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**PREDICTORS FOR TREATMENT SUCCESS IN
PATIENTS WITH METASTATIC COLORECTAL
CANCER AND DIABETES MELLITUS**

ABSTRACT

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Both diabetes mellitus and cancer represent two of the most frequent and severe chronic diseases worldwide. Due to this fact, reciprocal effects, no matter how small, can have a significant impact.

Epidemiological studies have shown that the risk of developing cancer is increased in people with diabetes mellitus. Certain types of cancer that are known to be associated with this disease include breast, colon, and liver. Some mechanisms and defining characteristics of patients living with diabetes have an impact on their cancer risk. Among these mechanisms, hyperinsulinemia is incriminated as a favoring factor in cancer development through insulin's anabolic and mitogenic effect, the action insulin exerts in malignant cells being favored by receptor and post-receptor level mechanisms. Other hypothesized mechanisms implicated were slower bowel transit time, as well as the often-observed increased concentrations of fecal bile acid.

The 10th edition of the International Diabetes Federation (IDF) Atlas corroborates data regarding the continuously increasing number of people with diabetes, in other words, of diabetes prevalence, this pathology posing a challenge for the entire world, directly impacting the health and quality of life of the individual, with reverberations echoing through the lives of those individuals' families and eventually, enveloping entire societies. The estimated number of individuals of adult age (between 20 and 79 years) living with diabetes in 2021 was of 537 million, a rather steep increase from the 463 million cases predicted by the IDF Atlas in 2019. An additional 541 million people are estimated to have had impaired glucose tolerance in 2021, thus being at an increased risk of developing type 2 diabetes mellitus (T2DM). Furthermore, approximately 240 million adults (signifying almost 1 in 2) that are living with diabetes are undiagnosed.

In the Romanian population ages between 20 and 79 years, the PREDATORR study found that a percentage of 11.6% individuals lived with diabetes, and 16.5% had either impaired glucose tolerance or impaired fasting glucose. A higher prevalence of diabetes was encountered among the male gender, while impaired glucose tolerance and impaired fasting glucose were more commonly encountered in the female gender. The main characteristics of those diagnosed with diabetes were a lower level of education, abdominal or generalized obesity and dyslipidaemia. According to data published by the National Health Insurance House (NHIH), there are 782.430 individuals living with diabetes that are included in the National Diabetes Program.

Cancer represents one of the leading causes of deaths globally, affecting both developed and developing countries. The number of cancer cases are growing as a consequence of population aging on one hand, and the increased prevalence of established risk factors, on the other. The most commonly encountered risk factors for cancer are smoking or tobacco consumption of any kind, overweight, a decrease in physical activity, as

well as changes in reproductive patterns that appear as a consequence of economic development and urbanization. It has been observed that less developed countries have begun to surpass developed countries in what number of new cases (57%) and mortality rates are concerned (65%). In 2012, Globocan estimated an incidence of cancer by age 75 of 4.3% in more developed countries, while in less developed countries, that percentage was of only 1.6%. This observation could have been due to a disparity between risk factors, availability of screening programs, funds allocation or availability of treatment.

In Romania, Globocan 2020 estimated the number of new cancer cases to be approximately 98.886, the number of deaths due to cancer to be roughly 54.486, the risk of developing cancer before the age of 75 to be of 26.9%, and that of dying from cancer before the age of 75 to be of 14.6%. Regarding the top 5 most frequent cancers, in order of frequency, in the female gender there is breast, colorectum, cervical, lung and uterine cancers, whereas in the male gender the observed types were lung, prostate, colorectum, bladder and stomach cancers.

Globocan reported that in 2020, the number of new CRC cases was approximately 1.931.590. The risk of developing CRC during their lifetime has been estimated to be of 4% in women (1 in every 25 women), while in men it was found to be slightly higher, around 4.3% (1 in every 23 men).

In women, CRC is the second most common type of newly diagnosed cancer after breast cancer, in 2020 there being an estimated number of 865.630 new cases, accounting for 9.4% of the total number of malignancy cases diagnosed worldwide.

In men, CRC occupies the third position, constituting 10.6% of all new cases of malignancies, after lung cancer in the first position (14.3%), and prostate cancer in the second (14.1%).

