Long-Term Nutritional and Digestive Consequences of Pelvic Radiation

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Objective: To study long-term changes in nutritional status and gastrointestinal (GI) functions of 15 women previously treated with radiotherapy for gynecological cancer. Two years prior to this research, these patients had been assessed twice: before external radiotherapy and 5 weeks later, at the completion of the external dose (45–50 Gy).

Methods: Each patient was given complete clinical evaluation, consisting of dietary, physical activity and digestive symptoms questionnaires. Blood was drawn for routine clinical laboratory tests (hemoglobin, white blood cell count, creatinine, lipoproteins, glucose, total proteins, albumin, and C reactive protein). Body composition was assessed by classical anthropometric indicators and double beam X-ray absorptiometry (DEXA), while muscle strength was measured through a hand dynamometer. Resting energy expenditure (REE), obtained by indirect calorimetry, was subtracted from energy ingestion, derived from dietary records, to calculate energy balance.

Results: This third evaluation included fifteen patients. A significant increase in body mass index (BMI), % body fat and waist circumference were observed in comparison to earlier evaluations. The lean compartment decreased significantly, and REE descended in parallel. Meanwhile, total energy, fat and protein intake increased, compared to previous measurements. The changes in bowel habits observed during radiotherapy persisted at this third evaluation, with the exception of diarrhea, which was less reported. Abdominal bloating and rectal symptoms were the most prevalent complaints.

Conclusions: After radiation treatment for gynecological cancer, patients gained more body fat than expected in Chilean women around menopause. In spite of high protein ingestion, the loss of fat-free mass observed during radiation treatment was not recovered along with weight increase. This is probably associated with infrequent physical activity, both during and after treatment, and hyperphagia.

INTRODUCTION

Gynecological cancer is one of the main causes of death in Chile [1]. Radiation therapy is crucial for adequate treatment; however, the dose is limited by adverse effects of ionizating radiation on the bowel involved in the radiation field [2,3]. Complications can be acute or chronic [3,4]. Radiation enteritis (RE) is a long-term complication, typically manifesting two years after radiotherapy, and gradually advancing over the years, with significant morbidity and mortality [5,6]. Its reported incidence varies from 0.5 to 11% [7–11], and often requires surgery [2]. This complication occurs whenever the overall radiating dose exceeds 45 to 50 Gray; however, some patients develop RE with lower doses. Several predisposing factors have been postulated, such as low weight, simultaneous chemotherapy, previous abdominal surgery, inflammatory pelvic conditions, arterial hypertension and diabetes mellitus [2,3,7,12]. The nutritional status of patients suffering from RE can be severely deteriorated due to alterations of nutrient absorption secondary to mucosal damage, or digestive symptoms that lead to reduced food ingestion [13–15].

In a group of patients with gynecological neoplasm, studied before and immediately after completing pelvic radiotherapy, we reported that the treatment induced acute morpho-functional changes of the small bowel, together with a deterioration of nutritional status, especially in the lean compartment [16].

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Abbreviations: DEXA = double beam X-ray absortiometry, REE = resting energy expenditure, TEE = total energy expenditure, BMI = body mass index, RE = radiation enteritis, ICRT = intracavitary radiotherapy, FFM = fat free mass, GI = gastrointestinal, RDA = recommended dietary allowances.

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Since long-term digestive and nutritional evolution after this localized radiation has seldom been reported [17], we sought to reevaluate patients two years after completion of their treatment. Moreover, follow-up of nutritional status in patients treated for several types of cancer reported that an initial weight loss was followed by a disproportionate gain of fat mass occurs [18,19] with unclear cause.

The aim of the present research was to study long-term nutritional and digestive changes in these patients.

METHODS AND PATIENTS

We planned to include nineteen patients that were treated with pelvic external radiotherapy, plus intracavitary radiotherapy (ICRT) or surgery two years prior, for gynecological cancer at a national cancer institution (Fundación Arturo López Pérez in Santiago, Chile). These same patients had participated in a study about the acute effects of pelvic radiation on digestive and nutritional parameters [16]. Each one agreed to participate in this follow up, only provided small bowel biopsies were not repeated again, by signing a written informed consent. The study was approved by ethics committees of both institutions involved.

