokines such as IL-6 and IL-8, production of which is induced by a tumor factor, proteolysis inducing factor (PIF). Cachectic cancer patients also show an increased expression of uncoupling protein-3 in muscle, which may act as an energy sink, increasing energy expenditure. Loss of adipose tissue appears to be due to an increase in degradation of triglycerides, rather than a decrease in synthesis. One candidate for this effect is a tumor lipid mobilizing factor (LMF), which stimulates lipolysis directly through a cyclic AMP-mediated process via interaction with a β3-adrenergic receptor. Loss of skeletal muscle arises from both a depression in protein synthesis and an increase in protein degradation. The major proteolytic pathway involved in intracellular protein breakdown in cachectic muscle is the ATP-ubiquitin-dependent proteolytic pathway. Both PIF and TNF-α, but not other cytokines, can induce expression of the key regulatory components of this pathway (Tisdale MJ. 2003).

3.2.2. Cancer-specific metabolism – Aerob glycolysis

When treating diabetes patients, A. Braunstein observed already in 1921 that in those patients who developed cancer, glucose secretion in the urine disappeared. Moreover, by culturing tissues of benign and malign origin in glucose-containing solutions, he quantified the much higher glucose consumption by cancer tissue compared to muscle and liver. One year later, R. Bierich described the remarkable accumulation of lactate in the micromilieu of tumor tissues and demonstrated lactate to be essential for invasion of melanoma cells into the surrounding tissue. Otto Warburg observed in 1923 that tumor tissue *ex vivo* would convert high amounts of glucose to lactate even in the presence of oxygen, a metabolic phenotype now referred to as the Warburg effect. The underlying cause of the switch from oxidative phosphorylation to glycolysis seen in cancer cells even in the abundance of oxygen (the so-called aerob glycolysis) may be the irreversible damages accumulated in the mitochondria. Furthermore, most mutations of the onco- and tumor suppressor genes in cancer cells directly or indirectly facilitate aerob glycolysis via the activation of signaling pathways such as the IGF1R/IR/PI3K/mTOR signaling pathway (Klement & Kämmerer. 2011).



Impairment of metabolism in cancer cells (Klement & Kämmerer. 2011)

Ketogenic diets (low-carbohydrate, high-fat diets with controlled protein intake) simultaneously target glucose metabolism and glucose-related signaling in tumor cells. A reduction in circulating glucose levels compromises energy production and macromolecular biosynthesis. The concomitant reduction in blood insulin/IGF1 levels decreases signaling by the PI3K/Akt/mTOR pathway, thus impairing glycolytic metabolism and macromolecular biosynthesis. Moreover, in contrast with normal cells, tumor cells are unable to efficiently adapt to metabolize ketone bodies (Branco et al. 2016).

The ketogenic diet - a treatment for medically refractory epilepsy - has been suggested as an alternative strategy to inhibit tumor growth by altering intrinsic metabolism, especially by inducing glycopenia. In a mouse model of glioma ketogenic diet treatment significantly reduced the rate of tumor growth and prolonged survival. Further, the ketogenic diet reduced reactive oxygen species (ROS) production in tumor cells. Gene expression profiling demonstrated that the ketogenic diet induces an overall reversion to expression patterns seen in non-tumor specimens. Notably, genes involved in modulating ROS levels and oxidative stress were altered, including the ones encoding cyclooxygenase 2, glutathione peroxidases 3 and 7, and periredoxin 4. Besides improving survivability in this mouse model of glioma, these results suggest that the mechanisms accounting for this protective effect likely involve complex alterations in cellular metabolism beyond simply a reduction in glucose (Stafford et al. 2010). The potential application of these biochemical changes in the therapeutic approaches for cancerous diseases are already being investigated. Xu et al. demonstrated that inhibiting glycolysis induces apoptosis in multidrug resistant cancer cell lines. Thus, deprivation of cellular energy supply may be an effective way to overcome multidrug resistance (Xu et al. 2005).

3.2.3. Low carbohydrate diet

According to the data from the National Health and Nutrition Examination (NHANES, USA, 1971-2000), the increase in calorie intake in the American diet during the investigated 30 years was almost entirely due to the increase in carbohydrate intake (Hite et al. 2011). In a prospective cohort study of about 65,000 subjects, abnormal glucose metabolism was associated with a statistically significant increased overall risk of cancer in women and an increased risk of cancer at many sites in women and man, independently of obesity. This is in accordance with the findings of some other large cohort studies, suggesting that abnormal glucose metabolism is a general risk factor for cancer development (Stattin et al. 2007.)

In an Italian case-control study of 578 patients with histologically confirmed bladder cancer and 608 controls, bladder cancer risk was directly associated with high dietary glycemic load and with consumption of high quantity of refined carbohydrate foods (Augustin et al. 2017). In a pooled analysis of 2 case-control studies (500 cases altogether) of esophageal and gastric cancer, the risk of developing esophageal adenocarcinoma was increased by 51% to 58% in association with sucrose intake, sweetened desserts/beverages and glycemic index, comparing the intake in the highest with the lowest quintile (Li et al. 2017).

The prospective investigation of cancer risk and dietary glycemic index (GI) / glycemic load (GL) in the EPIC-Italy cohort revealed that after a median 14.9 years, 5,112 incident cancers and 2,460 deaths occurred among 45,148 recruited adults. High GI was associated with increased risk of colon and bladder cancer. High GL was associated with increased risk of colon cancer, increased risk of diabetes-related cancers, and decreased risk of rectal cancer. High intake of carbohydrate from high GI foods was significantly associated with increased risk of colon and diabetes-related cancers, but decreased risk of stomach cancer, whereas high intake of carbohydrates from low GI foods was associated with reduced colon cancer risk (Sieri et al. 2017).

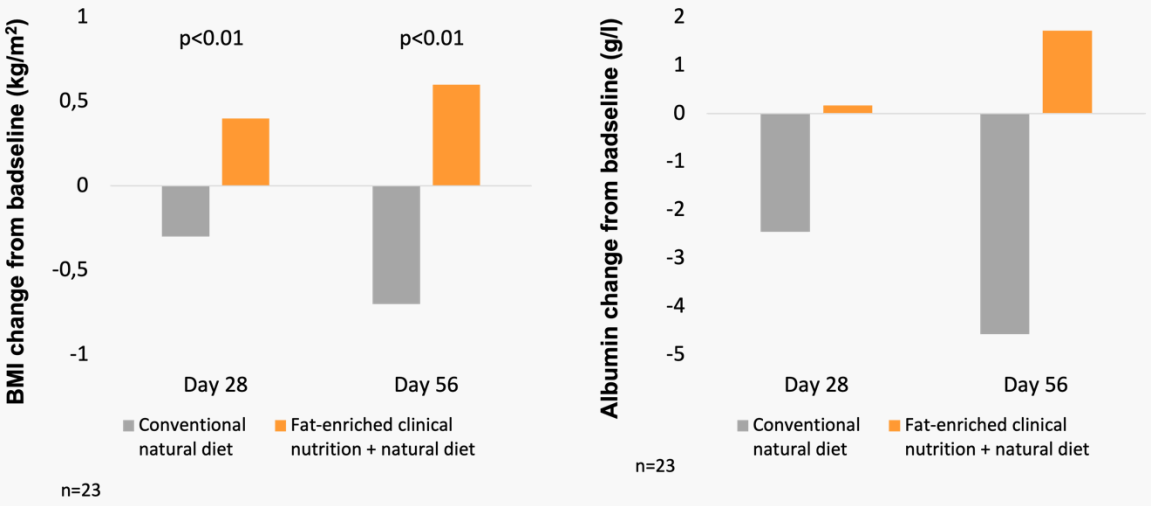
The biochemistry that relates low-carbohydrate nutrition to weight loss and chronic disease is already well-known. Dietary carbohydrate causes insulin release that is directly related to the amount of glucose in the bloodstream. Insulin increases fatty acid synthesis via the stimulation of acetyl-CoA carboxylase and increases triacyl-glycerol synthesis in the liver through lipoprotein lipase. Cholesterol synthesis increases via the activation of hydroxyl-methyl-glutaryl-CoA-reductase. Storage of fatty acids is favored since insulin inhibits the release of fatty acids from the cell through the activation of the hormone-sensitive lipase. Thus, reducing dietary carbohydrate intake seems to create a metabolic milieu that can positively affect appetite and reduce fat storage as well as or more effectively than other dietary strategies (Hite et al. 2011).

In HeLa tumor cell cultures, the effect of partial deprivation of D-glucose and L-glutamine (to typical physiological concentrations) during 0 to 6-h exposures was studied. Reduction of glucose levels from 6 to 3 mM (and glutamine levels from 1 to 0.5 mM) led to a cancer cell survival of 73% after 2-h exposure and 63% after 4-h exposure. Reducing glucose levels from 6 to 0 mM (and glutamine levels from 1 to 0 mM) for 4 h resulted in 53% cell survival. These data reveal that glucose (and glutamine) deprivation to typical physiological concentrations result in significant cancer cell killing after as little as 2 hours (Mathews et al. 2014).