In terms of prevalence, over a 5-year period in 2020, among the female population, colorectal cancer was second only to breast cancer, with percentages of 9.3% and 30.3%, respectively. In the male population, the prevalence of colorectal cancer was higher than in the female gender (11.5% vs. 9.3%), though it similarly occupied the second position, following prostate cancer, which was the most prevalent type of cancer in men (20%), significantly outnumbering lung cancer cases (6.4%) found in the third position.

In the latest Globocan factsheet (2020) regarding our country, colorectal cancer represents the most frequently encountered new cases of cancer, amounting to 12.938 cases (13.1%) of the total of 98.886, surpassing lung cancer (12.3%) by almost 1%.

By gender considerations, in the Romanian female population, colorectal cancer represented the second most frequent type of cancer (11.8%) among newly diagnosed cases, after breast cancer (26.9%). In the male population, CRC occupied the third place (14.1%), after lung cancer (16.8%) and prostate cancer (14.9%).

PAF is the acronym for population attributable fraction, a metric that is calculated in relation to other variables in order to determine the impact they have on a certain pathology. In a study published in *Lancet Diabetes and Endocrinology*, researchers calculated the PAF of cancers attributable to obesity and DM. Results showed that 5.7% of all incident cancer cases in 2012 had been related to the coalescent effects of obesity and DM. When a sub-analysis regarding only the twelve malignancies that were known to be related to adiposity, among which colorectal cancer was included, and six types of cancer related to DM (colorectal cancer being also included in this subgroup) was performed, results showed that between 13.5% and 15.3% of the cancers ascribable to the coalescent effects of obesity and DM.

Cachexia is associated to a plethora of chronic diseases, cancer being among the most severe. Both morbidity and mortality significantly increase in case of cachexia, while surgical complications in cancer patients are more frequent. Furthermore, it has been found that this syndrome reduces the patient's quality of life, and diminished the efficacy of chemotherapy while increasing its toxicity. According to a study conducted by Argilés et al that was published in 2014, a percentage of 50% to 80% of patients with cancer presented cachexia, leading to cancer-related deaths in 20% of cases and being responsible for 80% of mortality rates.

Cancer cachexia leads to loss of both adipose tissue and, as a defining characteristic, skeletal muscle tissue. Often patients with cancer experience loss of appetite, and a reduction in food intake, two elements that paired with the intense catabolism induced by cancer lead to significant weight loss. Efforts are being made in compensating the aforementioned weight loss through conventional nutritional support, to date this approach being able to only partially reverse weight loss.

Prevention of colorectal cancer represents one of the most important measures designed to contain the global cancer burden, thus lifestyle measures need to be implemented to ensure this outcome.

The incidence of colon cancer is significantly influenced by diet, red meat consumption being particularly associated with an increased risk of developing this disease, as opposed to a diet high in fruit and vegetables such as the Mediterranean diet has been shown to have protective effects.

Colorectal cancer outcomes are influenced by the chemotherapy regimens instituted, by the surgical interventions performed, as well as lifestyle interventions. Physical activity, a

healthy Nordic or Mediterranean have proved to have protective effect, while a higher recurrence rate and a higher mortality rate in stage III CRC were encountered in patients with higher BMIs, a Western diet and increased glycemic load of consumed food.

Primarily, the Mediterranean diet consists of a decreased content of saturated fats, emphasizing the inclusion of lean protein sources, unsaturated fat derived from fish in the form of polyunsaturated fatty acids, and whole grains as a source of fiber. Even more so, the numerous servings of fruits, vegetables, and especially nuts and seeds represent other significant attributed of this diet.

One of the dietary components that has been receiving increasing attention due to their capacity of improving overall health and to reduce mortality in various pathologies are nuts and seeds. Aside from their role in the reduction of cardiovascular incidence and mortality, an increasing body of evidence suggests that nuts might assist in the prevention of malignancies.

It is a well-known fact that nuts have antioxidant properties, as well as anticarcinogenic ones, due to their high tocopherol content, alongside their concentrations of phytosterols, minerals and folic acid. The anti-malignancy properties of nuts could further be due ellagitannins and urolithins, although the exact mechanism through which these polyphenols exert their actions is yet unknown. Both ellagitannins and urolithins have been found to inhibit the proliferation of cancerous cells, particularly in colon cancer cases, the effect being proportional to the utilized dosage. The two mechanisms through which phytochemicals found in nuts can act are by acting as blocking agents that inhibit tumor initiation, such as indole-3-carbinol, ellagic acid and flavonoids, or by acting as suppressing agents, inhibiting tumor progression, such as inositol penta-/hexakisphosphate, resveratrol, and betacarotene.

