INTEGRATION OF FUNCTIONAL ASSESSMENT AND MONITORING OF HEALTH STATUS IN PATIENTS DIAGNOSED WITH COLORECTAL CANCER

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Abstract. *Introduction. Physical exercise plays a critical role in managing and preventing colorectal cancer, significantly influencing survival, quality of life, and disease progression. This preliminary study evaluated 11 subjects (mean age: 65 years), including 6 with colorectal cancer and 5 with high-grade dysplasia. Functional, haematological, and biochemical assessments focused on inflammatory markers' response to physical activity. Assessment tools included the SF-36 questionnaire for quality of life, the Karnofsky Performance Status Scale for functional capacity, and the EQ-5D-5L questionnaire for health status. Inflammatory markers, such as IL-6 and fibrinogen, were also analysed alongside hemogram, Quick time, and APTT. A physical exercise program was implemented with the purpose of reducing fatigue, improve postural control, fitness, muscle strength, range of motion, and enhance overall quality of life. Functional capacity improved in 8 out of 11 patients (72.72%), with blood parameter changes observed in hemogram (27.27%), APTT (18.18%), fibrinogen (9.09%), and IL-6 (9.09%). Quality of life improvements were recorded in 90.91% (SF-36), 100% (Karnofsky scale), and 100% (EQ-5D-5L) of patients. The study highlights that structured physical exercise reduces fatigue, anxiety, depressive symptoms, and pain, while enhancing self-confidence and the ability to participate in daily activities. These findings support integrating exercise programs into therapeutic strategies for colorectal cancer management.*

Keywords: *colorectal cancer; physical exercise; inflammatory markers; quality of life.*

Introduction

Colorectal cancer is one of the most common forms of cancer worldwide and represents a major health issue with a significant impact on patients and healthcare systems. This type of cancer generally develops from polyps, which are benign growths in the colon or rectum. Colorectal cancer can occur in various parts of the colon or rectum and tends to progress slowly. Multiple risk factors contribute to the development of colorectal cancer, including genetic predisposition, aging, diets rich in saturated fats and red meat, sedentary lifestyles, as well as various environmental influences. (Sung et al., 2021)

It is important to be aware of these risk factors and to perform regular screenings to detect colorectal cancer early, as early diagnosis can increase the chances of cure. Screening methods may involve testing for occult blood in the stool, alongside procedures such as sigmoidoscopy and colonoscopy. (Siegel et al., 2020)

Worldwide, colorectal cancer ranks as the third most prevalent cancer among men and the second among women, with estimates of 746,000 and 614,000 new cases, respectively, in 2012. Prognostic outcomes have improved notably in recent decades, with the Netherlands reporting a 63% five-year survival rate between 2008 and 2012. The growing number of survivors has drawn increased focus on the adverse effects associated with both the illness and its treatment.

One of the adverse effects is the onset of fatigue, which usually intensifies during chemotherapy. Even in the years following treatment, the prevalence of moderate to severe fatigue remains at 27%. Cancer-related fatigue is a debilitating symptom that can have various consequences, including emotional distress, non-compliance with treatment, a negative impact on work, reduced functionality, and an overall lower quality of life.

Meta-analysis results, including most studies conducted on cancer patients, have shown beneficial effects of exercise-based interventions both during and after adjuvant treatment. A meta-analysis of the effects of exercise-based interventions in patients with colon or rectal cancer during or after adjuvant treatment, including three randomized controlled clinical trials, showed short-term improvements in physical capacity following exercise-based interventions but found no evidence for effects on quality of life or fatigue. Two of these three clinical trials included only patients after adjuvant treatment.

The third investigated the effects of a home-based exercise intervention in colorectal cancer survivors within 3 months post-surgery, of whom only a portion were receiving adjuvant chemotherapy at the time of inclusion. To date, the effects of a supervised exercise-based intervention on patients with colorectal cancer during chemotherapy, starting from an assessment of functional status and adapting the exercise program to the functional status of these patients, have not been sufficiently investigated.

In one study (Van Vulpen et al., 2016), an 18-week supervised exercise program during adjuvant chemotherapy for colon cancer significantly reduced physical fatigue at 18 weeks and general fatigue at 36 weeks compared to usual care. Additionally, patients in the intervention group reported significantly better physical functioning compared to patients in the usual care group. The beneficial effects observed of the exercise program on fatigue contrast with the results of other meta-analyses that found no evidence for the effects of exercise-based interventions on fatigue in patients with colorectal cancer.

