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Epidemiología Clínica

Efecto de una dieta anti-inflamatoria, en comparación con una dieta baja en residuo, sobre el estado de nutrición y la expresión de citocinas en pacientes con cáncer cervicouterino localmente avanzado: ensayo clínico aleatorizado.

Tesis

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ABREVIATURAS

AST: aspartato aminotransferasa.

ALT: alanina aminotransferasa.

BIA: Análisis de Bioimpedancia (de las siglas en inglés bioimpedance analysis).

CaCu: Cáncer Cervicouterino.

Cm: centímetros.

CTCAE: Criterios de terminología común para eventos adversos (de las siglas en inglés, Common Terminology Criteria for Adverse Events).

DEXA: absorciometría dual de rayos X (de las siglas en inglés Dual-Energy x-ray Absorptiometry).

DHA: ácido docosahexaenoico.

DII: índice inflamatorio de la dieta.

EC: ensayo clínico.

ECE: etapa clínica de la enfermedad.

ECOG: grupo oncológico cooperativo oriental (de las siglas en inglés Eastern Cooperative Oncology Group).

VGS-GP: Evaluación global subjetiva generada por el paciente.

ESPEN: Sociedad Europea de nutrición clínica y metabolismo (de las siglas en inglés, The European Society for Clinical Nutrition and Metabolism).

g: gramos.

IBD: enfermedad inflamatoria intestinal.

IL: interleucina.

IC: Intervalo de confianza.

IL: interleucina.

IMC: índice de masa corporal.

INCan: Instituto Nacional de Cancerología.

INEGI: Instituto Nacional de Estadística y Geografía.

IFN: interferón.

Kcal: kilocalorías.

Kg: kilogramos.

MMPs: metaloproteinasas de matriz extracelular.

NK: asesinas naturales (de las siglas en inglés natural killer).

PET-CT: tomografía por emisión de positrones.

PP: pérdida de peso.

PVH: papilomavirus humano.

OMS: Organización Mundial de la Salud.

QT: quimioterapia.

QT-RT: Quimio-Radioterapia.

RIQ: Rango intercuartilar.

Rpm: revoluciones por minuto.

RT: radioterapia.

SC: superficie corporal.

TAC: Tomografía Axial Computarizada.

TAM: macrófagos asociados a tumores.

TNF: factor de necrosis tumoral.

CONTENIDO

RESUMEN

Antecedentes: El cáncer cervicouterino (CaCu) es la segunda causa de muerte por cáncer en las mujeres mexicanas. El tratamiento estándar para el CaCu es la combinación de quimio-radioterapia concomitante seguida de braquiterapia (QT-RT). Debido a que la RT se dirige a la pelvis, ésta causa daño al epitelio del intestino y produce inflamación. Se calcula que entre el 60-80% de las pacientes puede presentar síntomas derivados del tratamiento. Con el objetivo de aminorar los síntomas por la RT, se han llevado a cabo intervenciones nutricionales entre las que se encuentra la dieta baja en residuo (DBR). Se ha observado que DBR aminora la diarrea por el tratamiento con RT pélvica, pero la pérdida de peso tiende a ser la misma que sin intervención y no se ha medido su efecto sobre el estado nutricional ni parámetros inflamatorios. En el presente estudio buscamos producir un patrón dietario que ayude a prevenir la desnutrición y la inflamación por el tratamiento con QT-RT. Algunos de los componentes dietéticos que han demostrado tener efectos antiinflamatorios son: aceites omega-3, EGCG, curcumina, vitaminas, antioxidantes, fibra soluble y probióticos. Este patrón dietario lleva por nombre dieta antiinflamatoria (DAI).

Objetivo general: Evaluar el efecto de una dieta anti-inflamatoria, en comparación con una dieta baja en residuo, sobre el estado de nutrición, la expresión de citocinas y marcadores de inflamación en las pacientes con CaCu localmente avanzado (IB2-IVA).