In an in vitro study of the effect of long-term glucose deprivation on cancer cell survival, normal and cancer cell lines (MCF-7, HeLa, and MDA-MB-231) were cultured initially at a glucose level of 25.52 mmol/l, L-glutamine level of 4 mmol/l, and sodium-pyruvate level of 1 mmol/l. Cells were then exposed to the experimental conditions of 6 mmol/l glucose, 0.6 mmol/l L-glutamine, and 0 mmol/l sodium pyruvate. After proliferation stabilized in these conditions (reached a plateau), cells were exposed to the experimental condition of 3 mmol/l glucose, 0.6 mmol/l L-glutamine, and 0 mmol/l sodium pyruvate, until cell growth stabilized again. The study demonstrated that long-term glucose deprivation affected the investigated cancer cell lines more than non-cancer cell lines. Moreover, different cancer cell lines were differently affected by long-term glucose deprivation. A period when the in vitro cancer cell lines were at their most vulnerable could be determined. During the experimental conditions, cancer lines recovered, but not fully. This result illustrates the need for adjuvant therapies (chemotherapy, irradiation, etc.) besides glucose deprivation (Mathews et al. 2020).

In a HER-2/neu-induced mammary tumor animal model, female mice were fed by Western or 15% carbohydrate diet parallel with mTOR inhibitor or anti-inflammatory drug treatment and were monitored for tumor development. Tumors grew slower in mice fed with the 15% carbohydrate diet, while the animals did not lose weight. Additive antitumor effects were observed with the mTOR inhibitor CCl-779 and especially with the COX-2 inhibitor celecoxib, a potent anti-inflammatory drug. Whereas only 1 mouse on the Western diet achieved a normal life span, more than 50% of the mice on the low-carbohydrate diet reached or exceeded the normal life span. These data offer a compelling preclinical illustration of the ability of a low carbohydrate diet in cancer development and progression (Ho et al. 2011).

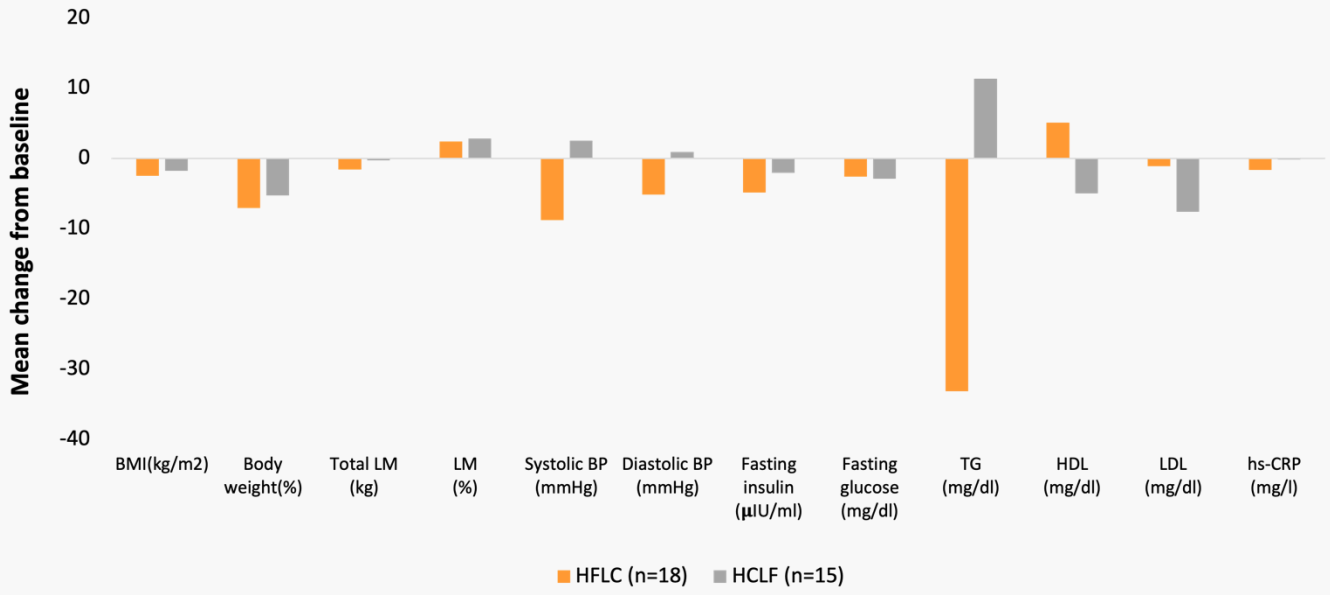
Twenty-three moderately malnourished patients with gastrointestinal carcinomas were randomized to receive either a conventional diet supplying 35 non-protein kcal and 1.1 g of protein/kg per day (group A, n=11) or a fat-enriched artificial liquid diet (20 non-protein kcal/kg per day) plus normal meals (group B, n=12) for a period of eight weeks. The fat content of the artificial diet was 66% of the non-protein calories. At weeks 4 and 8, the consumption of non-protein calories did not differ significantly between the two patient groups. An average weight gain in group B contrasted with an average weight loss in group A after 4 ($p<0.01$) and 8 weeks ($p<0.05$). Fat-free mass showed an intergroup difference in favour of group B after 8 weeks ($p<0.05$). Body cell mass was maintained throughout the study in group B but declined significantly up to weeks 4 and 8 in group A (intergroup difference: $p<0.05$ and 0.01, respectively) (Breitkreuz et al. 2005).



Low-carbohydrate-high-fat nutrition increases body weight, lean body mass and albumin level in cancer patients (Breitkreutz et al. 2005)

A strong body of evidence has demonstrated the clinical benefits of nutritional ketosis in intractable epilepsy and conditions associated with insulin resistance, now including cancer. Keto-adaptation results in less reliance on the glucose/insulin axis and profound changes in substrate use characterized by accelerated fatty acid oxidation and decreased glucose flux, which may provide a therapeutic mechanism for different types of tumors. Keto-adaptation also restores the hormonal and inflammatory environment of the host in ways that would be expected to deter tumor growth. Decreased insulin concentration and signal transduction should translate into less activation of growth factors and oncogenic pathways associated with PI3K/Akt, mTOR and hypoxia inducible factor. Keto-adaptation promotes an anti-inflammatory phenotype that may result in a decreased invasiveness and increased progression free survival. The emerging role of beta-hydroxy-butirate as a potent Class I histone deacetylase inhibitor and ligand for cell receptors that target specific pathways involved in cancer etiology provides an epigenetic mechanism by which ketoadaptation may improve outcomes in individuals with breast cancer. The safety and acceptability of well formulated ketogenic diets are high when implemented appropriately. Thus, even if a ketogenic diet fails to directly decrease tumor burden through any of the above-mentioned mechanisms, the consistent benefits on comorbidities (i.e., decreased body fat, improved glucose control, improved dyslipidemia, etc.) make the benefit to risk ratio highly favorable (Hyde et al. 2017).

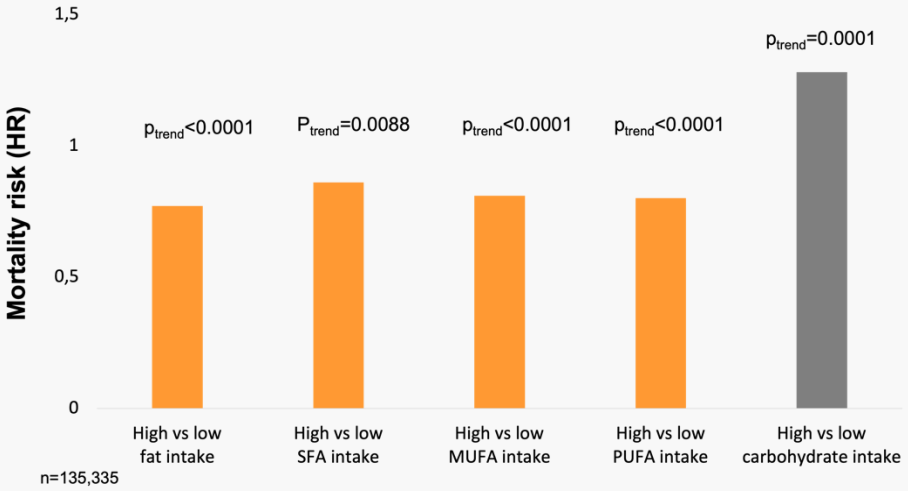
Larosa et al. were the first to demonstrate in 1980 (and confirmed by others my times since) that low-carbohydrate diets (30-130 g/day) do not necessarily require higher fat or protein intakes, and a spontaneous decrease in overall calorie consumption frequently results in little protein or fat added back for the carbohydrate removed (Larosa et al. 1980). This causes the phenomenon that a very low carbohydrate diet ameliorates all the investigated anthropometric laboratory parameters (BMI, abdominal fat, triglycerides, HDL, triglycerides/HDL ratio, ApoB/ApoA1 ratio, small LDL, blood glucose, plasma insulin, saturated fatty acid) of patients with atherogenic dyslipidemia (Hite et al. 2011). In a study, which randomized obese subjects (29.0-44.6 kg/m2) recruited from Boston Medical Center to a hypocaloric low-fat-high-carbohydrate / LFHC (n=26) or high-fat-low-carbohydrate / HFLC (n=29) diet for 12 weeks, the HFLC group had greater improvements in blood lipids and systemic inflammation with similar changes in body weight and composition, relative to the LFHC group (Ruth et al. 2013).



