Original Article

NUTRITIONAL STATUS AND SYSTEMIC INFLAMMATORY ACTIVITY OF COLORECTAL PATIENTS ON SYMBIOTIC SUPPLEMENTATION

Avaliação nutricional e atividade inflamatória sistêmica de pacientes com câncer colorretal submetidos à suplementação com simbiótico

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ABSTRACT - ***Background*** - Nutritional depletion in patients with advanced colorectal cancer, even with adequate weight, may be associated with co-morbidity factors such as: reduction of immunity, increased rate of infections, impaired cicatrization and muscle weakness. Immunomodulating diets have recently been used as a nutritional approach to cancer patients. Prebiotics, probiotics and symbiotics (a mixture of the first two) have been studied. ***Aim*** - To assess the Nutritional Status and Systemic Inflammatory Activity of colorectal patients on symbiotic supplementation. It was a progressive longitudinal study in colorectal cancer patients. ***Methods*** - All patients underwent assessment of nutritional status and subsequent serological analysis, daily use of the symbiotic supplement, anthropometric and biochemical assessment every three months Besides anthropometric data, the following blood components were measured: C-reactive protein (CRP), carcino-embryonic antigen (CEA) and albumin. ***Results*** - The mean CRP level at baseline, before symbiotic administration, was 11 mg/dL, with a reduction to below 6 mg/dL at the end of the study. ***Conclusion*** - There was a beneficial effect of symbiotic supplementation, because although albumin and CEA levels were stable during the study, there was a CRP reduction in meantime.

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RESUMO - ***Racional*** - A depleção nutricional é observada em pacientes com câncer colorretal em estado avançado mesmo com medidas de peso adequadas. Esta perda pode estar associada a fatores de co-morbidades como: redução da imunidade, aumento de infecções, cicatrização prejudicada e fraqueza muscular. Atualmente, dietas imunomoduladoras estão sendo utilizadas na abordagem nutricional de pacientes com câncer. O uso de prebióticos e probióticos ou, a mistura dos dois, os simbióticos, estão entre os estudados. ***Objetivo*** - Avaliar o estado nutricional e a atividade inflamatória sistêmica em pacientes com câncer colorretal submetidos à utilização de suplemento simbiótico. ***Métodos*** - Foi realizado um estudo longitudinal prospectivo com pacientes com câncer colorretal. Todos os pacientes foram submetidos à avaliação do estado nutricional e subsequente análise sorológica, uso diário do suplemento simbiótico e à avaliação antropométrica e bioquímica a cada três meses. Foram coletados dados antropométricos e exames de sangue para avaliação da proteína C-reativa (PCR), antígeno carcionoembrionário (CEA) e albumina. ***Resultados*** - Os índices médio da proteína C-reativa eram de 11 mg/dL no início do estudo, antes da administração do simbiótico, e reduziram-se para valores menores que 6 mg/dL no final do estudo. ***Conclusão*** - A suplementação com o simbiótico foi benéfica, pois, embora tendo os níveis de albumina e CEA mantido-se estáveis, os índices de PCR diminuíram ao longo do estudo.

INTRODUCTION

With the increase in life expectancy of the Brazilian population, cancer is gaining higher importance in the mortality all over the country. It is the second cause of death and sets up as public health problem[4].

Late diagnosis is responsible for high mortality of colorectal cancer. Approximately 150 000 new cases were estimated for the year 2009 in the world, accounting for approximately 10% of all incident cancers[1]. The death estimation for 2009 is 6 000 cases[1].

This cancer has multiple origins as heredity, ability to acquire inflammatory diseases, age, diet, obesity and sedentary lifestyle. Regarding diet, a high intake of calories, fats, red meat and low consumption of fruits and vegetables are associated with the risk of development colorectal cancer[5]. Among the environmental factors, diet contributes about 35%. It is believed that a proper diet can prevent three to four million new cases per year[12].

Among the risk factors, obesity stands out due to the epidemic proportion took in many parts of the world, it is large public health problem[15]. The main mechanisms responsible for the association between obesity and cancer may be the insulin resistance in obese patients[33], and the consideration thar obesity is a sub-inflammatory condition. It results in increased circulating levels of adiponectines which is associated with the risk of colon cancer[17].