The benefits observed in cases of colon cancer following nut consumption could also be attributed to another mechanism, namely the changes this food group determines in the microbiota, that further leads to a modulation of cell signaling and protein-kinase signaling.

Even though the benefits derived from the inclusion of "nuts" as an umbrella term have been proven through many studies, it must be taken into account that the extent of the effect is closely related to the type of nut in question, an unsurprising fact given that the concentrations of various components differs among nut types.

1. DIABETES MELLITUS AND OTHER PREDICTORS FOR mCRC TREATMENT SUCCESS

The aim of the present research piece was to assess how the presence or absence of certain factors, among which DM, influence time to treatment failure of various chemotherapy lines in patients with metastatic colon cancer.

Of the 1069 cases of colorectal cancer, 468 cases also presented metastases, more than half of these cases (55.55%, meaning 260/478) being present in male patients. 988 chemotherapy line were included for the purpose of the present thesis, amounting to 8669 treatment cycles.

The percentage of patients that had mCRC and also had a DM diagnosis out of the total of 468 was 13.46%, a value that is mirrored in the general Romanian population, as per the findings of the PREDATORR study. This percentage of DM found in CRC is similar to other findings identified in literature that identified between 8.5% and 13.8% to 22.6% such cases. In patients with stage III CRC, the percentage was higher, with 18.6% of patients associating DM, a value which was lower than the one encountered in other studies.

A similar percentage of patients both with and without DM underwent treatment with oxaliplatin, with a slightly higher one being observed in patients with DM: 68.3% versus 67.7%, respectively. One of the well-known chronic complications of DM is represented by neuropathy, and one of the main adverse effects of oxaliplatin treatment is represented by neurotoxicity, as a consequence the association of this particular chemotherapy agent in these particular patients is not one to be desired as a first resort.

Among patients included in the present study, 28.95% received irinotecan in their chemotherapy regimen, with 45% of patients without DM and 55% of patients with DM having this agent included in their treatment. With advancement in age, patients with DM undergoing irinotecan treatment were observed to have shorter time to treatment failure after the age of 60, an observation that barely missed statistical significance with a p-value of 0.06.

37.14% of the patients enrolled underwent antiangiogenic treatment. The efficacy of treatment materialized in time to treatment failure did not significantly vary based on gender. Upon performing sub-analysis of the patient lot based on diabetes status, women with DM undergoing bevacizumab treatment presented significantly lower mean TTF than their counterparts who did not have DM: 81.08 days compared to 193.09 days, respectively (p-value < 0.001).

Present results identify diabetes mellitus as a risk factor for shorter time to treatment failure and negative predictive factor for women treated with bevacizumab. In male patients,

bevacizumab did not prove to lead to a shorter TTF nor a negative predictive factor to this sub-group, even though these findings were not mirrored in other research materials.

In the patients included in this study, a complete blood panel was performed, leading to some important observations, namely that anemia was a significant predictive factor for mCRC outcomes, that a higher lymphocyte count led to improved outcomes, as well as the fact that a higher monocyte count led to an unfavorable effect in patient undergoing antiangiogenic treatment.

Anemia was found to bear a negative predictive quality regarding time to treatment failure in the entire studied lot, and in sub-group analysis, in those patients treated with antiangiogenic agents. The protective effects of higher hemoglobin values were even more notable in patients with diabetes mellitus. These findings are in accord with other studies that demonstrated that pretreatment anemia significantly impacts survival of patients with CRC, these patients in particular having a prevalence of anemia between 30% and 67%. One study found a staggering 76.6% of patients with CRC that had undergone surgery had anemia at discharge, their hospital stays being longer, their overall survival rates being lower, and their quality of life being impacted even at the 5-year mark.

In female patients, higher lymphocyte levels represented a positive predictive factor, in accord to the findings of other authors suggesting that lymphocytic reaction to CRC may be indicative of a good host immune response and lead to a longer survival in these patients, impacting even racial disparity encountered in survival of patients.

A poor prognosis was seen in patients with elevated monocyte levels considered to be mirroring the levels on tumor-related macrophages that favor tumor development. Numerous studies and meta-analyses have identified peripheral monocyte count as a reliable predictive factor of a poor outcome in CRC, irrespective of ethnicity or gender. The same conclusion was reached in the present study, underlining the value of peripheral monocyte count in the evaluation of patients with CRC and in the evaluation of the microenvironment of the tumor.