Findings from another study (Singh et al., 2020) suggest that exercise is safe and feasible for individuals with colorectal cancer both during and after treatment. There is also evidence supporting that exercise is effective in improving quality of life, physical capacity, fatigue, upper body muscle strength, sleep quality, reducing depressive states, and body fat percentage after a colorectal cancer diagnosis. Participation in physical exercise was associated with a low risk of adverse effects, occurring in approximately 1% of participants among the 1293 participants who exercised and those who received usual care.

Currently, the publication titled "Exercise and colorectal cancer: a systematic review and meta-analysis of exercise safety, feasibility, and effectiveness" appears to be the first to offer a comprehensive cumulative analysis of exercise-related adverse events, while also systematically assessing feasibility outcomes such as recruitment, adherence, and dropouts among individuals with colorectal cancer.

Current findings suggest that exercise after a colorectal cancer diagnosis is associated with a low risk of adverse effects, is feasible, and has beneficial effects on a wide range of health status parameters, regardless of the type of exercise, level of supervision, duration, or timing concerning chemotherapy or surgical intervention.

Treatment for colorectal cancer may include surgery, chemotherapy, radiotherapy, or biological therapies, depending on the stage and specific characteristics of each patient.

Education and awareness about this disease are particularly important for the effective prevention and management of colorectal cancer.

The impact of physical exercise is extremely beneficial for patients with colorectal cancer. Studies show that engaging in regular physical activity can significantly improve the quality of life for these patients. For example, individuals who engage in regular exercise report lower levels of fatigue, anxiety, and depression. Additionally, physical exercise can enhance both physical and emotional functioning in these patients.

Regular physical activity can also reduce the risk of complications associated with colorectal cancer treatment. For instance, it can help maintain optimal weight, improve immune system function, and reduce inflammation. Furthermore, physical exercise can enhance patients' ability to cope with the side effects of therapies, such as nausea, loss of appetite, or weight loss.

Functional assessment is essential for personalizing exercise programs for patients with colorectal cancer. Functional evaluations can include measuring cardiorespiratory capacity, muscle strength, flexibility, and balance. Based on these assessments, individually tailored exercise programs can be developed to address the specific needs and capabilities of each patient.

Taking into account the patient's overall health condition and the progression stage of the disease is essential, and any ongoing treatments. Physical exercises can positively impact the quality of life for colorectal cancer patients by improving functionality, reducing fatigue, managing stress, and maintaining a healthy weight. Therefore, adapting exercise programs to the individual needs of patients is crucial for achieving maximum benefits.

Physical exercise can play an important role in reducing the risk of colorectal cancer recurrence and improving long-term prognosis. Thus, integrating physical activity into the daily routine of patients can be beneficial not only physically but also emotionally and mentally. (Schmitz et al., 2010)

The aim of our study is to obtain a comprehensive overview of the functional and hematological status, specifically regarding inflammatory markers, of a group of subjects who will subsequently be included in an exercise program. The effects of this program will be objectively measured through these evaluations. By monitoring the functional, hematological, and biochemical profiles following the exercise program, we can obtain valuable information about the impact of regular physical activity in managing these medical conditions. The results obtained could contribute to the development of personalized intervention strategies to improve the quality of life for patients with these conditions.

Based on the documentation we propose in our research a pilot study for creating an algorithm for the assessment and implementation of physical exercise programs at cancer patients, using scales for functional evaluation, quality life evaluation and components of physical aspects and psychosocial problems. At the same time, the physical exercise program is a novel element, because it is an original program that includes combination of aerobic exercises and increases muscle force.

Materials And Methods

The present study is a preliminary study conducted on a total of 11 subjects with an average age of 65 years, out of which 6 were diagnosed with colorectal cancer and 5 with high-grade dysplasia. They were assessed functionally using evaluation scales and hematologically by

monitoring inflammatory markers. It is worth mentioning that a baseline hematological evaluation was conducted to assess the health status.