BMI: body mass index, LM: lean mass, BP: blood pressure, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, hs-CRP: serum high sensitivity C-reactive protein

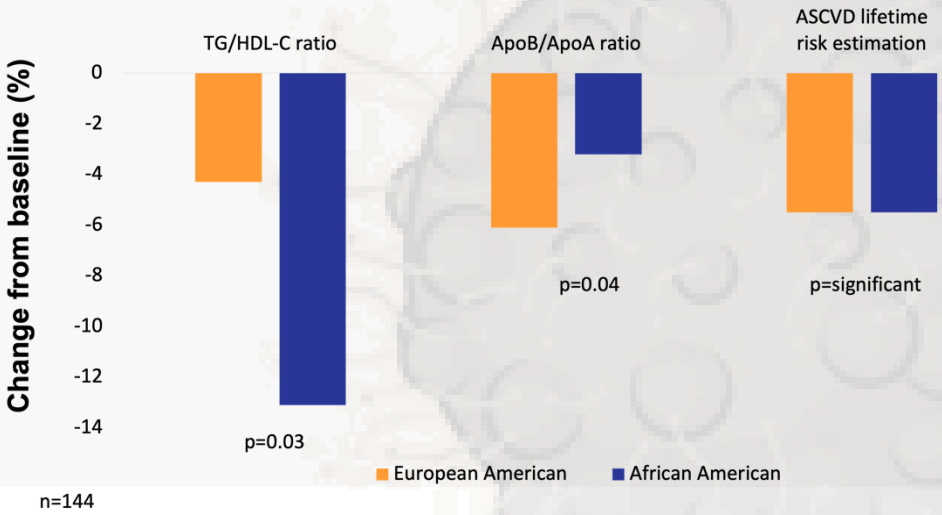
Beneficial effects of a low-carbohydrate diet (Ruth et al. 2013)

In a large, epidemiological cohort study of individuals aged 35–70 years in 18 countries with a median follow-up of 7.4 years (IQR 5.3-9.3), dietary intake of 135,335 individuals was recorded using validated food frequency questionnaires. Participants were categorized into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy provided by nutrients. During follow-up, 5,796 deaths and 4,784 major cardiovascular disease events were documented. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] *vs* lowest quintile [quintile 1] category, HR=1.28 [95% CI 1.12-1.46], p_{trend}=0.0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 *vs* quintile 1, total fat: HR=0.77 [95% CI 0.67-0.87], p_{trend}<0.0001; saturated fat, HR=0.86 [0.76-0.99], p_{trend}=0.0088; monounsaturated fat: HR=0.81 [95% CI 0.71-0.92], p_{trend}<0.0001; and polyunsaturated fat: HR=0.80 [95% CI 0.71-0.89], p_{trend}<0.0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 *vs* quintile 1, HR=0.79 [95% CI 0.64-0.98], p_{trend}=0.0498). Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality. Based on these results, the authors suggest the reconsideration of global dietary guidelines (Dehghan et al. 2017).



In a large, epidemiological cohort study, high carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality (Dehghan et al. 2017)

A study recruited 144 premenopausal women of age 21-50 years with class I/II obesity (BMI 30-39.9 kg/m^2) to keep a balanced high-fat diet (50% fat, 30% carbohydrate, 15% protein, with a balanced fat content – 1/3 saturated fatty acids, 1/3 monounsaturated fatty acids, 1/3 polyunsaturated fatty acids) for 16 weeks. In order to control the effects of high simple carbohydrate intake, total carbohydrate was maintained as 50% sugars (mono- and disaccharides) and 50% starches. Results in European American and African American participants were analyzed separately. Consuming the balanced high-fat diet significantly reduced cardiovascular risk by 5.5% (increased HDL particle size, increased the number of large HDL particle size, and increased apolipoprotein AI level) in both groups. In addition, European American women had significant reductions in fasting insulin levels (by 24.8%) and in HOMA-insulin resistance (by 29%). In the group of European American women, the most significant improvements occurred in VLDL particle size, apolipoprotein B levels, serum triglyceride, number of plasma LDL particles, and serum LDL cholesterol (Niswender et al. 2018).



High-fat balanced diet improves atherosclerotic cardiovascular disease risk in obese premenopausal women (Niswender et al. 2018)

Although they vary in their anticancer effects, ketogenic diets might prolong survival in animal models and human studies, as suggested by metaanalyses, primarily in brain neoplasia. Mice with intracranial glioblastomas exhibit improved tumor-reactive innate and adaptive immune responses, including increased cytokine production and cytolysis of tumor cells by specific CD8+ T cells, after treatment with a ketogenic diet. This effect is coupled to a decrease in markers of T cell exhaustion, such as PD-1 and CTLA-4. Similarly, a ketogenic diet inhibits lactate production by glycolytic tumors, an effect secondary to a decrease in circulating glucose concentrations, and thereby reduces lactate-mediated local immunosuppression, which in turn decreases the frequency of myeloid-derived suppressor cells and improves anticancer immune responses (Zitvogel et al. 2017).

According to several human studies, a low-carbohydrate diet is safe and tolerable for cancer patients (Cohen et al. 2018, Schmidt et al. 2011, Fine et al. 2012, Rieger et al. 2014, van der Louw et al. 2019).

3.2.4. Anti-inflammatory properties

3.2.4.1. ω-3 fatty acids

Some cytokines are also involved in the development of cachexia: the production of pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), proteolysis-inducing factor (PIF) and lipid-mobilizing factor (LMF) by tumor cells is the initial mechanism (Nicolini et al. 2013).

Diminishing the chronic inflammatory processes may also enhance the efficacy of the primary anti-tumor therapy and may ameliorate the quality of life of patients with malnutrition and cachexia (Samaras et al. 2014, Colomer et al. 2007, Giacosa & Rondanelli. 2008, Ioannidis et al. 2011, Guagnozzi et al. 2012). Eicosapentaenoic acid (EPA) can reduce inflammation and has the potential to modulate nutritional status/body composition (Pappalardo et al. 2015). A diet rich in EPA would negatively modulate the inflammatory cascade (Laviano et al. 2013).

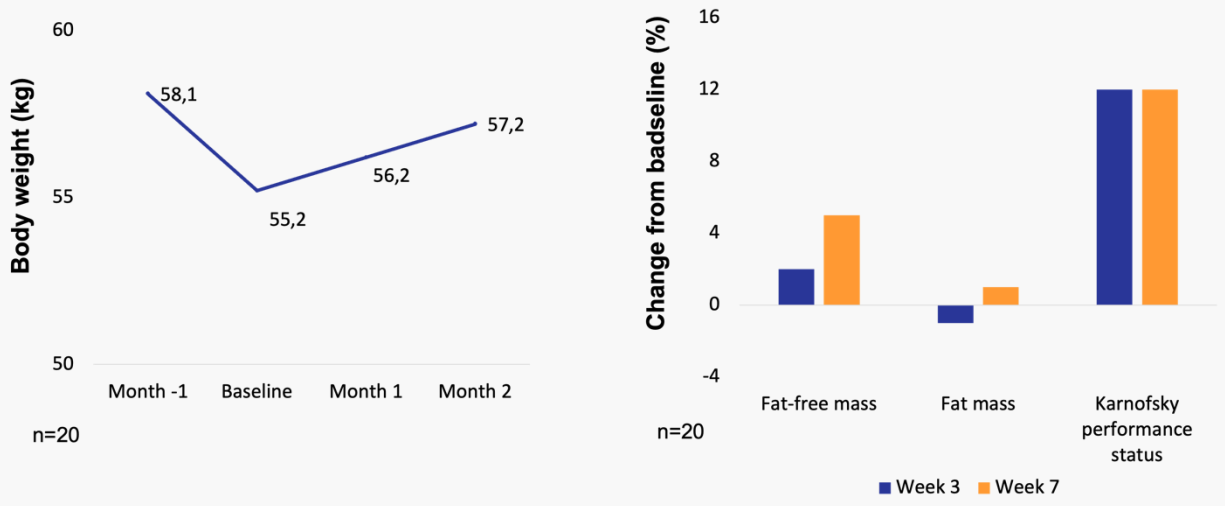
The main sources of the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are fish oil and krill oil, while vegetable oils (canola, walnut, flaxseed, soy) contain significant amount of the ω-3 fatty acid α-linolenic acid (ALA). ALA is converted to EPA and DHA in the human body when EPA and DHA levels are low, e.g. in non-fish eater vegetarians and vegans (Gillingham L. 2013). According to the results of a study, the conversion rate of ALA – EPA – DHA increases when the EPA and DHA levels are low in the body – there was only a minimal difference in the EPA and DHA levels of fish-eating and non-fish-eating meat-eaters, vegetarians, and vegans (Welch et al. 2010). Therefore, it is safe to state that ALA administered via ONS is converted into EPA and DHA ω-3 fatty acids in the malnourished patients. Other studies that directly compared the effect of mustard oil and fish oil on the frequency of cardiovascular diseases found that ALA is not less effective in decreasing cardiovascular risk than EPA or DHA (Singh et al. 1997, Singh et al. 2002). Thus, it can't be supposed that ALA is a less effective ω-3 fatty acid that either EPA or DHA.