The strength of this study resides in it being one of the only such studies conducted in Romania. What is more, it is the first to be conducted in the Western Region of Romania. Despite there being numerous other similar studies worldwide, the Romanian population presents a set of unique characteristics that must be considered: the growing prevalence of diabetes mellitus and colorectal cancer, the socioeconomic status of its population, their culture, as well as education levels, and the availability of screening programs or willingness to partake in them. The study lot was comprised of 468 patients with metastatic CRC and 8669 chemotherapy cycles, DM being encountered in an almost identical percentage to that of the country's, being representative of the Romanian population.

A possible limitation of this study might be represented by the lack of delimitation by DM treatment agents, this representing the basis for future research to be undertaken by our research team.

Because of the complex and multilateral metabolic imbalance caused by the coexistence of diabetes mellitus, obesity, and cancer, it is of paramount importance that further research be conducted in order to optimally care for these patients and ensure the best lifespan and quality of life possible.

2. Nutrition as a tool in improving cachexia outcomes in cancer

In colorectal cancer, between 50% and 61% of patients have cachexia, this clinical complication being accountable for approximately 20% of deaths among them. Myopenia and myosteatorsis have both been found to be independent prognostic factors associated with worse outcomes in patients with malignancies, leading to lower rates of disease-free survival, overall survival, and shorter cancer-specific survival. One study in particular found cachexia to be an independent risk factor for 6-month mortality.

This systematic review primarily aimed to identify nutritional interventions that might mitigate weight fluctuations in patients with cancer and associated cachexia, with emphasis on dietary supplements.

26 studies met the inclusion criterion, as well as the quality assessment request and were incorporated in the present analysis. Initially, 5735 research papers were screened, of which 143 were taken into consideration following the evaluation of the title and abstract.

There were both randomized and non-randomized clinical trials included. Of the 26 studies, one described various types of cancer in the pediatric subgroup of patients, the remaining 25 referring to the adult population suffering from various types of cancer among which: colorectal, gastro-intestinal, pancreatic, metastatic intra-abdominal, non-small cell lung, head and neck squamous cell, and solid tumors. Interventional arms consisted of a number of patients ranging between 9 and 235, with a study duration of up to 24 weeks.

Interventions were defined as the administration of supplements, either by oral or parenteral means. The supplements consisted of one of the following, administered either individually or as a combination: L-carnitine; leucine; branched-chain amino acid (BCAA); essential amino acids (EAA); eicosapentaenoic acid (EPA); fish oil (FO); ω -3 fatty acids; medium-chain triglycerides (MCTs); Ethanwell/Ethanzyme (EE); Guarana; megestrol acetate (MA); marine phospholipids (MPL); oleic acid (OA); cannabinoids; oral nutrition supplementation (ONS); cannabinoid extract (CE); delta-9-tetrahydrocannabinol (THC); total

parenteral nutrition (TPN); β -hydroxy-beta-methyl butyrate (β HMB); HMB, arginine, and glutamine combination.

Outcome measures across the included trials were changes in body weight, in body composition, skeletal muscle mass (SMM) improvement before and after treatment (chemotherapy + radiotherapy), psoas major muscle area (PMA) before and after treatment (chemotherapy + radiotherapy), protein anabolism, nutritional status and performance status, quality of life, appetite, fatigue, biological parameters and inflammation status, complications that might have occurred, and compliance to the proposed nutritional intervention.

Even though the majority of studies included for the purpose of this systematic review were represented by randomized trials, and as such they were structured to comprise a control group and an intervention group, the latter included only a modest number of patients, leading to the classification of more than 75% as being at high risk of bias.

Among the included studies there were six trials that reported a decrease in body weight irrespective of the nutritional intervention that included the administration of ω -3 fatty acids, EPA, CE and THC, TPN, Nabilone, LCTs, LCTs + MCTs. A singular study on pancreatic cancer that included 31 cachectic patients reported a decrease in body weight after the supplementation with EPA. However, these patients experienced an improved post/pre ratio of SMM, proportional to the supplement dosage ($p=0.02$). The patients included in the NI group presented significantly lower PMA post/pre ratio than the NI group. 33 of the pediatric patients included in the study conducted by Bayram et al., ages between 7.7 ± 2.7 years, did not manage to gain weight after supplementation with EPA. They did, however, show a lower percentage of BW loss in patients that took the EPA supplement: 6.1% compared to the 47.4% BW loss that patients who did not take the supplement experienced ($p\text{-value}= 0.001$). As a direct consequence, the BMI was also less impacted in the NI group of patients: 12.1% decrease compared to 52.6% in the group without NI ($p\text{-value}= 0.002$), and so was the weight percentile: 6.1% compared to 31.6% ($p\text{-value}= 0.021$).