Metodología: Se llevó a cabo un ensayo clínico aleatorizado, controlado, estratificado y abierto, en el que se invitaron a participar a pacientes con CaCu del INCan, que fueran candidatas a recibir QT-RT seguida de BT, que cumplieran con los criterios de inclusión y que aceptaran participar en el estudio. Cada una de las pacientes firmó un consentimiento informado y fue aleatorizada al brazo DAI o al brazo DBR.

El seguimiento de las pacientes se llevó a cabo en 5 tiempo: 2 semanas previas a la QT-RT (T1), el día de inicio de la RT (T2), al tercer ciclo de la QT-RT (T3), al finalizar la braquiterapia (T4) y tres meses luego de haber concluido el tratamiento oncológico (T5). La participación de las pacientes fué de aproximadamente 6 meses. Se recolectó información sobre: Antecedentes personales, dietéticos, antropométricos y síntomas gastrointestinales; adicionalmente, se recolectó una muestra de sangre (para medir los marcadores de inflamación a nivel sistémico). En la primera visita las pacientes del brazo DAI recibieron té verde, cúrcuma, chía y jengibre, con el propósito de que conocieran los alimentos y promover su consumo inmediato.

Resultados: Un total de 56 pacientes fueron analizadas, 29 en el brazo DAI y 27 en el brazo DBR. No se observaron diferencias en la edad, presencia de comorbilidades, etapa de la enfermedad, histología, estado funcional o en las características del tratamiento oncológico. En el análisis por protocolo, el grupo DAI presentó un mayor consumo de fibra total, fibra soluble, lactosa, probióticos, polifenoles y agua natural que el grupo DBR. En el T2 se observaron mayores niveles de PCR en el grupo DAI (p=0.047) que en DBR; sin embargo, para el T5 se perdieron dichas diferencias. En el T3 el grupo DAI tendió a desarrollar más desnutrición (33.3% vs 0%, p=0.27). En el T5 ya no se observaron diferencias en la desnutrición; sin embargo, el grupo DBR presentó un mayor número de pacientes con xerostomía (43% vs 0%, p=0.036).

No se observaron diferencias significativas en los niveles de citocinas ni en el resto de las toxicidades gastrointestinales.

Conclusiones: No existe suficiente evidencia científica que sustente la recomendación de DBR durante el tratamiento de las pacientes con CaCu que reciben QT/RT. La intervención con DAI podría ayudar a modular parámetros inflamatorios como la PCR y a aminorar la xerostomía. El consumo de DAI no produce mayor toxicidad gastrointestinal que DBR por lo que se podría considerar como segura para su uso antes, durante y después del tratamiento oncológico.

1 MARCO TEÓRICO

1.1 EPIDEMIOLOGÍA DEL CÁNCER

De acuerdo con la Organización Mundial de la Salud (OMS) el cáncer "es la multiplicación rápida de células anormales que se extienden más allá de sus límites habituales y pueden invadir partes adyacentes del cuerpo o propagarse a otros órganos, un proceso que se denomina «metástasis" [1].

En las últimas décadas, el cáncer se ha encontrado entre las principales causas de muerte a nivel mundial. Se estima que, tan solo en el 2020, hubo aproximadamente 10 millones de muertes atribuídas a este padecimiento [1].

De acuerdo con estadísticas del Instituto Nacional de Estadística y Geografía (INEGI) en México, en el 2019 el cáncer fue la tercera causa de muerte. Cabe resaltar que la principal causa de muerte en las mujeres de entre 25 y 54 años son los tumores malignos [2].

En el año 2020 los cánceres con mayor incidencia fueron: mama, próstata, colorrectal, tiroides y cervicouterino (CaCu), en ese órden de importancia [3].

1.1.1 CÁNCER CERVICOUTERINO

A nivel mundial el CaCu es la cuarta neoplasia más común. Se estima que en 2020 hubo 640,127 nuevos casos, de los cuales el 83% fueron en las regiones menos desarrolladas. Además, este neoplasia es la cuarta causa de muerte por tumores malignos en las mujeres con aproximadamente el 7.7% de las defunciones reportadas. Se calcula que en el año 2020, al menos 340,841 mujeres murieron a causa del CaCu [3].

