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A NARRATIVE REVIEW ON DIETARY SUBSTITUTION OF MEDIUM CHAIN TRIGLYCERIDES AND IT'S EFFECT ON TUMOR METABOLISM IN ONCOLOGY

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Abstract: Cancer is a significant global public health issue. Even while the most recent technology is being used in many aspects of the struggle against cancer, there is still much space for improvement. In order to control cancer cachexia, nutrition management is essential. One significant energy source is glucose. However, a significant portion of the global obesity and weight gain epidemic currently occurring is probably caused by food that contains an excessive amount of sugar. Fast food, highly processed food, and excessive sugar intake are also considered to be contributing factors to the rising rate of cancer in low- and middle-income nations. It has been seen that a diet high in protein and high in energy can help cancer patients with cachexia gain weight. Fats are a concentrated energy source. Medium-chain triglycerides (MCTs), a type of lipid, are readily absorbed from the small intestine by bile without the need for micelle synthesis. The portal vein then carries the MCTs to the liver. Although the results of early clinical trials are uncertain, an MCT-rich ketogenic diet plan appears to have potential as a supportive therapy for the treatment of cancer.

Keywords: Cancer, Nutrition Management, Medium Chain Triglycerides

Introduction:

Cancer is a major social, public health, and economic issue in the twenty-first century. According to recent global figures, there were about 10 million cancer-related deaths and nearly 20 million new instances of the disease in 2022. According to projections based on demographics, there would be 35 million new instances of cancer annually by 2050, a 77% rise over the 2022 figure. (Bray et al. 2022) Although historically high-income nations had the highest cancer rates, low- and middle-income nations are currently experiencing a cancer epidemic. This is particularly true for cancers including breast, prostate, colon and rectal, kidney, liver, pancreas, uterine, ovarian, and others that are thought to be linked to lifestyle choices and obesity. Many believe that the "Westernization" of diets—which involves consuming more highly processed meals and added sugars—is to blame. (Epner et al.2022) According to research findings, sugar consumption in India appears to be rising, coming from both traditional and sugar-sweetened beverages (SSBs). Reducing the intake of sugar and sugar-containing foods is advised by several reputable scientific organizations, such as the Institute of Medicine of the National Academies, the American Diabetes Association, and the WHO. (Gulati ans Misra 2014) The purpose of this study is to (1) evaluate the literature on the relationship between processed foods and added sugars in diet and cancer risk, prevalence, progression, and sickness burden. (2) Provide an

overview of the nutritional aspects for patients with cancer. (3) examine the role of medium chain triglycerides.

Excess Sugar and Weight gain

Sucrose, sometimes known as table sugar, is a disaccharide that contains equal parts fructose and glucose. All carbs and starchy meals contain glucose, a monosaccharide that is essential for cellular metabolism in all animals, including humans. Another monosaccharide that occurs naturally in fruit is fructose, which has been used as a major added caloric sweetener in a variety of meals. Compared to glucose, fructose is metabolized, absorbed, and digested differently. Hepatic metabolism of fructose favors de novo lipogenesis, in contrast to glucose metabolism. Furthermore, the fructose included in sugar, HFCS, and some meals does not promote the synthesis of leptin or insulin, two hormones that control appetite and increase satiety. Thus, an abundance of fructose in food probably plays a major role in the global obesity and weight gain epidemic that is currently underway. Consequently, more research on fructose-containing added sugars is needed to ascertain if their influence on chronic illnesses, including cancer, stems primarily from their tendency to contribute to obesity or from another, more focused mechanism. (Wang et al. 2009) (Bray et al.2004)

The World Health Organization has issued a conditional advice to limit the amount of added sugar consumed to less than 5% of total calories, or roughly 100 calories. (Epner et al.,2022) The main reason foods high in sugar are seen negatively is that they may lead to weight gain. A normal metabolism is found in 20% of obese individuals, while 40% of those with normal body mass indices (BMIs) experience the development of diabetes, hypertension, heart disease, and non-alcoholic fatty liver disease. According to recent studies, sugar may have a significant impact on the development and a etiology of cancer. Research studies also shows that high-sucrose or high-fructose diets activate various molecular pathways, suggesting that excessive sugar consumption may be associated with the onset and progression of cancer independently of weight increase. (Lustig et al. 2012) (Nebeling et al.,1995)