ω-3-polyunsaturated fatty acids (ω-3-PUFA), have been proposed to be very active in reducing either tumor growth or the associated tissue wasting, particularly that of the adipose mass (Argiles et al. 2010). Administration of ω-3 fatty acids in a dose of at least 1.5 g/day for a prolonged time is associated with an improvement of clinical, biological and functional parameters and with amelioration of quality of life in advanced cancer patients with weight loss (Colomer et al. 2007, Giacosa et al. 2008). ω-3 PUFAs have been shown to modulate levels of pro-inflammatory cytokines, hepatic acute phase proteins, eicosanoids, and tumor-derived factors in animal models of cancer cachexia. Moreover, it was shown that EPA induced apoptosis in three different pancreatic cancer cell lines and inhibited cell growth in a dose-dependent manner.

When muscle cells or animals are treated with purified PIF, intense protein catabolism is elicited, and this appears to be substantially inhibited by EPA. An identical factor is found in humans, and there is provocative preliminary evidence that its presence is associated with weight loss in cancer patients (Tisdale MJ. 2003).

Administration of an EPA-enriched oral supplement seems effective in improving the nutritional status and quality of life of lung cancer patients undergoing chemotherapy (Guarcello et al. 2007). In a prospective, randomized, unblinded clinical trial with long-chain ω-3 fatty acids, giving the patients fish oil demonstrated a significantly ($p<0.001$) longer survival time of patients with generalized solid tumors. A prospective, randomized, single center, open-label study of 52 patients with pediatric malignant disease and receiving intensive chemotherapy demonstrated a decrease in cancer-induced weight loss when fed a protein and energy dense nutrition supplement containing EPA (Mueller et al. 2014). EPA can reduce inflammation and has a potential to modulate nutritional status/body composition (Pappalardo et al. 2015). Combination of chemotherapy and ω-3 supplementation appears an effective strategy to enhance the clinical outcome of cancer patients in their curative and palliative clinical trajectory. A diet rich in EPA would negatively modulate the inflammatory cascade. Feeding animals with a diet supplemented with high levels of EPA and DHA inhibits the growth of human pancreatic cancer xenografts in athymic nude mice by inducing oxidative stress and cell death. In 40 lung cancer patients receiving multimodality treatment, an EPA enriched oral nutritional supplement administered for 5 weeks improved quality of life and functional status when compared to the control isocaloric standard supplement. In 40 lung cancer patients receiving active treatment, fish oil supplementation (2.5 g EPA + DHA / day) resulted in maintaining weight while patients in the control group experienced an average weight loss of 2.3 kg. Daily supplementation of 0.3 g EPA and 0.4 g DHA increased body weight, blood polymorphonuclear cell number, phagocytosis and superoxide production in cancer patients receiving 5-fluorouracil and leucovorin, while non-supplemented patients lost 2.5 kg of weight during the 8 weeks of study and had significantly decreased number and function of blood polymorphonuclear cells. Since tumor growth appears to be related to the circulating levels of glucose and IGF1, any nutritional intervention inhibiting the IGF1 axis may also lead to increased sensitization of cancer cells to chemotherapy and increased resistance of normal cells to cancer treatment toxicity. Experimental evidence showed that plasma IGF1 decreased with increasing dietary ω-3:ω-6 ratio. Therefore, ω-3 fatty acid supplementation could represent a clinically relevant adjuvant therapy in cancer patients. In a study of 25 breast cancer patients with rapidly progressing visceral metastases, the addition of 1.8 g DHA /day to an anthracycline based chemotherapy regimen increased survival. Patients who had high incorporation of DHA into cell membranes had a survival of 34 months, almost the double of that of the low incorporating group (18 months), and longer than the average overall survival reported in the literature (18-23 months). In 46 lung cancer patients receiving first-line chemotherapy, fish oil supplementation (2.5 g EPA + DHA daily) during chemotherapy cycles resulted in an increased response rate (60.0% vs 25.8% in the standard of care group), and greater clinical benefit (80.0% vs 41.9% in the standard of care group). 1-year survival also tended to be greater in the fish oil group (60.0% vs 38.7%, $p=0.15$) (Laviano et al. 2013). EPA supplemented early enteral nutrition is also associated with preservation of lean body mass post-esophagectomy compared with a standard enteral nutrition (Ryan et al. 2009).

In a study of 20 patients with unresectable pancreatic adenocarcinoma, 2 cans of a fish oil-enriched nutritional supplement (620 kcal, 32.2 g protein, 2.18 g EPA in total) per day in addition to their normal food intake, patients had significant weight-gain at both 3 (median 1 kg, $p=0.024$) and 7 weeks (median 2 kg, $p=0.033$) (Barber et al. 1999). After 3 weeks, there was a significant fall in production of IL-6 (from median 16.5 to 13.7 ng/ml, $p=0.015$), a rise in serum insulin concentration (from 3.3 to 5.0 mU/l, $p=0.0064$), a fall in the cortisol-to-insulin ratio ($p=0.0084$), and a fall in the proportion of patients excreting proteolysis inducing factor (from 88% to 40%, $p=0.008$). These changes occurred in association with weight gain and may account for the reversal of weight loss previously seen in the patients (Barber et al. 2001).

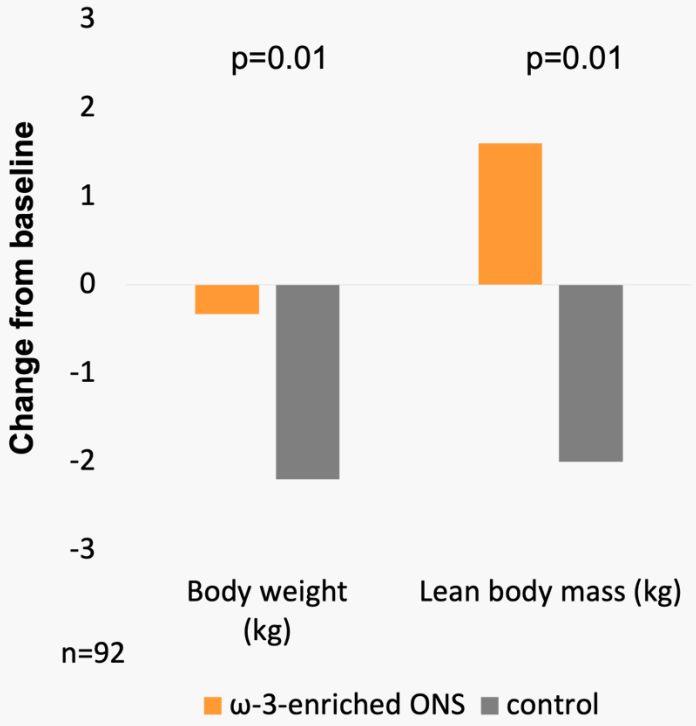


ω-3 supplementation increases body weight, lean body mass and performance status in advanced pancreatic cancer (Barber et al. 1999)

Several studies have investigated the effects of ω-3 fatty acids on different nutritional parameters. In a study of 27 patients with advanced lung cancer, 66-day ω-3 fatty acid supplementation (510 mg EPA, and 340 mg DHA daily) significantly increased body weight, and significantly decreased the levels of inflammatory markers such as CRP, and IL-6, when compared to baseline values (Finocchiario et al. 2012). In 40 patients with stage III NSCLC, administration of 2 cans/day of a protein- and energy-dense oral nutritional supplement containing ω-3 fatty acids (2.0 g EPA +0.9 gDHA/day) led to a better weigh management than the administration of an isocaloric supplement in the control group (van der Meij et al. 2010.) Another study of 90 patients with advanced NSCLC found that consuming an oral nutritional supplement containing EPA significantly increased energy ($p<0.001$) and protein ($p<0.001$) intake, and increased body weight gain ($p=0.01$) versus an isocaloric diet (Sanchez-Lara et al. 2014).

In 37 ambulatory postsurgical patients with head and neck cancer, consumption of 2 units / day of a hypercaloric and hyperproteic oral supplement enhanced with ω-3 fatty acids for a 12-week period significantly increased BMI and fat-free mass in the group receiving no radiotherapy, and significantly increased the albumin level in all patients with or without radiotherapy (de Luis et al. 2015).