En México en el año 2020 aproximadamente 9,439 mujeres fueron diagnosticadas con CaCu (aproximadamente el 8.9% de todos los casos de cáncer) y fueron reportados un total de 4,335 muertes por la misma causa; lo que convierte al CaCu en el segundo tumor más común y en la segunda causa de muerte por cáncer en las mujeres mexicanas [3].

Se estima que el 99% de los casos del CaCu se originan de una infección de transmisión sexual por determinados tipos de papilomavirus humanos (PVH). En la actualidad hay más de 100 tipos de PVH de los cuales al menos 15 son causantes de CaCu y otros tipos de cánceres. La mayoría de las personas se infectan por algún tipo de PVH poco después de iniciar su vida sexual; sin embargo, en el 90% de los casos la infección se elimina al cabo de 2 años. En los casos en los que la infección no remite, pueden pasar entre 15-20 años para desarrollar la enfermedad y entre 5-10 años en aquellas mujeres con un sistema inmunológico debilitado [4].

Una vez que el PVH se encuentra en la cavidad cervical éste atraviesa las capas de la mucosa a través de una microabrasión hasta alcanzar las células madre de la membrana basal del epitelio y empezará a replicar su genoma viral. Por una parte, la oncoproteína E1 ayuda a la replicación episomal del ADN

helicasa, y por otro lado la oncoproteína E2 actúa como factor de transcripción; adicionalmente, la oncoproteína E5, también temprana, previene la diferenciación celular [5].

Aunque los PVH 16 y 18 son los más comunes, se ha considerado la siguiente clasificación de acuerdo con el grado de riesgo para el desarrollo de CaCu [6].

- Alto riesgo: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 y 82.
- Probable alto riesgo: 26, 53 y 66.
- Bajo riesgo: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 y CP6108.

En los países desarrollados se han puesto en práctica programas dirigidos a la población femenina a través de los cuales son detectadas lesiones precancerosas, éstas son tratadas fácilmente y no evolucionan, previniendo hasta un 80% los casos de CaCu. Por otra parte, en los países en desarrollo el panorama es distinto debido a que son escasos los programas de detección temprana de la enfermedad, por lo que los casos son detectados en etapas avanzadas. Debido a que la infección no genera síntomas en etapas tempranas, aquellas mujeres afectadas serán atendidas hasta que los manifiesten; es decir, en etapas avanzadas, donde los tratamientos son limitados y las expectativas de vida son menores. Ésta es la causa de que ocurra un mayor número de muertes en los países en desarrollo. El elevado número de muertes por CaCu podría reducirse hasta en un 52% con programas de detección y tratamientos eficaces [4].

Actualmente existen 2 vacunas que protegen tanto a hombres como a mujeres contra los PVH, la primera se conoce como bivalente (incluye los PVH 16 y 18) y la segunda como tetravalente (incluye a la PVH 6, 11, 16 Y 18). En algunos países se han empezado a implementar dichas vacunas como método de prevención primaria; incluso la OMS recomienda vacunar a las niñas de entre 9 y 14 años de edad, además de proporcionar educación sexual y proporcionar información sobre el riesgo por consumo de tabaco y desarrollo de cáncer [4]. México es uno de los países que ha tenido la iniciativa de vacunar a las niñas de estas edades y se prospecta comenzar a ver resultados para el año 2026. Adicionalmente, esta vacuna ya se encuentra incluida en el cuadro básico de vacunación en México [7].