In oncology, immunology has been dedicated to the research of the host immune response against the tumor cells and on the mechanisms that facilitate the evasion of these cells from immune natural surveillance. Thus, efforts have been done in developing methods to modulate the immune system, and so, to recognize and eradicate tumor cells. There is lack of knowledge about the effects of certain nutritional changes on this immune response. Despite several observations quantifying relations on immunology with nutritional status, there is no conclusive comprehension of it[34]. Nutritional depletion is evidenced by the loss of lean mass and fat.

In recent years, different approaches to nutritional treatment have been used to correct the deficits observed in patients with cancer: dietary counseling, oral, enteral and parenteral supplements. It is widespread the medical and nutritional use of immunomodulatory diets, ie, rich in immunonutrients capable of modulating immune function.

Currently, the use of immunomodulators nutrients associated with antioxidants, is proposed to stabilize and reduce the damage of peroxidative catabolism[11].

Probiotics are alive microrganisms, which beneficiates the host by improving the balance of intestinal microbiota[20], The current accepted definition is that "they are live microorganisms administered in adequate concentrations conferring health benefits to the host"[7,31]. Prebiotics are non-digestible food ingredients that have beneficial effect by stimulating, selectively, the proliferation of bacteria in the colon.

Symbiotics are among the most studied immunomodulators, involving the interaction between probiotic and prebiotic agents. In vivo the adaptation may be favored by the previous existence of prebiotic. In some cases, the competitive advantage for the probiotic is its consumption together with the prebiotic. Alternatively, this symbiotic effect may target to the various "targeted regions" of the gastrointestinal tract. Consumption of probiotics and prebiotics together can increase the beneficial effects of each, since the stimulus of probiotic strains leads to selection of ideal symbiotic pairs[16,23,26].

The objective of this study was to verify the influence of symbiotic food supplement on nutritional status and inflammatory activity in patients with colorectal cancer.

METHODS

The study protocol was approved by the Ethics Committee of the Universidade Federal de Juiz de Fora - MG under number 391/2007.

The design was prospective longitudinal sample of nine both genders adult patients in the postoperative phase of colorectal cancer, who underwent surgery and daily use of symbiotic supplement composed of four probiotic strains and 6 g of fruit-oligosaccharides/sachet, in the Outpatient Hospital Jose Maria Baeta Reis, in Juiz de Fora, MG, Brazil.

The inclusion criteria were: colorectal cancer in patients aged above 18 years, both genders, stage I to IV according to the current TNM classification and the International Union Against Cancer and patients that had signed the consent form (ICF). The exclusion criteria were: those with inflammatory diseases, with infections and collagen vascular disease, as well as tumors in other organs and in use of anti-inflammatory or antibiotics for any reason.

All patients underwent assessment of

nutritional status, serological analysis, daily use of the symbiotic supplement and were submitted to anthropometric and biochemical evaluation every three months.

Anthropometry

Was made based on clinical and physical parameters, diet, social circumstances, anthropometric measurement and laboratory tests. The nutritional diagnosis permited the classification of nutritional status and nutritional needs of patients. Anthropometric evaluation was obtained through height, BMI according to World Health Organization WHO (1995), muscle arm circumference (CB) and braquial muscle circumference (CMB) by the criteria of Blackburn[8,9,29]. All these measurements were done by the researchers to minimize errors.

Body weight was measured every three months, using a Filizola® calibrated scale, with a capacity of 150 kg and an accuracy of100 g, standing in the center of the base, barefoot and wearing light clothing. To measure the height was used a stadiometer affixed to the scale, barefoot positioning with heels together, back straight position and arms extended at sides.

The CB and triceps skinfold (TSF) were measured every three months by inextensible fiberglass tape in centimeters with an accuracy of millimeters with technique proposed by Lohman et al.[36], using the mean of three measurements. The PCT was obtained by caliper Sanny®.

Biochemical / serological analysis

In all patients were collected blood samples. They were centrifuged at 2500 rpm for 10 minutes to separate the serum (material of the study) the formed elements (red cells, white and platelets). A portion of the serum was immediately used to quantify the level of C-reactive protein (PCR). All samples were properly recorded through the patient's initials and date of collection.

Regarding biochemical parameters were used serum albumin (reference value: 3.5 to 5.2 g / dl) and CEA every three months.

The PCR analysis was performed every three months. The measurement was performed immediately after blood collection. Lipemic and hemolyzed samples were discarded. Values above 10 mg/l were indicative of inflammatory activity.