In each case a complete clinical evaluation was obtained, including validated dietary records [20] and daily physical activity records [21] . Energy cost of total activities was calculated according to FAO/WHO/UNU 1985 [22]. A fasting blood sample was drawn to perform routine clinical laboratory tests (hemoglobin, white blood cell count, creatinine, lipoproteins, glucose, total proteins, albumin, and C reactive protein), using automated methods with kits from Abbott. Body composition was assessed by classical anthropometric measures [23] and double beam X ray absorbtiometry (DEXA) in a Lunar DPX-L densitometer. As an additional nutritional indicator we measured grip muscle strength (hand dynamometer model 0032, by Therapeutic Instruments) according to Klidjian [24]. For estimation of energy balance, we measured resting energy expenditure (REE) by indirect calorimetry, according to standard techniques [21] (Sensor Medics model 2900 calorimeter). Total energy expenditure (TEE) was calculated as REE $\times$ energy cost of various activities, obtained from the daily physical activity recalls [22].

As indicators of intestinal function, we performed a semiquantitative recollection of gastrointestinal symptoms (including vomiting, diarrhea, abdominal distension, pain, bloody diarrhea, and rectal complaints, such as urgency, tenesmus, and rectal bleeding), measured intestinal transit velocity by the lactulose breath test [25] and gastrointestinal permeability by the urinary excretion of ingested lactulose, manitol and sucrose [26,27].

The present study therefore represents a third follow-up (Time 3). These patients had been studied before initiation of treatment (Time 1) and at the 5th week of radiotherapy, corresponding to completion of the external radiation dose (Time 2) [16]. Results are expressed as mean $\pm$ standard deviation. Normally distributed variables obtained on the three occasions were analyzed by ANOVA for repeated measures, and nonparametric variables through Wilcoxon paired test or Friedman's X_{r^2} for repeated series. A logistic regression model was employed to explain occurrence of GI symptoms during the three periods analyzed.

RESULTS

Three women from the initial group of nineteen had died due to recurrence of the primary illness, and one declined to participate for personal reasons. Thus, the final sample was constituted by 15 patients, aged 48.9 $\pm$ 9.8 years. The average external radiation dose was 45–50 Gy, delivered by a Cobalt-60 unit (Phoenix 80, SSD 80 cm) using the 4-field box technique. The total dose was fractioned in 180–200 cGy per day, during five weeks. Seven patients had been operated on prior to radiotherapy (hysterectomy plus oophorectomy), and 14 received ICRT (10–15 Gy) after completing external radiation.

Among the fifteen patients, seven were menopausal before cancer treatment, and 8 became menopausic thereafter. At Time 3, only five patients were on irregular hormonal replacement therapy. Physical examination was normal in all cases, without tumor recurrence.

Most laboratory parameters were within normal ranges during the three periods, with the exception of serum lipid levels. At Time 2 and 3, hemoglobin and total proteins increased compared to basal values, however a radiation-induced fall in white blood cell count persisted at Time 3, with definite leukopenia in three patients (Table 1).

A significant increase in body mass index (BMI) and waist circumference was observed after two years. In contrast, handgrip strength tended to decrease in parallel, although not significantly (Table 2).

Changes in body composition were confirmed by DEXA, which showed a significant increase in body fat and a contraction of the fat-free compartment in Time 3, compared to the previous examinations (Table 3).

Energy expenditure (REE and REE/FFM) decreased significantly in this third evaluation compared with the previous measurements. Physical activity was classified as sedentary throughout the study, and the calculated TEE declined progressively (Table 4).

In contrast, ingestion of energy, protein, fat and vitamin B12 increased significantly two years after completion of cancer treatment compared with the other periods (Table 5). However, the ingestion of several micronutrients (thiamin, tocopherol, pyridoxin, folic acid) and fiber remained below the RDAs.