1.1.1.1 ETAPIFICACIÓN

La etapificación del CaCu debe ser llevada a cabo por un médico experimentado y debe basarse en los criterios propuestos por la Federación Internacional de Ginecología y Obstetricia (FIGO). De manera general, el CaCu puede ser clasificado de la etapa I a la IV [8]:

I. Etapa I: Carcinoma cervical confinado al cuello uterino (ignorar la extensión al corpus).
    i. Etapa IA: Carcinoma invasivo diagnosticado por microscopía. Invasión estromal con profundidad máxima de invasión <5 mm.
        a. Etapa IA1: Invasión estromal medida <3 mm de profundidad.
        b. Etapa IA2: Invasión estromal medida ≥3 mm y <5 mm.
    ii. Etapa IB: Carcinoma invasivo con una profunda máxima ≥5 mm, lesión limitada al cérvix útero
        a. Etapa IB1: Carcinoma invasivo ≥5 cm de profundidad de la invasión estromal, y <2 cm en su dimensión más grande.

b. Etapa IB2: Carcinoma invasivo ≥2 cm y <4 cm en su dimensión más grande.
c. Etapa IB3: Carcinoma invasivo ≥4 cm en su dimensión más grande.

II. Etapa II: El carcinoma cervical invade más allá del útero, pero no a la pared pélvica o al tercio inferior de la vagina o la pared pélvica.
   i. Etapa IIA: Invasión que involucra los 2/3 superiores de la vagina sin invasión parametrial.
      a. Etapa IIA1: Carcinoma invasivo <4 cm en su dimensión más grande.
      b. Etapa IIA2: Lesión clínicamente visible ≥4 cm en su dimensión más grande.
   ii. Etapa IIB: Tumor con invasión parametrial, pero que no toca la pared pélvica.

III. Etapa III: El tumor se extiende a la pared pélvica y/o involucra el tercio inferior de la vagina y/o causa hidronefrosis o riñón no funcional y/o presencia de nódulos linfáticos paraórticos.
   i. Etapa IIIA: El tumor involucra el tercio inferior de la vagina, sin extensión a la pared pélvica.
   ii. Etapa IIIB: El tumor se extiende a la pared pélvica y / o causa hidronefrosis o riñón no funcional.
   iii. Etapa IIIC: El tumor involucra la pelvis y/o nódulos linfáticos paraórticos, independientemente de la extensión de la enfermedad y del tamaño.
      a. Etapa IIIC1: Únicamente nódulos pélvicos metastásicos.
      b. Etapa IIIC2: Únicamente nódulos paraórticos metastásicos.

IV. Etapa IV: El carcinoma se ha extendido más allá de la pelvis verdadera o ha involucrado la mucosa de la vejiga o el recto.
   i. Etapa IVA: El tumor invade órganos vecinos.
   ii. Etapa IVB: El tumor se extiende más allá de la pelvis verdadera, invade órganos a distancia.

Además del sistema de clasificación FIGO, se recomienda el uso de algún estudio de imagen con el objetivo de obtener algunos factores pronósticos como el tamaño del tumor, implicación parametrial o afectación de la pared pélvica, invasión de órganos adyacentes o metástasis ganglionar linfática, así como para medir la repuesta al tratamiento oncológico [8, 9]. Entre los estudios de imagen se encuentran la Tomografía axial computarizada (TAC), la resonancia magnética y la tomografía por emisión de positrones (PET-CT); éste último también se emplea cuando se requiere confirmar lesiones con actividad metabólica, así como establecer su morfología y localización [8, 10].

1.1.1.2 HISTOLOGÍA

La histología hace referencia al tipo de tejido del cual se originó la enfermedad [11]. Así pues, los tipos de histologías del CaCu son [8]:

- Carcinoma epidermoide: es el tipo histológico más frecuente con alrededor del 36% de todos los casos. Éste se clasifica de manera genérica en tres grandes grupos (1) queratinizante de célula grande, (2) no queratinizante de célula grande y (3) no queratinizante de célula pequeña. Dentro de esta categoría de tumores se reconocen otras variedades menos frecuentes (basaloide, verrucoso, condilomatoso, papilar, tipo linfoepitelioma y escamoso-transicional).
- Adenocarcinoma: este tipo histológico es el segundo más frecuente con más o menos 12% del total. Cabe mencionar que en los últimos años ha ido incrementando su incidencia. El tipo más frecuente de adenocarcinoma de endocérvix es el endocervical, aunque existen otras variedades (enteroide, de células en anillo de sello, de desviación mínima, villoglandular, endometrioide, de células claras, seroso y mesonéfrico).
- Otros: existen otras categorías de carcinomas menos frecuentes como el carcinoma adenoescamoso, carcinoma adenoide quístico, carcinoma adenoide basal y carcinoma neuroendocrino, que tienen diferentes connotaciones pronósticas e incluso varían en el tratamiento.