A unicentric, prospective, observational study that enrolled 30 patients with different cancer types (lung, ear-nose-throat, and breast cancers) simultaneously being treated with radiotherapy, chemotherapy, and/or surgery, demonstrated that a 6-day administration of high-energy, high-protein, ω-3 fatty acids-rich and low-volume oral nutritional supplement increased median weight, BMI, and protein intake (Garcia-Almeida et al. 2017). In a study of 13 patients with stage IV colorectal cancer, administering 2 packs/day of an oral nutritional supplementation enriched with ω-3 fatty acids plus dietary counseling for 12 weeks significantly increased body weight ($p=0.045$) and ameliorated quality of life when compared to dietary counseling only (Trabal et al. 2010). In lung cancer studies, ω-3 fatty acid supplementation significantly increased or maintained body weight, increased lean body mass, and significantly decreased the levels of inflammatory markers e.g. CRP, and IL-6 when compared to baseline values (Sanchez-Lara et al. 2014). In a randomized, open, controlled, and longitudinal study of 68 outpatient gastric cancer patients, 30-day clinical nutrition with an ω-3 fatty acids-enriched *vs* a standard formula increased weight gain (1.2 kg *vs* 0.7 kg, $p=0.03$), reduced IL-6 level (5.7 pg/ml *vs* 6.3 pg/ml, $p=0.03$) and maintained nutritional status (Feijo et al. 2019).



ω-3 fatty acid-enriched nutrition ameliorates nutritional status in non-small cell lung cancer patients by week 8 of chemotherapy (Sanchez-Lara et al. 2014)

In a randomized study of 61 patients undergoing neoadjuvant chemotherapy for esophageal cancer, 31 patients received ω-3 fatty acids-enriched enteral nutrition (900 mg ω-3 fatty acids/day), and 30 patients received enteral nutrition poor in ω-3 fatty acids (250 mg ω-3 fatty acids/day) for 15 days during chemotherapy. ω-3-rich enteral nutrition support significantly decreased the frequency of chemotherapy-induced mucosal toxicities, such as stomatitis (p=0.018), and decreased the frequency of aspartate aminotransferase (p=0.012) and alanine aminotransferase (p=0.015) elevations, compared with the ω-3-poor enteral nutrition support. Grade 3 / 4 diarrhea decreased also occurred less frequently in the ω-3-rich group, though the difference did not reach a significant level (p=0.068) (Miyata et al. 2017).

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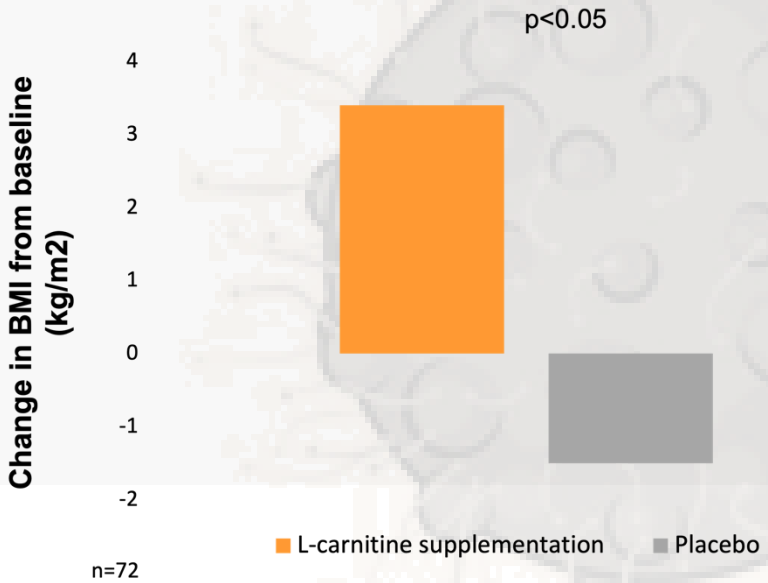
In a study of 46 advanced non-small cell lung cancer patients who received chemotherapy as a first line treatment, concomitant ω-3 fatty acids supplementation (2.5 g EPA + DHA daily) in 15 patients increased response rate (60.0 % *vs* 25.8%, p=0.008) and led to greater clinical benefits (80.0% vs 41.9%, p=0.02) compared to the 30 patients who received standard of care. The incidence of dose-limiting toxicity did not differ between groups (p=0.46). One-year survival also tended to be greater in the supplemented group (60.0% vs 38.7%, p=0.15) (Murphy et al. 2011).

3.2.4.2. L-carnitine

4-N-trimethylammonium-3-hydroxybutyric acid (L-carnitine) is an endogenous mitochondrial membrane compound (Yu et al. 2011) with antioxidant effects and is found to be a protective agent against many diseases including cancer (Borghi-Silva et al. 2006). Since the levels of inflammatory cytokines as well as increased oxidative stress are related to cachexia, therapeutic strategies to ameliorate such conditions may be extremely important to counteract these deleterious effects. There is evidence that L-carnitine is able to reduce chronic inflammation and oxidative stress in cancer patients. There may also be potential beneficial effects of L-carnitine supplementation with regards to the central nervous system. Hypothalamic carnitine palmitoyltransferase is involved, along with fatty acid synthase in the regulation of the melanocortin system, and since many factors including TNF-α and IL-1 inhibit fatty acid oxidation, it is conceivable that L-carnitine supplementation may affect energy intake in cachectic patients (Silverio et al. 2011).

As an add-on therapy to breast cancer patients maintained on tamoxifen, the objectives of carnitine treatment are diverse: improving tamoxifen-related side effects, offering better cancer prognosis by reducing the risk of developing cancer recurrence or metastasis, and modulating the growth factors which may be, in part, a prospective illustration to overcome tamoxifen resistance (El-Ashmawy et al. 2014). L-carnitine facilitates the transfer of activated long-chain fatty acids from the cytoplasm to the mitochondria, where they are processed by oxidation to produce energy in the form of ATP (Silverio et al. 2011).

In a prospective, multi-center, placebo-controlled, randomized, double-blind trial of 72 advanced pancreatic cancer patients, administration of 4 g/day oral L-carnitine for 12 weeks resulted in an increase of BMI, while BMI decreased in the placebo group, and the difference between the two groups was significant (p<0.05). Nutritional status (body cell mass, body fat) and quality of life parameters also improved under L-carnitine. There was a trend towards an increased overall survival and a reduced hospital stay in the L-carnitine group (Kraft et al. 2012).



L-carnitine supplementation improves nutritional parameters in cancer patients (Kraft et al. 2012)

According to an animal study investigating the effect of acetyl-L-carnitine on cisplatin-induced ototoxicity by audiologic tests, histomorphologic, immunohistochemical and ultrastructural examination, acetyl-L-carnitine improves cisplatin-induced auditory impairment, and also antioxidative and antiapoptotic properties of L-carnitine on cisplatin-induced ototoxicity were supported by the findings (Gunes et al. 2011).

In cultured cells treated with different concentrations of hydrogen-peroxide (H2O2), pretreatment with L-carnitine for 3 hours inhibited H2O2-induced cell viability loss, morphological changes, intracellular reactive oxygen species generation, and lipid peroxidation in a concentration-dependent manner. Endogenous antioxidant defense components including total anti-oxidative capacity, glutathione peroxidase, catalase, and superoxide dismutase were also promoted by L-carnitine. Meanwhile, H2O2-induced down-regulation of Bcl-2, up-regulation of Bax, and DNA damage and apoptosis were also inhibited in the presence of L-carnitine. These data suggest that L-carnitine may function as an antioxidant inhibiting H2O2-induced oxidative stress as well as regulation of Bcl-2 family and preventing the apoptotic death of neuronal cells, which might be beneficial for the treatment of oxidative stress in neurodegenerative diseases (Yu et al. 2011).

Based on the available data, L-carnitine should be given along with doxorubicin, cisplatin, carboplatin, oxaliplatin, cyclophosphamide and ifosfamide since it is able to block these agents' multiple organ toxicities and permit larger doses of these anticancer drugs to be administered, thereby killing more cancer cells and increasing the chances of patient survival (Sayed-Ahmed et al. 2010).

3.2.5. Enhancement of wound-healing

Wound healing is very important after surgery and undisturbed closure of wounds is sometimes a major problem. Intensive efforts are made to improve wound healing using numerous approaches. In recent years, the oral application of specific bioactive collagen peptides has demonstrated positive effects on matrix synthesis and skin physiology. In an observational trial of 22 (12 treated/10 placebo) patients with postsurgical wounds and a second group of 20 (10 treated/10 placebo) patients with badly healing wounds, patients treated with bioactive collagen peptides had a clearly better outcome regarding wound healing compared to the placebo groups who showed suboptimal or bad results in the majority of cases. No side effects or intolerance to the product were reported in the trial. The results of this investigation confirmed the positive impact of collagen peptides on wound healing (Knefeli & Durani. 2017).

3.2.6. Choline

Choline was officially recognized as an essential nutrient by the Institute of Medicine in 1998. There is a significant variation in the dietary requirement for choline that can be explained by common genetic polymorphisms. Because of its wide-ranging roles in human metabolism, from cell structure to neurotransmitter synthesis, choline-deficiency is now thought to have an impact on diseases such as liver disease, atherosclerosis, and possibly neurological disorders. Choline is found in a wide variety of foods. Based on estimated dietary intakes and studies reporting liver damage with lower choline intakes, the Institute of Medicine, Food and Nutrition Board set the adequate intake for choline at 425 mg/day for women aged 19 and older, and 550 mg/day for men aged 19 and older (Zeisel & da Costa. 2009).