Statistical analysis

Was accomplished by descriptive and inferential statistics. For statistical analysis and preparation of graphs and tables was used SPSS ® (Statistical Packed for Social Sciences) version 13 and the application Microsoft Excel ® version 2007.

RESULTS

Were selected 28 patients; however, there were included nine colorectal cancer patients, three females and six males. There were 19 dropouts in the study due to death (five), lack of adherence to treatment (six), personal reasons (eight).

All subjects were evaluated every three months during one year. The nine patients were aged between 40 and 80 years, most between 50 and 60 years (sixn) and one patient in each 40´s, 60´s and 70´s. Regarding to staging, there was none in stage I, whereas in stages II and III there were four in each and at IV one patient.

Nutritional assessment

Figure 1 shows changes in the patient's BMI every six months. Was observed predominantly BMI> 25 kg / m^2 (five patients). The figure also shows the BMI variation for each patient at one month (inicial monitoring), 6th and 12th months. Five patients presented BMI> 25kg/m 2 characterized as overweight which shows the profile of patients with colorectal cancer. However, one had nutritional underweight status by BMI, and another began with slimness and ended eutrophic.
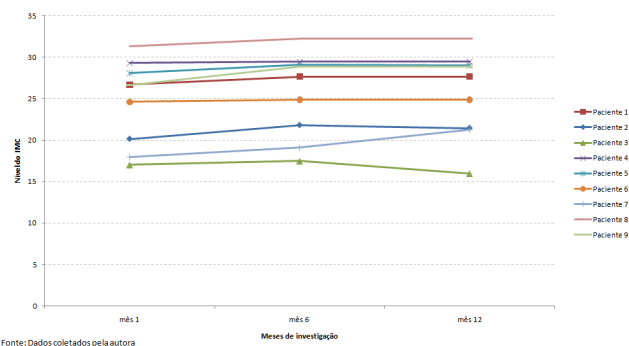

FIGURE 1 - Changes in BMI of each patient at one, six and 12 months analysis

Table 1 shows the relationship between the classification by BMI and nutritional adequacy of the PCT%, CB%, CMB% and between genders. Among the three women, one although classified as obese grade 1 by BMI was classified as moderately malnourished by the measures of adequacy PCT%, CB% and CMB%, showing the early cachexy process. Among the six men, one was eutrophic and mild malnourished by measures of adequacy PCT% CB% and CMB%. Another with overweight by BMI was malnourished by the measures of adequacy PCT%, CB% and CMB%, which showed, as well as in the female group,

TABLE 1 - Relationship between the classifications of nutritional status by BMI (anual average) and the adequacy of the PCT%, CB% and CMB%

Gender	Nutritional classification by BMI	Nutritional classification by PCT%, CB% and CMB%	N	%
Woman	Slimness grade I	Mild malnutrition	1	11%
	Eutrophic	Mild malnutrition	1	11%
	Obesity class I	Moderate malnutrition	1	11%
Man	Eutrophic	Mild malnutrition	1	11%
		Eutrophic	2	22%
	Pre-obese	Mild malnutrition	1	11%
		Eutrophic	1	11%
		Obesity	1	11%
		Total	9	100%

early loss of muscle mass and fat.

### Biochemical / serological evaluation
Protein C-reactive

Figure 2 demonstrates the dosages of the PCR at 1, 6 and 12 months. Difference is observed in averages and confidence intervals in the analyzed periods, occurring in significant decrease in 1 month in relation to 6th and 12th months. At 1st the average was 14.7 mg / l, on the 6th of 5.0 mg / l and 12 months of 8.3 mg / l. Besides the PCR average, was possible to observe that both the mean and the upper edges of the confidence interval, showed a decrease in PCR levels from the 1st to the 12th month, been the 6th month which showed lower values. In the 1st month the patients did not use the supplement and there was great variation in protein levels. On the 6th all presented values with smaller dispersion. On the 12th there was an increase in mean and dispersion compared to 6th, but in comparison to 1th, the dispersion and the maximum value of the confidence interval were smaller. The data suggest no benefit using the symbiotic supplementation in decreasing PCR.
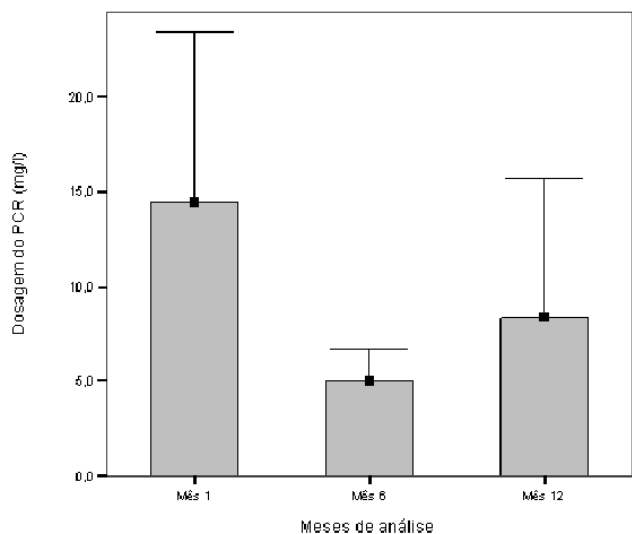
FIGURE 2 - Dosages of PCR in patients at one, six and 12 months analysis