The functional assessment was performed using the following scales:

SF-36 (Short Form 36) is an extremely valuable questionnaire in assessing the functional status of patients with colorectal neoplasms, as it covers a variety of domains relevant to patient well-being. By using this instrument, healthcare professionals can obtain a detailed picture of the impact of a condition on patient functioning and quality of life. (Ware & Sherbourne, 1992)

SF-36 is one of the most widely used generic health measures due to its effectiveness in assessing various aspects of patient life. This instrument covers multiple domains such as general health status, functional capacity, pain, mental and social status, thus allowing for a comprehensive assessment of the patient's perceived health status. (McHorney et al., 1993)

The Karnofsky Performance Scale is an evaluation scale of general health status and functionality of patients, particularly used in oncology to assess self-care capacity and patient functioning level. The Karnofsky Scale consists of a series of functioning levels, ranging from 0 (deceased) to 100 (completely healthy), each level representing a certain self-care and activity capacity. Using the Karnofsky Scale can provide a clear perspective on the overall patient's status and can contribute to improving the quality of care provided. (Oken et al., 1982)

The Karnofsky Scale is composed of several categories, each with an associated score, reflecting the degree of patient functional capacity, quantified with a score from 0-100. The score obtained on the Karnofsky Scale can be used to monitor the patient's status evolution over time and to evaluate treatment effectiveness and the impact of the disease on patient functionality.

The EQ-5D-5L questionnaire is a standardized and comparable instrument used for assessing quality of life, measuring the perceived health status by patients. It consists of a set of questions and an evaluation scale covering five main health domains, along with a self-assessment question of overall health status. This instrument is widely used in medical research and treatment effectiveness assessment, facilitating result comparison across various studies and contexts. EQ-5D-5L is useful in identifying patient needs, monitoring health status evolution, and in the medical care decision-making process. The use of EQ-5D-5L contributes to assessing improvement in patients' quality of life and optimizing resources in the healthcare system. (Janssen et al., 2013).

The domains of EQ-5D-5L are: mobility: the ability to move around; self-care: the ability to perform personal care activities; usual activities: the ability to carry out usual activities; pain/discomfort: the presence of pain or discomfort; anxiety/depression: the presence of anxiety or depressive symptoms.

Patients are asked to assess their current status in each domain using a five-level severity scale: "No problems," "Slight problems," "Moderate problems," "Severe problems," and "Extreme problems." These responses are then transformed into an overall health score, which can be used to compare health status between different populations or to monitor changes in health status over time.

The evaluation of inflammatory markers included the determination of IL-6 (interleukin-6) and fibrinogen, two important markers. In addition to these, it is crucial to consider the results of the complete blood count, prothrombin time (Quick time), and activated partial thromboplastin time (APTT) to obtain a comprehensive picture of the patient's health status.

These analyses provide valuable information about the presence of chronic inflammation, blood coagulation, and platelet function.

Based on these preliminary evaluations, we developed a rehabilitation program based on physical exercises, with the following therapeutic objectives: to reduce fatigue, improve global and segmental postural control, enhance fitness, develop muscle strength and range of motion, improve quality of life.

The purpose of this kinetic program is to prevent physical inactivity, improve muscle function, and increase tolerance to effort. Structured over days, the program pursues the same objectives, offering a holistic and personalized approach for each patient.

The rehabilitation program has been structured into three main components: aerobic training, muscle strength development, and improvement of range of motion. This program, tailored to the needs of each patient, was conducted for a duration of 35-50 minutes twice a week, over a period of 6 months, under the careful guidance of the physiotherapist.

The structure of a kinetic program:

Body warm-up for exercise: primarily aims to prepare the body for the kinetic program, during which a physical and psychological assessment of the patient's condition can be conducted before the training session. This will consist of movements involving the head and neck, upper limbs, trunk, and lower limbs.

Improvement of cardiovascular training - Stationary bicycle pedaling.

Development of muscle strength (physical resistance program) - The physiotherapist guides the patient throughout the exercise to understand the involvement of the respiratory factor in the exercise program. It begins from a supine position with knees bent, the patient holds a stick with both hands, lifting it above the head during inspiration, opening the chest widely, and lowers the arms during expiration.

Tonify of the upper limbs - Developing muscle strength through concentric contractions with resistance. The subject in quadruped position, with palms and knees on the mat, performs flexion and extension of the upper limbs.

Control of pelvic musculature - Improving muscle strength and range of motion in the hip joint with an emphasis on strengthening the pelvic muscles. The subject is in quadruped position with support on palms and knees, performing leg extension and abduction with the knee flexed, working alternately.

Activation of adductor muscles - Alternating concentric and eccentric contractions of the thigh muscles and hip joint. The subject in supine position performs a movement of hip joint adduction by flexing the thigh towards the abdomen, followed by abduction of the lower limb and knee extension. The exercise is performed bilaterally.