As regards digestive symptoms, patients mainly complained of diarrhea immediately after radiation therapy. Abdominal

Table 1. Laboratory Parameters during Follow-Ups

	TIME 1	TIME 2	TIME 3	*p*
Hematocrit	0.37 ± 0.48	0.37 ± 0.42$^{\alpha}$	0.39 ± 0.27$^{\beta}$	0.01
Hemoglobin (g/L)	124 ± 19	122 ± 15$^{\alpha}$	134 ± 09$^{\beta}$	0.01
Erythrocyte Sedimentation Rate (mm/h)	25.0 ± 18.5	30.6 ± 19.6	20.2 ± 12.9	0.22
White Blood Cell Count (10^9/L)	9.4 ± 7.6$^{\beta}$	3.9 ± 1.1$^{\alpha}$	4.6 ± 1.2	<0.01
Glucose (mmol/L)	5.1 ± 0.34	5.3 ± 0.48	4.94 ± 0.82	0.26
Creatinine (umol/L)	61.9 ± 26.5	61.9 ± 8.84	70.7 ± 8.84	0.72
Total Proteins (g/L)	75 ± 7$^{\alpha}$	76 ± 8	81 ± 5$^{\beta}$	0.01
Albumin (g/L)	42 ± 4	44 ± 3	43 ± 2	0.08
Total Cholesterol (mmol/L)	5.3 ± 1	4.9 ± 0.9$^{\alpha}$	5.6 ± 0.6$^{\beta}$	0.04
Triglycerides (mmol/L)	1.4 ± 0.5$^{\alpha}$	1.9 ± 0.9	1.8 ± 0.7$^{\beta}$	0.01

α and β = significantly different by Sheffeé *post-hoc* analysis.

Table 2. Nutritional Status Assessed by Anthropometry

	TIME 1	TIME 2	TIME 3	*p*
Weight (Kg)	64.9 ± 13.4$^{\alpha}$	64.4 ± 13.1	69.1 ± 15.2$^{\beta}$	<0.01
BMI (Kg/m^2)	27.3 ± 4.8$^{\alpha}$	27.0 ± 4.8	28.5 ± 5.8$^{\beta}$	<0.01
Waist (cm)	84.9 ± 10.6$^{\alpha}$	85.2 ± 10.9	88.5 ± 10.8$^{\beta}$	<0.01
Hip (cm)	99.5 ± 9.5	98.9 ± 8.9$^{\alpha}$	101.4 ± 7.0$^{\beta}$	0.03
Handgrip Strength (Kg)	27.4 ± 4.99	26.6 ± 4.3	25.1 ± 3.7	0.09

α and β = significantly different by Sheffeé *post-hoc* analysis.

Table 3. Nutritional Status Assessed by Double Beam X-Ray Absorptiometry

	TIME 1	TIME 2	TIME 3	*p*
Total Mass (Kg)	64.2 ± 13.3	63.5 ± 13.2$^{\alpha}$	68.5 ± 15.7$^{\beta}$	<0.01
Fat Free Mass (Kg)	38.7 ± 5.7	37.7 ± 5.9	38.6 ± 6.2	0.05
Fat Free Mass (%)	64.7 ± 6.6$^{\beta}$	63.7 ± 6.5	60.2 ± 4.3$^{\alpha}$	<0.01
Fat Mass (Kg)	23.3 ± 8.8$^{\alpha}$	23.6 ± 8.5	27.7 ± 10.4$^{\beta}$	<0.01
Fat Mass (%)	35.3 ± 6.6$^{\alpha}$	36.3 ± 6.5	40.0 ± 5.2$^{\beta}$	<0.01
Bone Mineral Content (g)	2216 ± 372	2210 ± 380	2166 ± 308	0.82

α and β = significantly different by Sheffeé *post-hoc* analysis.

Table 4. Energy Expenditure During Follow-Up

	TIME 1	TIME 2	TIME 3	*p*
REE (KJ/day)	7069 ± 966$^{\alpha}$	6879 ± 1222$^{\alpha}$	5384 ± 731$^{\beta}$	<0.01
REE/FFM (KJ/day)	183.5 ± 14.7$^{\alpha}$	183.1 ± 17.2$^{\alpha}$	139.4 ± 11.8$^{\beta}$	<0.01
TEE (KJ/day)	9437 ± 1445$^{\alpha}$	8929 ± 1478$^{\alpha}$	7056 ± 1403$^{\beta}$	<0.01

REE = Resting Energy Expenditure; TEE = Total Energy Expenditure; FFM = Fat Free Mass.
α and β = significantly different by Sheffeé *post-hoc* analysis.

bloating (twelve patients) and rectal symptoms such a rectal bleeding and tenesmus (eight patients), prevailed two years later. Bowel habits remained unchanged in six cases, while nine women experienced definite changes. In five cases a "correction" of previous constipation occurred, two developed mild intermittent chronic diarrhea, and two other presented moderate diarrhea (frequent and painful episodes of liquid stools, which interfered with daily life). Surgery prior to radiation did not affect the occurrence of these symptoms.