Choline deficiency increases leakage of reactive oxygen species from mitochondria consequent to altered mitochondrial membrane composition and enhanced fatty acid oxidation. Choline deficiency impairs folate metabolism, resulting in decreased thymidylate synthesis and increased uracil misincorporation into DNA, with strand breaks during error-prone repair attempts. Choline deficiency alters DNA methylation, which alters gene expression for critical genes involved in DNA mismatch repair, resulting in increased mutation rates. Any dietary deficiency which increases mutation rates should be associated with increased risk of cancers, and this is the case for choline deficiency. In rodent models, diets low in choline and methyl-groups result in spontaneous hepatocellular carcinomas. In human epidemiological studies, there are interesting data suggesting that this may also be the case for humans, especially those with single nucleotide polymorphisms that increase the dietary requirement for choline (Zeisel S. 2012).

Rats and mice fed a choline (and methyl) deficient diet first develop fatty liver, progress to liver fibrosis, followed by development of foci of abnormal enzyme-altered hepatocytes that are similar to those induced during initiation of cancer with one of many different chemical carcinogens. In choline deficiency, these altered foci of hepatocytes, which express γ-glutamyltranspeptidase and the placental form of glutathione S-transferase, precede the formation of adenomas and hepatocellular carcinomas (Zeisel 2012). In an animal study, Fischer 344 male rats fed a choline-methionine deficient diet from 13 to 24 months developed a 100% incidence of putative preneoplastic hepatocyte nodules and a 51% incidence of hepatocellular carcinoma. The addition of 0.8% choline chloride completely prevented the development of both the nodules and the cancer. The diet contained no added known carcinogen. Analysis of the deficient and supplemented diets revealed no detectable volatile nitrosamines or nitrosamides, nitrite, nitrate or malonaldehyde, <0.9 p.p.b. aflatoxin B1 and barely detectable levels of Ames positive material with one strain of Salmonella typhimurium. These findings indicate that a dietary deficiency of choline and methionine can be a major rate limiting factor in the development of liver cancer (Ghoshal & Farber. 1984).

In a cross-sectional survey that enrolled 1514 men (18–87 years of age) and 1528 women (18–89 years of age) with no history of cardiovascular disease (the ATTICA Study), compared with the lowest tertile of choline intake (250 mg/day), participants who consumed >310 mg/day had, on average, 22% lower concentrations of C-reactive protein ($p<0.05$), 26% lower concentrations of interleukin-6 ($p<0.05$), and 6% lower concentrations of tumor necrosis factor-α ($p<0.01$) in their fasting blood samples (Detopoulou et al. 2008).

Some of the epigenetic mechanisms that modify gene expression without modifying the genetic code depend on the methylation of DNA or of histones, and diet availability of choline and other methyl-group donors influences these methylations. In addition to its role in brain development, choline and other methyl-donors also have a role in carcinogenesis. Rodents fed low choline low methyl diets develop liver cancers. A meta-analysis of 11 studies in people calculated that diets low in choline increased the overall relative risk for developing cancer with the largest reported effects found for lung (30% increase), nasopharyngeal (58% increase) and breast cancer (60% increase) (Zeisel S. 2017).

According to the results of a meta-analysis of 11 studies, an increment in diet intake of 100 mg/day of choline and betaine (a metabolite derived from choline) helped reduce cancer incidence by 11% (Sun et al. 2016).

3.2.7. Immunonutrition

Dendritic cells, T and B lymphocytes, cytokines, antibodies, interleukins, and other molecules interacting with the immune system modulate a customized response against the cancer cell. Not only should patients' immune systems be unharmed, they must also be strengthened by external agents, anti-tumor antibodies, immune checkpoint blockades, and cancer vaccines. Immunonutrition improves the immune and inflammatory systems

via the modulation of their functional capacities by increasing the receptor densities on immune cell membranes and improving the ability to react against pathogens, maintaining CD4/CD8 lymphocytes and tumor necrosis factor (TNF)-α levels, and improving T cells and NK cytotoxicity functions (Prieto et al. 2017). The nutrients of immunonutrition formula usually include arginine, omega-3 fatty acid, glutamine and RNA, etc. ω-3 fatty acid could reduce the platelet-adhesive endothelial interactions and the synthesis of proinflammatory eicosanoids, while it could stimulate the production of glutathione which can decrease oxidative injury. Arginine is the sole substrate for nitric oxide (NO) synthesis, which is a crucial element of innate antimicrobial immunity in the host's first line of defense. It also plays an important role in maintaining the physiological balance of gastrointestinal tract and regulating the metabolism of many kinds of lymphocyte. Glutamine, as the major fuel source for macrophages, lymphocytes, and enterocytes, could increase the level of gut mucosal glutathione, thereby reduce free radical availability, and decrease inflammation (Xu et al. 2018).

A meta-analysis of 9 studies revealed that in colorectal cancer patients who underwent elective surgery, enteral immunonutrition improved length of hospital stay and frequency of infectious complications compared to standard enteral nutrition (Xu et al. 2018). In a double-blind, randomized clinical trial of 37 head and neck and esophageal cancer patients receiving chemotherapy, enteral immunonutrition vs standard immunonutrition significantly improved body weight, plasma albumin level and plasma antioxidant capacity, and helped maintain the quality of life of patients (Vasson et al. 2014). In a double-blind, randomized clinical trial of 28 head and neck and esophageal cancer patients, when compared to standard enteral nutrition, enteral immunonutrition improved immune response (CD4/CD8 ratio, CD3 membrane expression, number of peripheral mononuclear cells, expression of immune receptor coding genes, overexpression of antioxidant enzyme and NADPH-oxidase subunits). Immunonutrition can enhance immune cell responses through the modulation of their phenotypes and functions. By modulating the gene expression of immune cells, immunonutrition could make it easier for the organism to adapt to the systemic inflammation and oxidative stress induced by radio-chemotherapy (Talvas et al. 2015). The pooled analysis of 7 studies involving 583 patients showed that versus standard enteral nutrition, enteral immunonutrition when beyond a 7-day time-frame post-operatively, increased level of CD4+ (SMD=0.99; 95% CI, 0.65–1.33; p<0.00001), CD4+/CD8+ (standard mean difference [SMD]=0.34; 95% CI, 0.02–0.67; p=0.04), IgM (SMD=1.15; 95% CI, 0.11–2.20; p=0.03), IgG (SMD=0.98; 95% CI, 0.55–1.42; p<0.0001), lymphocyte (SMD=0.69; 95% CI, 0.32–1.06; p=0.0003), and proalbumin (SMD=0.73; 95% CI, 0.33–1.14; p=0.0004). Clinical outcomes such as systemic inflammatory response syndrome (mean difference -0.89 days; 95% CI, -1.40 to -0.39; p=0.005), and postoperative complications (RR=0.29; 95% CI, 0.14–0.60; p=0.001) were also significantly reduced in the enteral immunonutrition group (Cheng et al. 2018).

3.2.8. Micronutrients

In children, micronutrient malnutrition is a cause of stunting and may be accompanied by metabolic adaptations in response to nutrient deficiencies that increase the risk of later obesity and related chronic disease. In adults, deficiencies in key antioxidant micronutrients may promote oxidative stress, creating an environment in which the incidence and severity of diseases such as diabetes, CVD, and cancer are increased. Folate deficiency in adults may increase serum levels of homocysteine, an established risk factor for heart disease (Eckhardt CL. 2006).

Zinc (Zn) functions as a modulator of the immune response through its availability, which is tightly regulated by several transporters and regulators. When this mechanism is disturbed, Zn availability is reduced, altering survival, proliferation and differentiation of the cells of different organs and systems and, in particular, cells of the immune system. Zn deficiency affects cells involved in both innate and adaptive immunity at the survival, proliferation and maturation levels. These cells include monocytes, polymorphonuclear-, natural killer-, T-, and B-cells. T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in Zn status. While acute Zn deficiency causes a decrease in innate and adaptive immunity, chronic deficiency increases inflammation. During chronic deficiency, the production of pro-inflammatory cytokines increases, influencing the outcome of a large number of inflammatory diseases (Bonaventura et al. 2015).

Free radicals generated during cancer treatments are responsible for cellular damage and the killing of malignant cells as well as normal cells. Antioxidants that neutralize free radicals before vital molecules are damaged, include nutrients, e.g. vitamins A, C, and E, carotenoids, selenium, flavonoids/polyphenols), and enzymes synthetized in the body that need the presence of micronutrients, e.g. zinc, selenium, manganese, copper and iron (Berretta et al 2013).

Administration of 400 mg/ml of vitamin E oil twice daily to 18 patients undergoing a variety of different chemotherapy regimens resolved pre-existing mucositis in all but one patient. Concurrent administration of vitamin E with platinum- and taxane-based chemotherapy has also shown benefit in preventing chemotherapy-related neuropathy (Berretta et al 2013). In one study, 13 of 27 subjects receiving 300 mg of vitamin E twice a day throughout treatment with cisplatin experienced both decreased incidence (31% vs 86%; $p<0.01$) and severity of neurotoxicity ($p<0.01$) compared with patients receiving conventional care (Pace et al 2003).