The carcinoembryonic antigen (CEA)

Figure 3 demonstrates CEA in the 1st, 6th and 12th months of analysis. In the 1st the average was 3 ng / ml with low dispersion at the top of it confidence intervals. It was observed that at 12 months it was 10.1 ng / ml and the top edge of the confidence interval had great dispersion. The symbiotic had no influence on tumor and both the average and the top edges of the confidence interval increased from the 1st to the 12th months.
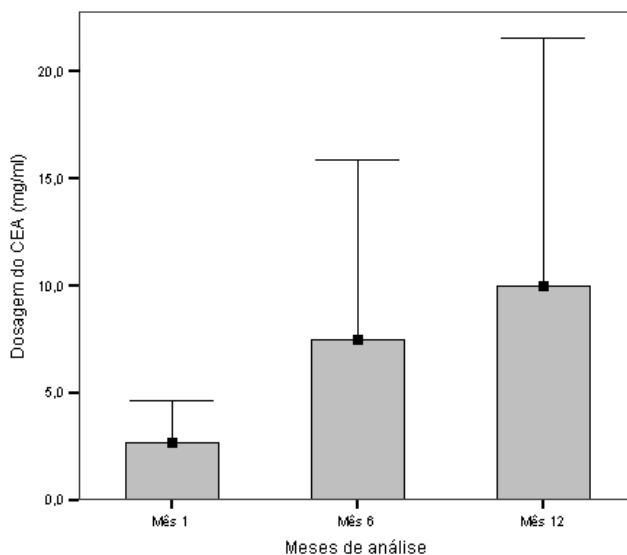
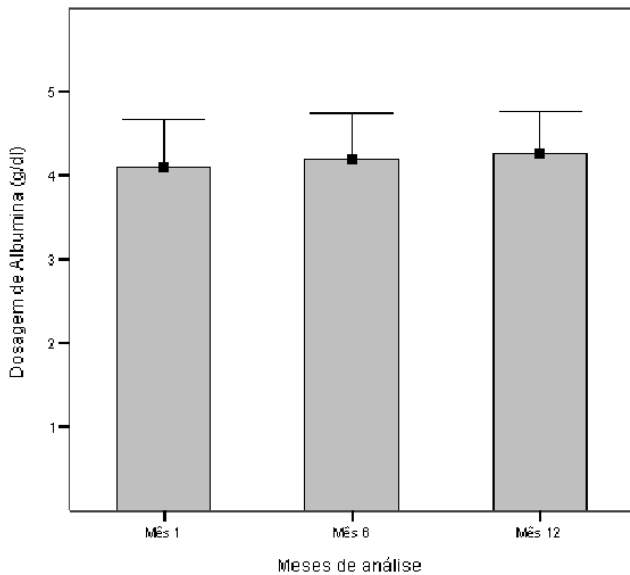**FIGURE 3** - Diagram of the CEA in one, six and 12 months analysis

Albumin

Figure 4 demonstrates the dosages of albumin at one, six and 12 months analysis. It can be observed that the values were above 3.5 mg / l after supplementation with symbiotic throughout the study.

What is pointed out is the amount of albumin that was above 3.5 mg / l, ie, nutritional status, with the top edge of the confidence interval with small dispersion after supplementation with the symbiotic. This suggests that the supplemental symbiotic food cooperated with maintenance of albumin values or did not permit it to diminish during the study.