1.1.1.3 TRATAMIENTO DEL CÁNCER CERVICOUTERINO

La progresión del CaCu aparentemente sigue un patrón ordenado, primero se disemina de manera loco-regional, luego a los órganos pélvicos y ganglios linfáticos aledaños, y finalmente a los órganos a distancia; sin embargo, la elección del tratamiento también dependerá de diversos factores como lo son la etapa clínica de la enfermedad (ECE), las dimensiones del tumor, la presencia de ganglios pélvicos, infiltrados por tumor, la histología y las comorbilidades [12].

De manera general y de acuerdo con la ECE, el CaCu puede ser tratado de la siguiente manera:

ECE IA1: la histerectomía total simple es el tratamiento de elección; si hay 2 o más factores de riesgo patológicos, se debe realizar linfadenectomía sistemática pélvica o biopsia de ganglio centinela. Los tumores en ECE tempranas (IA2-IB1) se tratan habitualmente mediante histerectomía radical y linfadenectomía pélvica, logrando tasas de curación por arriba del 90% [13, 14].

El tratamiento estándar para la enfermedad localmente avanzada (IB2-IVA) emplea la combinación de quimio-radioterapia concomitante seguida de braquiterapia (QT-RT + BT), que puede ser a base de cisplatino o gemcitabina [15, 16]. La quimioterapia (QT) considerada como estándar de oro es el Cisplatino, la dosis administrada es de 40 mg/m^2 de superficie corporal (SC) de manera semanal y se aplican desde 4 hasta 6 ciclos. [17]. La combinación de QT-RT + BT ofrece una sobrevida hasta del 72% a 5 años, pero también se ha observado que la toxicidad grave (grado 3 y 4) puede presentarse hasta en el 58% de las pacientes [14, 16]. Las diferencias en la sobrevida de las pacientes con CaCu dependen de la etapa en la que es diagnosticada la enfermedad. Narayan et al. [18], reportaron que la tasa de supervivencia a 3 años fue del 63% en etapa IB, 72% en etapa II, 50% en la etapa III, y 27% para la etapa IVA. En el estudio de Tae-Eung et al. [19], Se observó que la tasa de supervivencia a 5 años fue de 91.7% para las etapas IB1–IIA, 71.5% para la etapa IIB, 44.9% en la etapa III, y 20.9% para la etapa IVA. Cabe mencionar que el 86.8% de las pacientes terminaron el plan de tratamiento. Por otra parte, debido a la toxicidad renal del Cisplatino,

para aquellas pacientes con lesión renal aguda, enfermedad renal crónica o fragilidad, se considera a la Gemcitabina como terapia de elección, la dosis recomendada es de 300 mg/m^2 de SC [20].

Para ambas combinaciones la radiación se aplica a dosis total de 50.4 Gy en 28 fracciones, 5 días a la semana.[17, 20]. Posterior al tratamiento con QT-RT se aplica la braquiterapia, este término hace referencia a la radioterapia intersticial, intracavitaria y superficial. Utiliza pequeñas fuentes selladas o parcialmente selladas que pueden colocarse sobre o cerca de la superficie del cuerpo o dentro de una cavidad corporal natural o implantarse directamente en los tejidos [21]. La braquiterapia se aplica después de 1-2 semanas de terminar la QT-RT concomitante. La braquiterapia intracavitaria puede ser de baja tasa de dosis con Cesio 137, o de alta tasa de dosis con Iridio, el uso de braquiterapia de alta o baja tasa queda a criterio del radio-oncólogo.

En el Instituto Nacional de Cancerología (INCan) 8 de cada 10 casos son diagnosticados con enfermedad localmente avanzada (IB2 – IVA), por lo que requerirán de tratamiento con QT-RT + braquiterapia.