At Time 3, intestinal permeability and transit time were lower than values at Time 1, but still within normal ranges. According to the logistic regression model, neither intestinal transit time nor intestinal permeability explained gastrointestinal symptoms (diarrhea and abdominal distention), and these were not associated with nutritional parameters.

DISCUSSION

The main finding of the present study, was the significant gain of body fat, observed after radiotherapy for gynecological cancer, together with a lack of recovery of the lean tissue lost during the treatment period, two years before, despite the high

Table 5. Dietary Ingestion Throughout the Study

	TIME 1	TIME 2	TIME 3	*p*
Energy (KJ)	8597 ± 3146	6611 ± 2806$^{\alpha}$	9778 ± 3956$^{\beta}$	0.01
Protein (g)	66.9 ± 29.4	51.2 ± 21.4$^{\alpha}$	87.8 ± 41.4$^{\beta}$	<0.01
Fat (g)	55.1 ± 28.9	34.2 ± 16.4$^{\alpha}$	81.4 ± 43.1$^{\beta}$	<0.01
Carbohydrate (g)	323.5 ± 114.8	264.9 ± 131.6	316 ± 154	0.35
Fiber (g)	5.6 ± 3.0	4.2 ± 3.2	5.7 ± 2.9	0.38
Thiamin (mg)	1.5 ± 1.1	1.1 ± 0.7	1.4 ± 0.8	0.27
Riboflavin (mg)	1.2 ± 1.0	1.0 ± 0.9	1.7 ± 1.2	0.01
Niacin (mg)	12.1 ± 7.6	9.0 ± 4.5	13.6 ± 7.1	0.10
Pyridoxine (mg)	1.1 ± 1.0	0.8 ± 0.6	1.3 ± 0.5	0.17
Vitamin E (mg)	1.4 ± 0.6	0.8 ± 0.5	1.1 ± 0.9	0.01
Vitamin C (mg)	123 ± 161	102 ± 153	58 ± 39	0.34
Vitamin A (UI)	1241 ± 358	856 ± 1104	886 ± 1203	0.49
Vitamin B12	3.0 ± 3.1	2.0 ± 1.8$^{\alpha}$	4.7 ± 3.3$^{\beta}$	0.01
Folate (mcg)	168 ± 92	142 ± 92	150 ± 104	0.69
Calcium (mg)	559 ± 307	426 ± 242	741 ± 865	0.27

α and β = significantly different by Sheffeé *post-hoc* analysis.

protein ingestion. We expected to find the undernutrition, especially in those patients with more radiation-induced GI symptoms, suggesting the existence of RE, as reported. The discrepancy with previous studies on radiation complications is probably due to case selection; malnutrition is often detected in patients requesting medical assistance due to severe actinic complications, such as ulcerations and fistulae.

In our patients, muscle strength tended to decrease, instead of increasing in paralell with body mass growth. Energy expenditure, both unadjusted and when corrected for FFM, declined. This change can be attributed to the correction of a moderately hypermetabolic state prior to cancer treatment. Measured REE was 1.24 ± 0.2 times higher than calculations by Harris-Benedict before treatment, and decreased by 1.21 ± 0.16 and 0.92 ± 0.06 times, in later measurements. Hypermetabolism has been described in several neoplasms, both metastatic and nonmetastatic [28–31]. TEE, however, can be lower, due to a decrease in physical activity energy expenditure [32]. While normometabolic during the recovery period, our patients significantly increased food ingestion, especially protein and fat. Combined with less physical activity, increased food ingestion promoted a positive energy balance, leading to weight gain.