Effects of zinc supplementation on mucositis during radiation therapy was investigated in a double-blind study of 50 head-and-neck patients. Patients in the control group developed Grade 2 mucositis and dermatitis earlier and sooner than patients in the experimental group. There was also a significant difference in the development of Grade 3 mucositis and dermatitis between the two groups. Patients in the experimental group were found to have milder mucositis and dermatitis. (Lin et al. 2006). In a double-blind, randomized controlled trial of 50 adult patients who underwent chemotherapy, the incidence of grade 3 mucositis was lower in the zinc sulfate group. In the first follow up, grade 3 mucositis was detected in 10% of patients. In the placebo group, grade 3 mucositis was seen in 46.6% of patients. By the fourth follow up, grade 3 mucositis was detected in 3.33% of patients in the intervention group and in 20% of patient in the placebo group. At the end of the study there was no grade 3 mucositis detected in the zinc sulfate group, whereas there were 3.57% of patients in the placebo group with grade 3 mucositis. The results also showed that zinc sulfate decreased the effects of xerostomia and pain in patients under chemotherapy treatment (Arbabi-kalati et al. 2012).

3.3. Summary

High energy and protein intakes are crucial in the treatment of disease-related malnutrition and cachexia in chronic conditions. The latest scientific data suggest that in cancer patients a low-carbohydrate diet may indirectly, by affecting the metabolism of cancer cells, have a beneficial effect on the success of the anti-tumor therapy without increasing the cardiovascular risk of these patients. Supplementation with ω-3 poly-unsaturated fatty acids significantly inhibits the intense protein catabolism and chronic inflammation process seen in cancer. Simultaneous administration of L-carnitine decreases the toxic side-effects of chemotherapy, thus enabling the use of higher doses and potentially increasing the survival chances of patients. Application of certain micronutrients (e.g. vitamin E, zinc) may diminish side effects of chemotherapy. Immunonutrition enhances immune system and inflammatory cascade functioning via ameliorating immune response and immune functions, which may play an important role in the body's defense towards cancer cells. Adequate choline intake is essential for several metabolic processes and helps maintain a lower inflammation and cancer risk level.

4. MediDrink Neo

4.1. Product descriptiom

MediDrink Neo is a nutritionally complete, 2.2 kcal/ml, ready-to-consume food for special medical purposes (as per the EU regulation 128/2016) for the dietary management of cancer-related malnutrition.

MediDrink Neo contains immunonutritional components.

MediDrink Neo must be used under medical supervision.

MediDrink Neo is suitable as a sole source of nourishment or as a supplemental nutrition.

4.2. Target groups

MediDrink Neo is indicated for enteral feeding to enhance the energy, protein, and micronutrient intake of adults and children above 3 years of age with cancer-related malnutrition. MediDrink Neo is suitable for all patients with a functional gastrointestinal tract who are unable to meet the nutritional requirements with oral nutrition alone.

MediDrink Neo is lactose-free (lactose content ≤0.1 g/100 ml), and is gluten-free, therefore, can be administered to patients with lactose- or gluten-intolerance.

4.3. Recommended dosage

The dosage of MediDrink Neo administered should be decided by a physician and varies from patient to patient according to individual needs and whether MediDrink Neo is used as supplemental nutrition or as the sole source of nutrition. The recommended daily allowance is 5-6 200 ml-packs or 3-4 330 ml-packs per day for adults as a sole source of nutrition or 1-3 200 ml-packs or 1-2 330 ml-packs per day as supplementation.

4.4. Precautions

MediDrink Neo is not suitable for children below 3 years of age, and for patients with galactosemia and hereditary fructose intolerance (fructosemia).

5. MediDrink Neo in the management of cancer-related malnutrition

Based on the data in the literature, we can extrapolate that due to its high energy and high protein content, MediDrink Neo is able to attenuate the deterioration of the nutritional status, to improve weight, to decrease the rate of complications, and to influence the modulators of the catabolic response in cancer patients with malnutrition and cachexia. Besides ameliorating the immune functions and thus decreasing the therapy-related immune suppression and the frequency of complications, facilitating wound healing after surgical treatments and radiotherapy, and facilitating the preservation of albumin level, the high energy and protein content of MediDrink Neo has a sparing effect on protein utilization in order to favor restauration of lean body mass, and can improve the cancer patients' status and consequently their quality of life as well.

Since most malignant cells are not able to metabolize significant amounts of fatty acids, depend on the steady glucose availability in the bloodstream and use carbohydrates as the main source of energy, the low carbohydrate content of MediDrink Neo may have an indirect beneficial effect on the tumor cell proliferation. The use of MediDrink Neo in cancer patients with malnutrition and cachexia may enhance the efficacy of the primary anti-tumor therapy via ameliorating the nutritional status and thus the ability of patients to follow through the total course of therapy, and have an indirect inhibitory effect on the growth of the neoplasm.

ω-3-PUFAs are known to be very active in reducing either tumor growth or the associated tissue wasting, particularly that of the adipose mass. Due to its high ω-3-PUFAs, MediDrink Neo should be able to modulate levels of pro-inflammatory cytokines and tumor-derived factors to improve the nutritional status, clinical, biological and functional parameters, the clinical outcome, and quality of life.

Simultaneous administration of L-carnitine decreases the toxic side-effects of chemotherapy, thus enabling the use of higher doses and potentially increasing the survival chances of patients. Due to its L-carnitine content, MediDrink Neo is beneficial in the clinical nutrition of cancer patients.

Application of certain micronutrients (e.g. vitamin E, zinc) may diminish side effects of chemotherapy. MediDrink Neo contains these micronutrients in the affective doses specified by the scientific literature, that ensures MediDrink Neo's beneficial effect on the nutritional status of cancer patients.

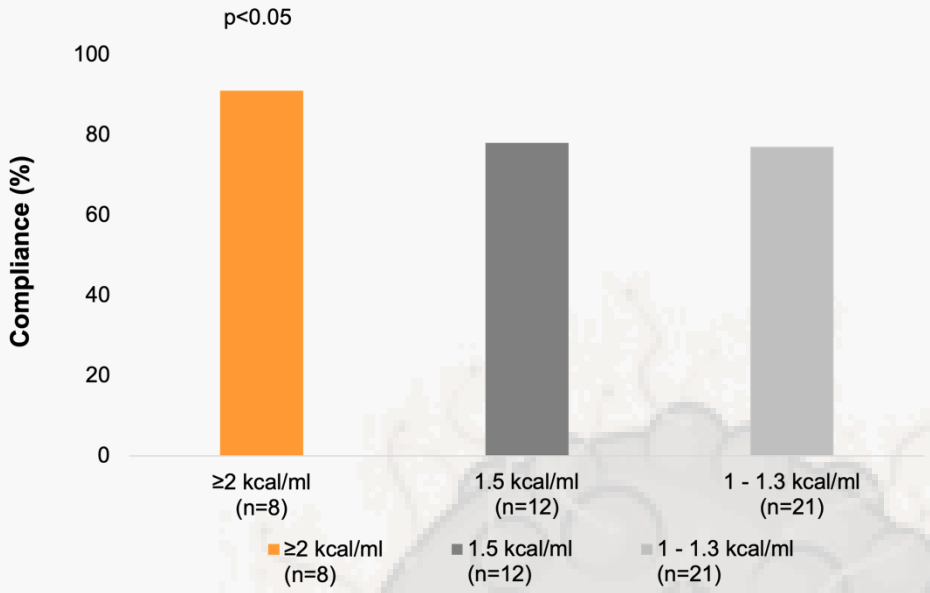
MediDrink Neo contains immunonutritional components that enhance immune system and inflammatory cascade functioning via ameliorating immune response and immune functions, which may play an important role in the body's defense towards cancer cells.

The choline content of MediDrink Neo is essential for several metabolic processes and helps maintain a lower inflammation and cancer risk level.

6. Safety and tolerability

6.1. Compliance

According to the data from a meta-analysis, the overall compliance to oral nutritional supplementation is good, especially with higher energy-density ONS, resulting in improvements in patients' total energy intakes that have been linked to clinical benefits. A range ONS-related attributes have been associated with compliance. Recent comparisons suggest significantly greater compliance and energy intakes with the use of small volume, energy dense ONS compared to standard 1.5 kcal/ml ONS. Therefore, in patients who struggle to ingest the prescribed volume of ONS, a change to a higher energy density ONS could increase total energy intake and reduce wastage. This strategy could be employed in the nutritional management of malnourished individuals (Hubbard et al. 2012).

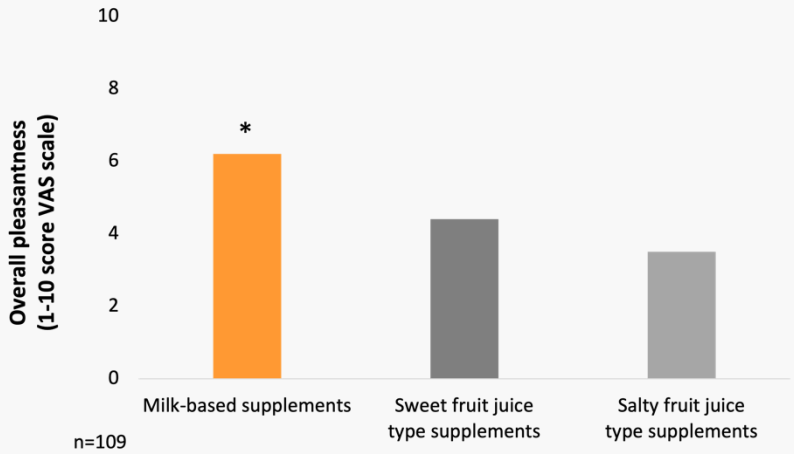


Compliance is greater with higher energy-density ONS (Hubbard et al. 2012)

A randomized controlled intervention trial of 77 elderly nursing home residents with high functional impairment showed that a low-volume, nutrient- and energy-dense oral nutritional supplement was well accepted and resulted in significant improvements of nutritional status and, thus, was effective to support treatment of malnutrition (Stange et al. 2013).