El tratamiento con radioterapia en sí mismo es un tratamiento agresivo que inevitablemente puede afectar tejido no tumoral, por lo que puede inducir daño en el intestino delgado, colon y recto. Estos efectos adversos son los principales factores limitantes de dosis [22].

1.1.1.3.1 TOXICIDAD POR EL TRATAMIENTO

Todos los trastornos que resultan del uso de fármacos son considerados como toxicidad. En este rubro se incluyen una amplia variedad de condiciones inducidas químicamente, como las interacciones medicamentosas y los efectos metabólicos de los productos farmacéuticos [23].

En el caso de los tratamientos antineoplásicos, las toxicidades por el tratamiento van a depender del mecanismo de acción de la droga y de las condiciones del individuo. En las pacientes con CaCu depende del tipo de quimioterapia utilizado como radiosensibilizador (Cisplatino o Gemcitabina).

- El mecanismo de acción del cisplatino está mediado principalmente por la unión del Cisplatino al ADN mitocondrial, esto lo logra mediante la generación de aductos de ADN nucleares. Los aductos se forman gracias a que las concentraciones citoplasmáticas de cloruro son muy bajas, entonces uno o ambos cloruros unidos al platino se desplazan por agua, lo que genera un electrófilo cargado positivamente que es altamente reactivo con sitios nucleofílicos. Entonces a medida que el platino libera agua, se une covalentemente al ADN, lo cual activa varios mecanismos de señalización, incluyendo la reparación del ADN, detención del ciclo celular y apoptosis. Debido a que este mecanismo de acción no es selectivo, va a llevarse a cabo no solo en las células tumorales, sino que también en aquellas de alto recambio, lo que produce toxicidades como la caída del cabello, diarrea, mucositis y disminución en la cuenta total de células hematológicas [24]. Sin embargo, a pesar de que las células del túbulo proximal del riñón y las células cocleares tienen bajas tasas de proliferación celular, estas son especialmente propensas a la citotoxicidad inducida por cisplatino. El cisplatino rompe el ADN bicatenario en células marginales estriadas y células ciliadas cocleares que son transcripcionalmente activas, alterando la fisiología celular e induciendo citotoxicidad. Adicionalmente existe otro mecanismo a través de la generación tóxica de especies reactivas de

oxígeno (ROS) y la unión a diversas moléculas citoplásmicas, incluyendo el antioxidante glutatión. La conjugación de cisplatino con glutatión también puede conducir al estrés oxidativo mitocondrial, lisis mitocondrial y disfunción a través de la peroxidación lipídica [24, 25].

- El mecanismo de acción de la Gemcitabina se lleva a cabo posterior a su afluencia a través de la membrana celular. La gemcitabina experimenta una compleja transformación intracelular a los nucleótidos gemcitabina difosfato (dFdCDP) y trifosfato (dFdCTP) responsables de sus acciones citotóxicas. La actividad citotóxica de la Gemcitabina puede ser el resultado de varias acciones sobre la síntesis de ADN. DFdCTP compite con desoxicitidina trifosfato (dCTP) como un inhibidor de ADN polimerasa. DFdCDP es un potente inhibidor de ribonucleósido reductasa, lo que resulta en el agotamiento de grupos de desoxirribonucleótidos necesarios para la síntesis de ADN y, por lo tanto, potenciar los efectos de dFdCTP. DFdCTP se incorpora en el ADN y después de la incorporación de un nucleótido más, conduce a la terminación de la cadena de ADN. Este extra nucleótido puede ser importante para ocultar el dFdCTP de las enzimas de reparación del ADN, ya que la incorporación de dFdCTP en el ADN parece ser resistente a los mecanismos normales de reparación [26]. Debido a su mecanismo de acción, la Gemcitabina causa menos efectos adversos que el Cisplatino, siendo el de mayor importancia la mielosupresión.