Preclinical research employing mouse models reveals that mice fed high-sucrose or high-fructose diets compared to isocaloric starch diets had higher tumor burdens, earlier onsets, and higher prevalence of several malignancies. Epidemiological studies and preclinical research in mice have indicated a substantial correlation between excess sugar consumption and cancer, even though no human clinical trials have investigated the links between fructose, sucrose, and cancer. (Epner et al.,2022)

The Evolution of Diet and Cancer

Cancer was once thought to be a sickness exclusive to the wealthy. However, 57% of cancer cases worldwide currently occur in low- and middle-income countries (LMIC). In just two decades, the World Health Organization (WHO) predicts that there would be a 57% increase in yearly new cancer cases and a 65% increase in annual cancer deaths, with 22 million new cancer cases and 13 million cancer deaths annually. (Global battle…2015) (Torre et al.2015) Significant rises in the incidence and death of breast, prostate, and colon cancer are currently being observed in countries like Brazil, India, and China that previously reported low rates of these malignancies. (Ziegler et al. 1993) (Mathur et al. 2020) Between 2010 and 2019, the incidence of cancer in India increased by 1.1 to 2.0 percent yearly, with lung cancer being the most frequent cancer in men and breast cancer in women. (Mathur et al.2020) (Global burden et al. 2022) As a proven risk factor for numerous malignancies, diabetes is most common in India and China, both in terms of incidence and population. (Lin et al. 2020) (Tomic et al. 2022) Global cancer cases are predicted to rise by more than 40% by 2040, with LMICs expected to account for two thirds of the increase. [15] It is believed that dietary changes, such as consuming more sugar, highly processed foods, and fast food, are to blame for the rising cancer incidence in low- and middle-income countries. (Epner et al.,2022)

Overview of nutrition characteristics in Cancer

Advanced cancer is characterized by progressive weight loss. Lack of ketosis in cancer patients contributes to treatment resistance and is a major cause of death from the disease. The loss of host muscle and adipose mass is a hallmark of the cachectic condition. (Tisdale et al. 1997) Cachexia is characterized by a significant propensity towards catabolism and a difficult-to-restore unfavorable protein-energy balance. Consequently, there is an irreversible loss in the total skeletal muscle mass of the body, which results in a decline in Activities of Daily Living (ADL), a worse prognosis, and a lower quality of life (QOL). As a result, to address muscle mass loss in cancer patients, dietary therapies should be used in a multimodal manner in addition to exercise and medication. (Tanaka et al. 2022) (Epner et al. 2022) Preventing muscle loss should be the main goal of nutritional treatment for cancer cachexia, as determined by nutritional risk assessment and evaluation. Supplementing with energy and protein on their own has been shown to improve weight in cancer patients who have cachexia or who have subjective outcomes like quality of life. (Tanaka et al.2022)

Dietary fat as an energy source

Dietary Fat are considered one of the major food constituents required for the normal functioning and growth of the human body. Lipids are required by human beings from all age groups starting from infants till old age. They serve as the source of essential fatty acids in the human diet and also serve as a concentrated source of energy-giving 9 kcal/g. (Jadhav and Annapure 2023) Dietary fat also functions as structural component of cell membranes, carries fat soluble vitamins, plays an important role in signal transduction and is a precursor for inflammatory mediators. Dietary fat is an important source of energy and contributes a significant caloric value to our diet. (Van de Worp et al. 2020)

Medium Chain Triglycerides as an energy source for people with cancer

A high-fat diet may be predicted to reduce host catabolism during cachexia, mostly by reducing tumor growth. (Shah and Limketkai 2017) Currently, there is limited information to support an ideal energy percentage of dietary fat in cancer cachexia. (Roopashree et al. 2022) (Watanabe et al. 2022)

Medium-chain fatty acids (MCFAs) are saturated fatty acids having 6–12 carbon atoms. Coconut oil (CO) and palm kernels are natural sources. Dietary medium-chain fatty acids are swiftly absorbed in the gastrointestinal tract and transferred into the bloodstream by direct interaction with albumin via the portal vein. They then enter the liver and are metabolized through β-oxidation in mitochondria. (Roopashree et al. 2022)