Core exercise - Activation of the abdominal muscles involving the lower limbs, trunk, and upper limbs. The subject will be in supine position and will perform thigh flexion towards the abdomen, grabbing the knee with both hands while lifting the head and performing trunk flexion, activating the abdominal muscles. The exercise is performed bilaterally.

Lower limb stretching - Static stretching involving the muscles of the lower limbs. The subject will be in supine position and will perform thigh flexion towards the abdomen, grabbing the knee with both hands and maintaining the final stretching position. The physiotherapist will guide and ensure the patient's comfort. The exercise is performed bilaterally.

Lumbar stretching - Static stretching involving the pelvic muscles and the lumbar area. The subject will be in supine position and will perform thigh flexion towards the abdomen for both lower limbs, grabbing both knees with both hands and maintaining the final stretching position. The physiotherapist will guide and ensure the patient's comfort.

Stretching for hamstrings - Static stretching involving the muscles of the lower limb, particularly the hamstring muscles. The subject will be in supine position and will maintain the lower limb in 90-degree flexion at the hip joint, supporting the dorsal aspect of the thigh in the distal third with both hands. The subject will then extend the knee with dorsiflexion at the foot and maintain the final stretching position. The physiotherapist will guide and ensure the patient's comfort.

Stretching for the lower back and oblique muscles - Static stretching involving the muscles of the pelvis, obliques, and lumbar area. The subject will be in supine position, and will maintain the lower limb in 90-degree flexion at the hip joint, 90-degree flexion at the knee joint, and dorsiflexion at the foot. The hand opposite to the already positioned leg will be placed at the knee on the lateral side. The leg will be lowered inward (adduction) with the trunk pressed to the floor, and the final stretching position will be maintained. The physiotherapist will guide and ensure the patient's comfort.

Quadriceps stretching - Static stretching involving the muscles of the lower limb, specifically the quadriceps muscles. The subject will be in a lateral decubitus position and will grab the foot of the same side of the lower limb with the hand, flexing the knee and maintaining the final stretching position. The physiotherapist will guide and ensure the patient's comfort.

All the exercises mentioned earlier were performed twice a week, structured in 3 sets of 5 repetitions each. For the stretching exercises, the position was maintained for 5-8 seconds depending on the patient's tolerance.

Results

Of the total number of patients, dysfunctional changes in the evaluation of functional capacity were noted, represented by negative changes in the measurement and assessment process of a person's ability to perform physical activities, in 8 out of 11 cases (72.72%).

The hematologic and biochemical profile of the patients who participated in our proposed rehabilitation program showed the following aspects: the complete blood count (CBC) recorded low values in 3 out of 11 patients (27.27%), activated partial thromboplastin time (APTT) also recorded slightly decreased values in 2 out of 11 patients (18.18%), fibrinogen showed an increase in 1 out of 11 patients (9.09%), and IL-6 – was elevated in 1 out of 11 patients (9.09%), indicating the presence of chronic inflammatory processes.

The results of the biochemical and hematological determinations are presented in Table 1.

Aspects of functional assessment, health status, and quality of life based on the scales used in the evaluation are presented below, highlighting the scores obtained at the initial assessment (before implementing the kinetic program) and at the second assessment. According to the SF-36 questionnaire results, 10 of the 11 patients reported an enhanced quality of life (90.91%) (Table 2). For the Karnofsky scale, an improvement in functional quality was recorded in all 11 patients (100%). (Table 3), while for the EQ-5D-5L questionnaire, an improvement in quality of life was noted in all 11 patients (100%) (Table 4).