Como se mencionó anteriormente, las condiciones de cada individuo los pueden hacer más susceptibles al desarrollo de diversas toxicidades. Por ejemplo: presentar un pobre estado funcional al momento del diagnóstico o debutar en edades avanzadas, incrementa el riesgo para el desarrollo de neutropenia [27]. En la literatura también se ha reportado que, debido a la nefrotoxicidad de algunos antineoplásicos como el cisplatino, aquellos pacientes con comorbilidades (como diabetes mellitus o hipertensión arterial) son más susceptibles al desarrollo de lesión renal aguda [28].

ESTADO FUNCIONAL

La escala ECOG (Eastern Cooperative Oncology Group, por sus siglas en inglés) mide el estado funcional del paciente oncológico, valora la evolución de las capacidades del paciente en su vida diaria, así como el impacto que la enfermedad va teniendo en el mismo [29]. El puntaje de esta escala va del 0 al 5. Cada valor representa el grado de funcionalidad del individuo, como se expresa a continuación:

0. El paciente se encuentra totalmente asintomático y es capaz de realizar un trabajo y actividades normales de la vida diaria.
1. El paciente presenta síntomas que le impiden realizar trabajos arduos, aunque se desempeña normalmente en sus actividades cotidianas y en trabajos ligeros. El paciente sólo permanece en la cama durante las horas de sueño nocturno.
2. El paciente no es capaz de desempeñar ningún trabajo, se encuentra con síntomas que le obligan a permanecer en la cama durante varias horas al día, además de las de la noche, pero que no superan el 50% del día. El individuo satisface la mayoría de sus necesidades personales solo.
3. El paciente necesita estar encamado más de la mitad del día por la presencia de síntomas. Necesita ayuda para la mayoría de las actividades de la vida diaria, por ejemplo: vestirse.

4. El paciente permanece encamado el 100% del día y necesita ayuda para todas las actividades de la vida diaria, como por ejemplo la higiene corporal, la movilización en la cama e incluso la alimentación.
5. Muerte.

De acuerdo con la experiencia de investigadores, en los pacientes con cáncer con un estado funcional deficiente la toxicidad es particularmente un problema debido a que son más frágiles y desarrollan con más facilidad toxicidad por el tratamiento antineoplásico; es por ello que aquellos individuos con un pobre estado funcional son excluidos de los ensayos clínicos. Los resultados sugieren que estos pacientes son más propensos al desarrollo de fatiga y trombocitopenia [27].

HERRAMIENTAS PARA MEDIR LA TOXICIDAD

Debido a que cada toxicidad puede manifestarse en diferentes niveles de gravedad, es necesario utilizar alguna herramienta que ayude a asignar los grados. Los principales sistemas para detectar y clasificar las toxicidades son los de "The Radiation Therapy Oncology Group/Acute Radiation Morbidity Scoring Criteria (RTOG/ARMSC)", con la herramienta CTCAE v.5, con la cual se reportar la toxicidad aguda secundaria al tratamiento con radioterapia (RT) y el "the National Cancer Institute/Common Toxicity Criteria (NCI/CTC)", el cual fue elaborado por la OMS, detecta principalmente los efectos adversos por el tratamiento con quimioterapia [30, 31]. Para ambos casos la gravedad se clasifica del cero al cinco, siendo cero la ausencia y el cinco la muerte por toxicidad.

La toxicidad por el tratamiento con RT puede aparecer en diferentes momentos [32, 33].

- Efectos adversos tempranos: son aquellos que suceden durante o justo después del tratamiento (dentro de los primeros 3 meses a partir del inicio de la radioterapia). Normalmente desaparecen unas semanas después de finalizar todo el tratamiento.
- Efectos adversos tardíos: son aquellos que pueden tardar meses o incluso años en manifestarse, aparecen regularmente de los 6 meses hasta los 3 años posteriores al inicio del tratamiento con radioterapia, y a menudo son permanentes.

En el estudio de Dueñas-González et al. [33], con un total de 515 pacientes de diferentes instituciones (Argentina, Bosnia y Herzegovina, India, México, Pakistán, Panamá, Perú y Tailandia), se reportaron las toxicidades por el tratamiento con QT-RT seguido de BT en las pacientes con cáncer de cérvix. En la tabla 1 se observa que las principales toxicidades tempranas de tipo gastrointestinal son la náusea, la diarrea y el vómito. La toxicidad se midió semanalmente durante el estudio y de nuevo 30 días después del último tratamiento del estudio.