The 5 kg increase over a two year period cannot be attributed to menopause, as it occurred both in previously menopausic women as well as in those who became menopausic due to radiation or surgical castration. The observed weight gain is higher than expected around menopause, according to Chilean data, which report an average weight increase of 4 kg in five years, irrespective of hormonal status and replacement therapy [33]. It is also higher than weight increase detected in climateric North-American women (from 200 up to 350 g/year) [34,35], Swedish (420 g/year) [36] and Spanish women (270 g/year) [37].

Nevertheless, the observed alterations in body composition are similar to those described in patients treated with chemotherapy for breast cancer [38] and other neoplasms [18,28,39]. They are also comparable to recovery from semistarvation or nutrient deprivation [40,41]. For example, the WHEL study reported that 60% of breast cancer patients gained weight after treatment, with an average increase of 2.7 kg [42]. Factors related to weight augmentation were dietary and physical activity habits, chemotherapy, African-American ethnicity and menopause. In a recent study, serial changes in body composition and energy expenditure in patients treated with chemotherapy resembled those of our patients, which are characteristic of sarcopenic obesity [19]. In the cited study, patients lost around 400 g during the treatment period, mainly at the expense of FFM, and a year later they had gained 2.2 kg of fat mass, without recovery of the lean compartment. These changes were more connected with a fall in energy expenditure by physical activity than with a significant increase in energy ingestion [19]. The decline in physical activity began during chemotherapy, but persisted a year later, explaining the long-term positive energy balance. A similar pattern was observed in the eight subjects that participated in the Biosphere 2 experiment. Six months after return to civilization, their weight had returned to previous levels, and was almost entirely accounted for by fat mass. However, adjusted 24 hour EE and spontaneous physical activity remained lower than controls [41], suggesting that an adaptive mechanism operates even in normal people subjected to long-term moderate energy restriction.

A compensatory hyperphagia has also been observed in semistarved individuals, which tend to recover weight with a disproportionate increase in fat mass. It has been shown that hyperphagia is associated with an incomplete restoration of lean tissues [40,43]. This point is controversial. Some studies report an adequate recovery of LBM [44–46], and others suggest that weight increase occurs at the expense of fat mass and body water, with an incomplete recovery of lean tissues or muscle strength [28,47–49]. Such discrepancies probably depend upon differences in age, pathological condition, nutrient supply and physical activity patterns in subjects [50]. In either case, it has been proposed that certain signals from adipose, and also from fat free tissues, somehow promote an increase in energy intake, leading to a "poststarvation obesity." As demonstrated in Biosphere 2, and also in Asian refugees [51], energy restricted subjects also tend to decrease spontaneous physical activity, even after weight recovery. Physical activity and exercise are important for adequate recovery of muscle mass, as demonstrated in HIV patients. In the latter, paradigm of muscle wasting, progressive resistance training is the most effective intervention to increase muscle mass and strength, and it is not enhanced by combined protein supplementation [52].

Apart from this physiological energy overcompensation, we observed a psychological component: our patients indicated that the amount of food ingested represented some sort of gratification because of their disease, and also a compensation for brief losses due to GI symptoms, which limited their intake during short periods. Also, some patients believed that their actual needs were higher, due to cancer.

In addition to the above, over 80% of patients experienced significant GI complaints, a prevalence clearly higher than is to be expected of a healthy Chilean population ($<$ 5% according to unpublished data). The main symptom after five weeks of radiotherapy was diarrhea. Abdominal distention, urgency, tenesmus and rectal bleeding prevailed two years later. Noteworthy, at Time 3, 60% of patients observed a change in their intestinal habits (increase in number of daily bowel movements, generally of normal consistency). This can be attributed to changes in transit time, which remained below basal levels with wide variability. These symptoms are important, because they affect patient quality of life.

The present study demonstrates that radiation therapy is associated with significant late sequelae both at nutritional and digestive levels, which contribute to deterioration of quality of life. Moreover, the changes in body composition described could be later associated with higher morbidity and mortality due to chronic cardiovascular diseases and cancers associated with obesity, stressing the importance of fat gain prevention and preservation of lean body mass in oncologic patients.

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