There were eight trials that proved unable to present data regarding a significant alteration in body weight. Among the eight studies, three entailed the administration of EPA supplements. Studies that included supplementation with FO, ONS or Guarana similarly failed to show a significant modification in the body weight of patients.

Four randomized controlled trials in which arginine, glutamine, EPA, β -HMB, or MLP supplementation was introduced, patients experienced significant weight increase. Further, patients undergoing supplementation with L-carnitine, EE plus ω -3 fatty acids, probiotics, micronutrients, FO, rich source of leucine or TPN paired with BCAA in high dosages showed an upheaval in body weight.

There was one study that found no beneficial effect of the administration of high leucine levels (under the form of a mixture containing EAA/Leucine) in patients diagnosed with non-small-cell lung cancer. Additionally, another trial found no differences between the effects of OA-EE or EPA-EE on body weight decline consecutive to the intervention.

3. The consumption of nuts in CRC

Diet and lifestyle factors have great influence in the pathogenesis of T2DM, as well as in colorectal cancer. Studies have been performed focusing on various modalities through which to assess the contribution one's diet and lifestyle have on carcinogenesis, disease progression and mortality, in both individuals with T2DM and in those without the disease.

More recently, the attention of the scientific world has turned towards preventative measures that would ensure a longer lifespan, as well as a longer healthspan of the individual. This has translated in studies on diet and lifestyle and their impact on numerous diseases including, but not being limited to cancer, cardiovascular disease, autoimmune diseases, diabetes and obesity. Though heterogeneous in many aspects at first, there is an increasing number of studies on diet in general, as well as on certain food groups that have high statistical power, rendering a notable degree of trust in their results. Such is the Global Burden of Disease Study published in The Lancet, which concluded that 44.4% of cancer deaths are attributed to modifiable risk factors and 42% of healthy years are lost due to the same preventable risk factors.

Of all the variables at play in an individuals' diet, one is particularly easy to include in everyday life and has a resounding effect on ones' health: nut consumption. It has been known to have beneficial effects on the cardiovascular system, on metabolic health, and appears to positively influence the risk for colorectal cancer.

A study conducted in Taiwan identified a reduction in risk of 58% in women who had higher intake of peanuts, compared to those who consumed peanuts seldomly or not at all, though statistical significance was not reached in men. Another study demonstrating the protective role of nut intake in the female gender is represented by EPIC, results indicating that even a quantity as low as 16 g of nuts per day led to a significant decrease in colorectal cancer, particularly distal colon cancer.

Aside from trials investigating the preventative attributes of nut consumption in patients that were cancer-free at enrollment, other researchers set on studying the effects that this dietary intervention might have in patients that had already been diagnosed with cancer. Such is a study showing that in stage III CRC patients' that had two or more servings of tree nuts per week, disease-free survival was increased by 42% compared to those with

lower nut intakes. If patients had even higher intakes of tree nuts, their overall survival was increased by 57%. Peanut or peanut butter intake did not render similar effects.

Regarding underlying mechanisms, nuts have been shown to exert numerous effects both systemically and at a cellular level, with walnut phenolic extract receiving special consideration from the scientific community. The effects of walnut phenolic extract vary from the inhibition of tumor-cell growth by up to 85.8%, depending on the length of treatment application, to the downregulation of cancer stem cell markers, impeding colony formation by cancer cells, regulating cancer cell renewal ability, as well as targeting telomerase activity and telomere connection.

The phytosterols contained by nuts also exert anti-inflammatory and have documented anti-cancer properties, their high concentrations providing further possible explanations for the beneficial effects that nut consumption have demonstrated.

It is extremely important that research in this area continue, that study designs be made rigorously, so that recommendations can be made in order to provide this complementary prevention and management tool to patients with CRC. Nut consumption represents an accessible, safe, and uncomplicated modality through which individuals can mitigate their cancer risk while improving their overall health, and through which they can improve their outcomes in case of an already diagnosed cancer.