As glucose is the primary energy source needed by tumor cells to multiply, ketone bodies produced from MCTs directly inhibited tumor cell growth. 23 The most prevalent medium-chain fatty acids include caproic acid (C:6), caprylic acid (C:8), capric acid (C:10), and lauric acid (C:12). [21] MCTs give 8.3 calories per gramme, respectively. 20 MCT-rich diets are being investigated in combination with traditional medicines such as chemotherapy and radiation therapy in advanced stage IV cancer or brain tumors that are difficult to remove surgically. (Watanbe et al. 2022) (Nebeling et al. 1995)

In an animal study, the effects of medium-chain triglycerides (MCTs) on chemically-induced hepatic carcinogenesis (HCC) in mice were studied, and it was observed that oral supplementation of MCTs or diets containing MCTs could be useful in therapies for hepatic carcinogenesis induced by inflammation caused by viral infection, fatty liver due to metabolic syndrome, alcoholic liver disease, and non-alcoholic fatty liver disease. (Wakana et al. 2023) Tisdale et al. found that a ketogenic diet [80% of calories given as medium chain triglycerides (MCT)] can partially reverse the cachectic phenotype in mice bearing the MAC16 tumor, resulting in reduced tumor growth and inhibiting body weight loss. Body composition analysis revealed that animals fed with high amounts of MCT retained both fat and fat-free carcass mass. In another study, an 80% MCT-based high-fat diet reduced both tumor weight and host weight loss, restoring both nitrogen balance and urea excretion to that of non-tumor-bearing animals. (Van de Worp et al. 2020)

In a human clinical experiment, the anticancer properties of capric (C10:0), caprylic (C8:0), and caproic (C6:0) acids were studied on colorectal, cutaneous, and mammary gland cancer cells. For 48 hours, cancer cells were treated with varying fatty acid concentrations. The study found that Capric,

caprylic, and caproic acids decreased cancer cell viability by 70% to 90% ($p < 0.05$) compared to controls. Real-time quantitative PCR (RT-qPCR) data revealed that these natural compounds caused anticancer effects by down-regulating cell cycle regulatory genes while up-regulating apoptotic genes. (Narayanan et al. 2015) Yamasaki et al. discovered that caprylic acid (C8:0) suppressed the proliferation of bladder cancer cells. (Yamasaki et al. 2014)

In another study, the clinical effects of one year of chemotherapy with a modified medium-chain triglyceride ketogenic diet on the recurrence of stage IV colon cancer were investigated, and it was discovered that chemotherapy for one year in combination with a ketogenic diet result in higher response and disease control rates than chemotherapy alone. As a result, patients with stage IV colon cancer may benefit from a ketogenic diet. (Furukawa et al. 2018) Only a few studies have looked into the anti-cachectic effects of ketogenic diets in cancer cachexia models. 19 research have found that MCTs have anti-inflammatory properties on activated macrophages. As a result, a diet rich in medium chain triglycerides decreases chronic inflammation and oxidative stress in the body. (Wakana et al. 2019)

Conclusion

Cancer is the number one cause of death worldwide. Cachexia is a necessary component of involuntary weight loss in the presence of disease-related wasting. It is characterized by inflammatory protein wasting, notably in skeletal muscle, as well as a loss of energy storage. (Gray et al. 2020) According to research, excessive sugar consumption activates many mechanistic pathways, including inflammation, glucose, and lipid metabolic pathways, implying a causal relationship between excess sugar consumption and cancer development and progression that is independent of weight gain. (Nebeling et al. 1995) Dietary fat provides a concentrated source of energy. Medium Chain Triglycerides (MCTs) have unique digestion, absorption, and oxidation properties. MCTs are a good source of calories since they are easily absorbed and do not require bile or pancreatic enzymes. (Roopashree et al. 2022) MCTs stimulate protein anabolism while inhibiting catabolism. Several preclinical investigations in cancer model mice revealed a synergistic effect of an MCT-rich ketogenic diet with radiation or chemotherapy. The ketogenic diet has been shown to be beneficial when used with conventional therapy in cases of advanced cancer. The MCT-rich ketogenic diet regimen appears to be a potential support treatment. However, the findings of early clinical trials are debatable. For a variety of reasons, it is challenging to conduct high-quality clinical research on cancer patients, hence more research is expected in the future.

References:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2024 May-Jun;74(3):229-263.
2. Epner M, Yang P, Wagner RW, Cohen L. Understanding the Link between Sugar and Cancer: An Examination of the Preclinical and Clinical Evidence. Cancers (Basel). 2022 Dec 8;14(24):6042.
3. Gulati S, Misra A. Sugar intake, obesity, and diabetes in India. Nutrients. 2014 Dec 22;6(12):5955-74.
4. Wang B, Bobe G, LaPres JJ, Bourquin LD. High sucrose diets promote intestinal epithelial cell proliferation and tumorigenesis in APC(Min) mice by increasing insulin and IGF-I levels. Nutr. Cancer 2009, 61, 81–93.
5. Bray GA, Nielsen SJ, Popkin B M. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am. J. Clin. Nutr. 2004, 79, 537–543.
6. Lustig RH, Schmidt LA, Brindis CD, Public health: The toxic truth about sugar. Nature 2012, 482, 27–2

7. Nebeling LC, Miraldi F, Shurin SB, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. J Am Coll Nutr. 1995 Apr;14(2):202-8
8. Global battle against cancer won't be won with treatment alone--effective prevention measures urgently needed to prevent cancer crisis. Cent Eur J Public Health. 2014 Mar;22(1):23-28.
9. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87-108
10. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, Wu-Williams AH, Kolonel LN, Horn-Ross PL, Rosenthal JF, Hyer MB. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1993 Nov 17;85(22):1819-27.
11. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Glob Oncol. 2020 Jul;6:1063-1075.
12. Global Burden of Disease Cancer Collaboration. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019, A systematic analysis for the global burden of disease study 2019. JAMA Oncol. 2022, 8, 420–444
13. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2020. Sci Rep. 2020 Sep 8;10(1):14790.
14. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol. 2022 Sep;18(9):525-539.
15. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
16. Tisdale MJ, Brennan RA, Fearon KC. Reduction of weight loss and tumour size in a cachexia model by a high fat diet. Br J Cancer. 1987 Jul;56(1):39-43
17. Tanaka K, Nakamura S, Narimatsu H. Nutritional Approach to Cancer Cachexia: A Proposal for Dietitians. Nutrients. 2022 Jan 14;14(2):345.
18. Jadhav HB, Annapure US. Triglycerides of medium-chain fatty acids: a concise review. J Food Sci Technol. 2023 Aug;60(8):2143-2152.
19. Van de Worp WRPH, Schols AMWJ, Theys J, van Helvoort A, Langen RCJ. Nutritional Interventions in Cancer Cachexia: Evidence and Perspectives from Experimental Models. Front Nutr. 2020 Dec 22;7:601329.
20. Shah ND, Limketkai, BN. The Use of Medium-Chain Triglycerides in Gastrointestinal Disorders.2017 Feb; 20-28.
21. Roopashree PG, Shetty SS, Shetty VV, Nalilu SK. Medium-Chain Fatty Acids and Breast Cancer Risk by Receptor and Pathological Subtypes. Nutrients. 2022 Dec 16;14(24):5351.
22. Watanabe S, Tsujino S. Applications of Medium-Chain Triglycerides in Foods. Front Nutr. 2022 Jun 2;9:802805.
23. Wakana H, Kono H, Fukushima H, Nakata Y, Akazawa Y, Maruyama S, Hagio K, Fujii H, Ichikawa D. Effects of Medium-chain Triglycerides Administration in Chemically-induced Carcinogenesis in Mice. Anticancer Res. 2019 Dec;39(12):6653-6660.
24. Narayanan A, Baskaran SA, Amalaradjou MA, Venkitanarayanan K. Anticarcinogenic properties of medium chain fatty acids on human colorectal, skin and breast cancer cells in vitro. Int J Mol Sci. 2015 Mar 5;16(3):5014-27.
25. Yamasaki M, Soda S, Sakakibara Y, et al. The importance of 1,2-dithiolane structure in alpha-lipoic acid for the downregulation of cell surface beta1-integrin expression of human bladder cancer cells. Biosci Biotechnol Biochem. 2014;78(11):1939-1942.

26. Furukawa K, Shigematus K, Iwase Y, Mikami W, Hoshi H, Nishiyama T, Ohtuka A, Abe H. Clinical effects of one year of chemotherapy with a modified medium-chain triglyceride ketogenic diet on the recurrence of stage IV colon cancer. Journal of Clinical Oncology. 2018 ; 36.
27. Gray A, Dang BN, Moore TB, Clemens R, Pressman P. A review of nutrition and dietary interventions in oncology. SAGE Open Med. 2020 Jun 1;8:2050312120926877.