Table 1. *Hematological and Biochemical Parameters Results*

Complete Blood Count												
Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Reference range
Red blood cells	3,900,000	4,120,000	5,100,000	4,570,000	4,470,000	4,910,000	4,540,000	4,360,000	4,950,000	4,940,000	5,760,00	3,900,000-5,200,000
Hemoglobin	12,4	12,6	15,0	15,0	13,3	14,7	13,2	13,7	13,8	15,3	11,2	12,0-15,6
Hematocrit	37,5	37,1	43,7	43,0	39,8	45,9	39,4	40,2	41,8	45,6	39,1	35,5-45,5
MCV	96,0	90,1	85,6	94,2	89,2	93,5	86,8	92,3	84,5	92,3	68,0	80,0-99,0
MCH	31,9	30,4	29,4	33,0	29,7	30,0	29,0	31,3	27,9	30,9	21,2	27,0-33,5
MCHC	33,2	33,8	34,3	35,0	33,3	32,1	33,4	34,0	33,1	33,5	31,1	31,5-36,0
RDW	11,9	13,1	13,3	13,0	13,2	13,4	14,0	13,8	14,1	13,7	19,0	11,5-14,5
Platelets	262,000	262,000	197,000	291,000	290,000	241,000	287,000	156,000	291,000	228,000	244,000	150,000-370,000
Leukocytes	9,890	4,820	9,010	8,860	8,680	8,540	6,940	5,290	10,230	7,470	6,580	4,050-11,840
Neutrophils	42,80	47,51	55,16	59,70	54,95	59,25	62,90	66,54	50,15	53,95	61,20	42,00-77,00%
Lymphocytes	50,70	44,19	34,18	33,70	36,53	32,79	29,40	27,41	43,2	39,22	30,00	20,00-44,00%
Monocytes	4,30	5,19	5,44	4,40	5,18	5,15	4,60	4,35	4,79	5,22	5,40	2,00-9,50%
Eosinophils	1,50	2,7	4,22	1,20	2,3	1,99	2,70	1,51	1,37	0,94	2,80	0,50-5,50%
Basophils	0,80	0,41	1,0	0,90	1,04	0,82	0,40	0,19	0,49	0,67	0,60	0,00-1,75%
Timp Quick – Sample												
TQ	13,3	13,2	12,0	13,4	11,6	11,8	13,1	12,0	11,9	12,0	12,4	
IQ	71	77	109	76	119	100	78	96	122	119	89	
INR	1,19	1,15	0,96	1,16	0,92	1,0	1,13	1,03	0,93	0,94	1,06	
Quick Time – Control												
TQ	11,4	11,7	12,5	11,7	12,5	11,8	11,8	11,7	12,6	12,6	11,7	
IQ	100	100	100	100	100	100	100	100	100	100	100	
INR	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	
APTT												
APTT	21	28,0	20,8	24,0	23,8	25,1	20,8	27,0	25,9	22,0	22,2	21,6-28,7
Fibrinogen												
Fibrinogen	3,57	2,99	3,81	3,43	3,26	3,72	4,12	2,47	3,48	3,30	4,88	1,70-4,20
Interleukin 6												
Interleukin 6	<4,62	<1,50	<1,50	<1,50	<1,89	<3,46	7,51	<1,50	<1,50	<2,69	<4,42	< 7,00

Table 2. *SF-36 Questionnaire Results*

Short Form 36																								
Domain	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9		Patient 10		Patient 11		Maximum score	
Physical Functioning	70	90	95	100	70	90	100	100	90	100	100	100	100	100	90	100	80	90	90	100	95	100	100	
Role Physical	90	100	100	100	80	90	100	100	90	95	100	100	100	100	100	100	90	100	90	100	80	100	100	
Bodily Pain	60	80	90	100	60	80	90	100	85	90	90	95	90	90	95	100	70	80	80	90	90	100	100	
General Health	80	100	100	100	90	100	100	100	90	95	100	100	90	100	80	90	80	90	90	100	90	100	100	
Vitality	90	100	90	100	80	90	100	100	90	100	95	100	90	100	90	100	70	90	90	100	90	100	100	

Social Functioning	90	100	100	100	90	100	100	100	90	100	90	90	100	100	80	100	70	70	90	100	90	100	100	
Emotional Role	90	100	90	100	90	100	100	100	90	100	100	100	100	100	90	100	70	70	90	100	90	100	100	
Mental Health	70	60	90	100	90	100	100	100	100	100	100	100	100	100	90	100	70	80	90	100	90	100	100	