6.2. Taste

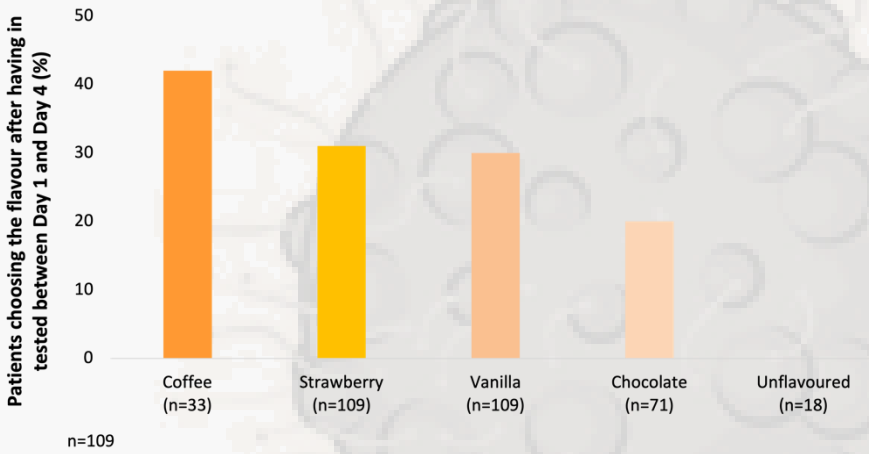
The investigation of taste preferences of milk-based and fruit juice-type supplements in malnourished in-patients showed that the overall pleasantness is significantly better for milk-based supplements that for sweet and salty fruit juice-type product).



*p<0.01 vs sweet fruit juice type supplements, and p<0.0001 vs salty fruit juice type supplements

Pleasantness of milk-based ONS is significantly better than that of sweet and salty fruit juice-type products (Darmon et al. 2008)

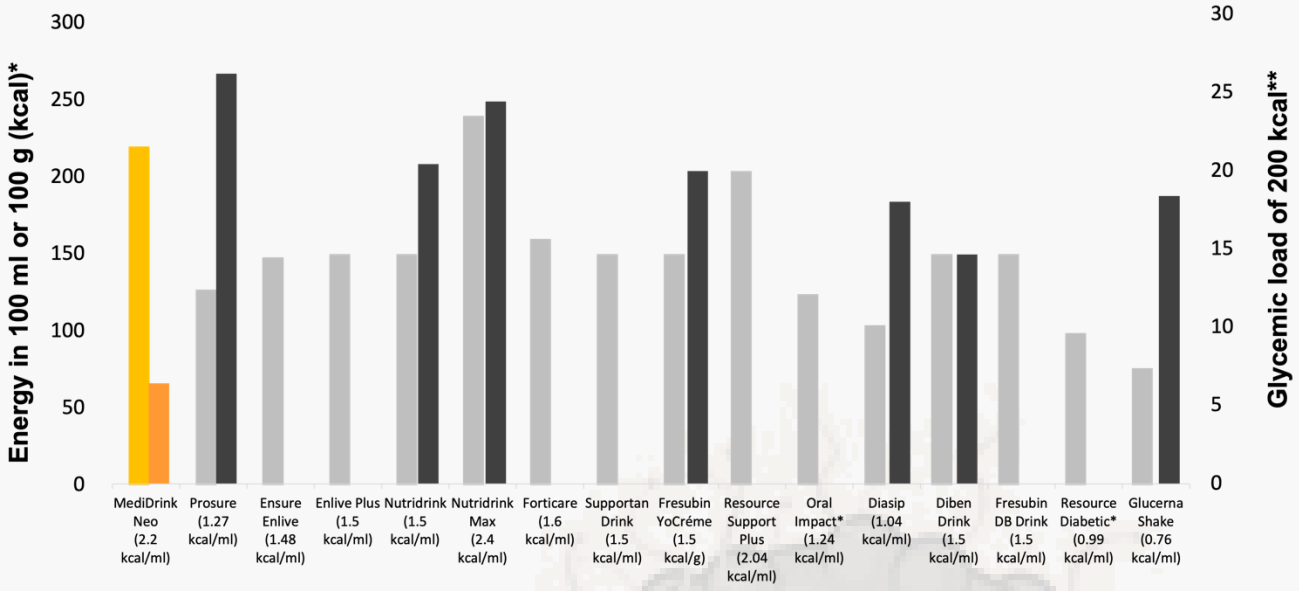
Among milk-based ONS, coffee, strawberry, vanilla, and chocolate are the most preferred flavours (Darmon et al. 2008).



Coffee, strawberry, and vanilla are the most preferred flavours among milk-based ONS (Darmon et al. 2008)

6.3. Glycemic load

The concept of glycemic load has been introduced by Walter Willett at the Harvard School of Public Health in 2004. While glycemic index (GI) ranks the different sources of carbohydrates according to the blood sugar-raising capacity, the glycemic load (GL) takes also into account the quantity of food / carbohydrates consumed. GL is calculated by multiplying the GI of the carbohydrates by the quantity of the carbohydrates taken in. Therefore, the GL of a certain food depends on not only the GI but also the quantity consumed (Fajcsák & Lelovics 2006, Venn & Green 2012). Based on the calculation of GL, MediDrink Neo has the lowest glycemic load and therefore the smallest strain on the carbohydrate metabolism of the patients among the different ONS depicted below. Thus, MediDrink Neo is suitable also for diabetic patients, since when consuming the same amount of kilocalories, the GL of MediDrink Neo is lower than that of the ONS specifically designed for the diabetic patients.



*When prepared according to the manufacturer's instructions
**Values are calculated on the basis of publicly available data (missing values are due to unavailable data)

Energy contents and glycemic load of several oral nutritional supplements

(Venn & Green 2007, Fajcsák & Lelovics 2006, Medifood data on file 2019, [Complete therapy with clinical nutrition] Nutricia 2016, https://nutrition.abbott/uk/product/prosure, https://abbottnutrition.com/ensure-enlive-advanced-nutrition-shake, https://www.nestlehealthscience.co.uk/brands/impact/impact, https://www.caringforlife.hk/filemanager/product/47/product_info_en.pd, http://manage.nutricia.com/uploads/documents/Forticare_ie.pdf, https://www.fresenius-kabi.com/no/documents/Factsheet_Supportan_DRINK_09_2017_VIEW.pdf, https://www.nestlehealthscience-me.com/en/brands/resource/resource-support-plus, https://abbottnutrition.com/glucerna-shake, www.fresenius-kabi.co.uk, www.fresenius-kabi.ie, https://www.fresubin.be/wp-content/uploads/2015/09/DB-drink-technische-fiche.pdf, https://www.nestlehealthscience.in/brands/resource-diabetic)

6.4. Tolerability

So far there are no tolerability study results available for MediDrink Neo.

7. Summary

Malnutrition and cachexia is developed in a wide range of chronic diseases including cancer. Since nutritional status has a significant effect on the outcome of the disease and the quality of life of patients, enteral nutrition with high calorie and protein content is extremely important in the nutritional therapy of these patients. L-carnitine supplementation helps increase the BMI of cancer patients.

Due to the deleterious effects of a high carbohydrate content in patients with cancer, nutritional supplementation with a low carbohydrate and high fat content is more beneficial for these patients than the enteral nutritional supplements with high carbohydrate and lower fat content.

Cachexia is a metabolic syndrome with underlying chronic inflammatory processes, therefore, any nutritional supplement with high ω-3 fatty acid composition able to decrease the level of this chronic inflammation has an additional favorable effect on the disease in cancer. The choline content of MediDrink Neo is essential for several metabolic processes and helps maintain a lower inflammation and cancer risk level.

With its high energy, high protein, high ω-3 fatty acid, low carbohydrate content, L-carnitine, and immunonutritional components, MediDrink Neo is an ideal enteral nutritional supplement for malnourished patients suffering from cancer.

The L-carnitine, vitamin E and zinc content of MediDrink Neo helps decrease the toxic side-effects of chemotherapy, thus enabling the use of higher doses and potentially increasing the survival chances of patients.

Due to its low carbohydrate content and low glycemic load, MediDrink Neo can be safely administered even as a sole source of nutrition to malnourished cancer patients with diabetes co-morbidity.

Due to its low-volume nutrient- and energy-dense content, nutrition with the milk protein-based MediDrink Neo in cancer patients should be well accepted and result in significant improvements of nutritional status and support for treatment of malnutrition

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