DISCUSSION

Obesity seems to affect mainly the early stages of carcinogenesis, being associated with a higher risk of advanced colorectal adenoma, important precursor of colorectal cancer[15].

In relation to anthropometric measures, health professionals should be alert to the use

FIGURE 4 - Diagram of the dosage of albumin in one, six and 12 months analysis

of BMI that may overestimate the patient's nutritional status and "mask" a future tumoral cachexy. It is suggested that oncology centers use PCT, CB, CMB measurements and also waist circumference.

More recent studies showed that waist circumference and waist-hip ratio - both markers of abdominal fat or visceral adipose tissue -, are most associated with the development of colorectal cancer than BMI. The findings suggest that adipose tissue distribution, rather than overall adiposity, is more strongly associated with the risk of developing colorectal cancer[9,13,14,21,25].

The assessment by the circumferences and skinfold demonstrates that BMI is not the only standard for nutritional assessment of patients with cancer and may overestimate the nutritional status of some patients who are developing loss of muscle mass and fat, typical in cachexy.

In a study of 100 patients with colorectal cancer undergoing operation, it was evident that more than half the population reported history of weight loss, being severe in 47% of the total. The high level of weight loss contrasts with high percentage of excess weight and eutrophy. This fact leads to the worrying position that, at the time before diagnosis of the disease, these individuals were excessively overweight, which is consistent with the assertion that obesity is increasingly prevalent among individuals and a recognized factor for colorectal cancer[2,22,24].

In the present study, it was found that patients classified as overweight or obese by BMI presented mild to moderate malnutrition in PCT and CMB measures. This last two nutritional assessment demonstrate loss of muscle and

adipose tissue characteristic of cachexy.

Differences in tumor phenotype or genotype of the host and their interactions can contribute to the development of cachexy, whose main feature is the loss of weight due to the reduction in food intake, increase energy expenditure or boths[8], especially when evidenced by the loss of lean body mass is associated with increased hospitalization time and mortality. Such association is directly associated with increased morbidity factors[19].

Laboratory evaluation in the diagnosis of malnutrition contributes to the correction of nutritional problems in the early stages. The tests used in most major centers are: measurement of plasma transferrin, prealbumin, retinol carrier protein and urinary creatinine. But they are expensive. In public hospital routine, serum albumin is used quite often in view of the low cost[32]. In this study, it was observed that patients throughout the study showed serum albumin values greater than 3.5 g / dl which shows that proper nutritional status[35].

The PCR is a protein that indicates the severity of inflammatory disease. The serum concentration is associated with the activity of pro - inflammatory cytokines such as IL1 and IL6, which can be responsible for the decreasing in synthesis of negative protein in acute phase[30]. Recent studies have demonstrated that serum level of PCR above 10mg/l in patients with colorectal cancer, can be considered as an independent factor of poor prognosis[3,6,30].

Koike et al.[18], evaluated PCR as an independent marker of prognosis in patients with early colorectal cancer. They evaluated preoperatively levels of PCR in 300 patients and correlated with clinical characteristics. In a univariate analysis revealed that only PCR and CEA are predictors of poor survival, whereas, in multivariate analysis, only PCR was predictive of poor survival.

The SYNCAN project was a innovative community-supported trial in Europe, which tested the efficacy of symbiotic supplementation in reducing colon cancer in experimental models and studies of dietary intervention with the supplement in humans. Were included 37 patients who were submitted to curative resection and 43 with risk of developing colorectal cancer in removed polyps. Of the patients who had curative resection, 19 had symbiotic supplement and 18 used placebo. The effect of intervention with symbiotics in various immunological markers was examined in the patients who has curative resection. There was no effect of the supplement on the secretion of IL10, IL12 and TNF-α. The intake of the symbiotic prevented the increase in

IL2 and the production of interferon γ[10,27,29].

The use of ratio PCR/albumin, as indicator of inflammatory status and nutritional severe risk patients, is being proposed in the evaluation by nutritionists[6].

Further studies should be conducted with more participants, as evidence shoows the need for the use of immunomodulatory supplements in dietary treatment of cancer patients.

CONCLUSION

Supplementation with the symbiotic was beneficial because, although having albumin levels and CEA remained stable, rates of PCR decreased throughout the study.

ACKNOWLEDGMENT

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