Table 3. *Karnofsky Scale Results*

Karnofsky Scale Patient	Karnofski Score		Description	
Patient 1	90%	100%	Able to perform normal activities, minor signs and symptoms	Normal, without issues
Patient 2	100%	100%	Normal, without issues	Normal, without issues
Patient 3	80%	100%	Normal activity with some signs and symptoms of the disease	Normal, without issues
Patient 4	100%	100%	Normal, without issues	Normal, without issues
Patient 5	80%	90%	Normal activity with some signs and symptoms of the disease	Able to perform normal activities, minor signs and symptoms
Patient 6	100%	100%	Normal, without issues	Normal, without issues
Patient 7	100%	100%	Normal, without issues	Normal, without issues
Patient 8	90%	100%	Able to perform normal activities, minor signs and symptoms	Normal, without issues
Patient 9	80%	90%	Normal activity with some signs and symptoms of the disease	Able to perform normal activities, minor signs and symptoms
Patient 10	90%	100%	Able to perform normal activities, minor signs and symptoms	Normal, without issues
Patient 11	90%	100%	Able to perform normal activities, minor signs and symptoms	Normal, without issues

Table 4. *EQ-5D-5L Questionnaire Results*

EQ-5D-5L questionnaire Domain	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9		Patient 10		Patient 11		Maximum score
Mobility	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	5
Personal Care	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5
Daily Activities	2	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1	5
Pain/ Discomfort	3	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1	1	5
Anxiety/ Depression	2	1	1	1	2	1	1	1	3	1	1	1	1	1	2	1	3	2	1	1	2	1	5
VAS Score (0-100)	85	95	95	100	90	100	95	100	90	100	85	100	90	95	90	90	80	85	90	100	80	90	100

Discussions

The results obtained in this preliminary research indicate a favorable evolution in terms of functionality, health status, and quality of life for these patients who were involved in the rehabilitation program. The positive association between physical activity and quality of life for colorectal cancer survivors has been previously confirmed for various types of cancer survivors in other studies. (Jung et al., 2021)

According to the scales that we used for assessing the evolution of the patient, our novel element of our research is that in literature we didn't find research that used the scales. Developing the algorithm of assessment the evolution during physical therapy treatment in cancer could be useful for increasing the quality of life. In this term we can report the study of (Ferioli et al., 2018). Physical activity is a sustainable therapeutic alternative for chronic (Ambrose & Golightly, 2015) and acute pain (Koltyn et al., 2014), in fact physical exercise can provoke an elevation of pain threshold. Different mechanisms have been described for the modulation of cancer pain by physical activity: it is able to reduce chronic muscle pain by lowering the phosphorylation, increased in chronic muscular pain, of a subunit (in particular NR1) of the N-methyl-D-aspartate receptor (NMDA, a receptor of glutamate) in the central nervous system.

At the same time, the fatigue analysis incorporated through the assessment scales in our study indicates that physical activity may alleviate chronic fatigue by enhancing functional capacity, supporting daily routines, and improving the ability to perceive reduced physical weakness and exhaustion.

Although substantial evidence highlights the positive impact of physical activity on the quality of life in colorectal cancer survivors, the underlying mechanisms through which these benefits occur remain only partially understood.. Therefore, the existence of in-depth studies is necessary to justify through the analysis of the evolution of biochemical parameters and pro-inflammatory markers following the involvement of patients in an exercise program. In the current research, we only conducted a hematological and biochemical profile of this group of patients, a profile that is intended to be monitored over a 12-month interval. The evolution of patients, in terms of functional assessment and quality of life, is explained in the context of the relationship between physical activity and quality of life, with studies highlighting the aspect that during the intervention of a physical exercise program, which also involves additional forms of social interaction (such as face-to-face or remote training), there is an increase in the quality of life of colorectal cancer survivors, especially in terms of social and emotional aspects. Future research is needed to clarify the etiological nature of the relationship between physical activity and quality of life among colorectal cancer survivors. (Higgins et al., 2024) Currently, there are challenges in implementing a physical exercise program for such patients, in terms of the frequency and intensity of the activity, which would allow for a protective effect. Many studies in the literature suggest that more intense activity is necessary to reduce the risk of colon cancer and that somewhere between 3.5 and 4 hours of intense physical activity per week could optimize protection. These aspects are supported by studies referring to multiple biological mechanisms to explain the association between physical activity and colon cancer; many of these mechanisms also support the observation that intense activities are the most protective. Biological mechanisms include: increasing intestinal motility through physical activity; improving the immune system; lowering insulin levels and insulin-like growth factors; reducing obesity; improving free radical elimination systems; and influencing prostaglandin levels. (Slattery, 2004)

A dose-response relationship between exposure and disease is a criterion used to determine a causal association. The assessment of the dose-response relationship has been examined in various ways. In studies on physical activity and colorectal cancer, increased benefits at higher levels of directed physical activity have been obtained through increases in the frequency,

duration, or intensity of the activity performed. Although the associations are quite consistent, evaluating these key elements of activity, namely frequency, duration, and intensity, is difficult to determine given the different methods used to assess and report physical activity associations. Considering the associations between physical activity and colon cancer and possibly rectal cancer, it is possible that multiple biological mechanisms are involved. (Tollosa et al., 2019).

Another important mechanism that may explain the favorable outcome under kinetic therapy is the fact that physical activity influences the immune response. Natural killer cells and macrophages are vital components of the immune system, acting as a frontline defense against the development and spread of malignancies. Physical exercises are known to consistently affect the activity of these cells, with their circulation doubling immediately after intense activity. Regular physical training has been shown to enhance the resting level of natural killer cell activity. Additionally, physical exercises have been demonstrated to influence cytokine levels, soluble mediators of the immune system produced by various immune cells. Interleukin-1, tumor necrosis factor, and interleukin-6 are the main cytokines secreted by macrophages, which have direct effects on natural resistance against tumors and have been shown to vary depending on the amount and intensity of physical activity performed by healthy individuals. (Lee et al., 2018).

When physical exercises are repeated several times per week over an extended period, cancer-fighting substances such as IL-6, released into the bloodstream, have the opportunity to interact with abnormal cells, repairing their DNA and reducing their growth into cancer. On the other hand, the response to the physical exercise program in colorectal cancer is influenced by the genetic component because there are inherited genetic variants or mutations in tumors that are acquired. In inherited genetics, mutations in genes with high penetrance, such as adenomatous polyposis coli (APC) or mismatch repair genes associated with hereditary non-polyposis colorectal cancer, are rare. More common are genetic variants or polymorphisms that can interact with physical activity or other dietary and lifestyle factors to modify risk. The interaction between physical activity and polymorphisms related to various biological mechanisms is important, although the existing literature in this research field is scarce. Although data are limited, assessing the effects of physical activity correlated with various types of genetic mutations in colon tumors may provide clues about the specific pathways of the disease and how lifestyle factors such as physical activity relate to these factors. For colon cancer, mutations in the adenomatous polyposis coli gene, p53, Ki-ras, and microsatellite instability have been examined in relation to physical activity. These genes are believed to regulate cell growth and apoptosis, and mutations in these genes lead to tumor growth. (Sun et al., 2015).

Currently, there are few studies reporting associations between tumor mutations and lifestyle factors such as physical activity.

On the other hand, the inflammatory marker IL-6, which as we've seen is mentioned by many authors in relation to the neoplastic process, represents an indicator of response to the exercise program. Many authors emphasize that elevated levels of IL-6 are produced in response to exercise more than any other cytokine. IL-6 is locally produced in skeletal muscle in response to physical exercise, and it is known that IL-6 induces hepatic glucose production and lipolysis. These facts indicate that IL-6 may represent an important link between

contracting skeletal muscles and metabolic changes related to physical exercise. (Pedersen & Febbraio, 2006)

Another marker, considered by us to be important in monitoring the evolution of the inflammatory response to physical exercise, is fibrinogen. According to other authors, levels of fibrinogen ≥400 mg/dL have been independently and positively associated with colorectal cancer, suggesting that this glycoprotein could be a potential biomarker for this type of cancer. (Parisi et al., 2022).

In their study, Gomez-Marcos et al., (2014) demonstrated that sustained physical activity is linked to reduced levels of inflammatory markers over a decade-long monitoring period. The findings suggested that physical activity could influence plasma fibrinogen concentrations. Accordingly, the correlation between objectively measured physical activity via accelerometers and subjectively reported activity through a 7-day log revealed consistent anti-inflammatory effects of exercise, including decreased fibrinogen levels. This supports the importance of tracking this parameter during exercise interventions. Moreover, research by Perk et al., (2012) suggests that lowering inflammatory markers through physical activity may be as effective as pharmacological treatments, indicating a broad anti-inflammatory potential of exercise.

Conclusions

The results obtained highlight a significant improvement in quality of life, reduction in anxiety and depressive symptoms, decrease in pain symptoms and syndrome, as well as an increase in self-confidence regarding participation in daily activities and reduction in fatigue. It is important to individualize the program, as it is currently difficult to determine the type of effort, intensity, and duration required to achieve a beneficial effect. Monitoring biomarkers is necessary to monitor and objectify the effects of exercise programs in patients with colorectal cancer.

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