En la tabla 2 se muestran la toxicidad tardía, reportándose que el 50% de las pacientes las desarrolla: el 18.7% desarrolla inflamación en la membrana de la mucosa y el 21.5% manifiestan síntomas en el intestino delgado y/o grueso. La toxicidad se midió 30 días después de la última dosis del fármaco en estudio y de nuevo cada 4 meses hasta un año después de completar el tratamiento oncológico.

La herramienta CTCAE V2.0 se utilizó para evaluar el grado de las toxicidades tempranas como las tardías.

Tabla 2. Toxicidad tardía por el tratamiento con quimio- radioterapia seguido de Braquiterapia.

Toxicidad	**Grado 0 (%)**	**Grado 1-2 (%)**	**Grado 3-4 (%)**
Alguno	50	48.7	1.3
Piel	83.6	16.4	0
Tejido subcutáneo	85	15	0
Membrana mucosa	81.3	18.3	0.5
Médula espinal	94.6	5.4	0
Intestino delgado/grueso	78.5	21.1	0.5
Vejiga	93.1	6.3	0.5

Toxicidades desarrolladas por una cohorte de pacientes con CaCu en etapas avanzadas (IIB-IVA), con Karnofsky ≥70, las cuales recibieron QT-RT seguido de braquiterapia. El 50% de las pacientes presentó efectos adversos tardíos. La toxicidad se midió 30 días después de la última dosis y de nuevo cada 4 meses hasta un año después de completar el tratamiento.

Tabla 1. Toxicidad temprana por el tratamiento con quimio- radioterapia concomitante seguida de Braquiterapia.

Toxicidad	**Grado 0 (%)**	**Grado 1-2 (%)**	**Grado 3-4 (%)**
Neutropenia	69.8	24.3	5.9
Diarrea	48.6	46.7	4.7
Náuseas	39.2	58	2.7
Anemia	64.3	33.8	2
Vómito	51.8	45.5	2.8
Fatiga	75.7	22.8	1.6
Dermatitis por radiación	73.7	15.7	10.6
Trombocitopenia	88.6	10.2	1.2
Dolor abdominal/calambres	84.3	15.2	0.4
Anorexia	85.5	14.5	0
Proctitis	91.8	7.9	0.4
Aspartato aminotranferasa	99.2	0.8	0
Alanina aminotranferasa	98.4	1.6	0
Creatinina	99.2	0	0.8
Neutropenia febril	99.6	0	0.4

Toxicidades desarrolladas por una cohorte de pacientes con CaCu en etapas avanzadas (IIB-IVA), con Karnofsky ≥70, las cuales recibieron quimio- radioterapia seguido de braquiterapia. El 46.3% de las pacientes desarrollaron toxicidades 3 y 4. Las toxicidades más frecuentes por el tratamiento fueron náuseas, diarrea y neutropenia. Todas las toxicidades fueron medidas de manera semanal.

1.1 PROCESO INFLAMATORIO EN LAS PACIENTES CON CÁNCER CERVICOUTERINO

1.1.1 PROCESO INFLAMATORIO SECUNDARIO AL CÁNCER CERVICOUTERINO

La presencia de células proinflamatorias en los tumores cancerosos es considerada como una respuesta inmunológica para controlar el crecimiento del tejido; sin embargo, se ha demostrado que la afluencia crónica de células inflamatorias en un proceso infeccioso está altamente asociada con el desarrollo tumoral. Además, la abundancia de células inmunes innatas, en particular las células cebadas y macrófagos, se correlaciona con angiogénesis y mal pronóstico [34, 35].

En el caso del CaCu, al iniciarse la infección con el VPH se activa la respuesta inmune innata, la cual tiene su origen en el estroma pero que se produce en el epitelio. Al igual que en cualquier otra infección se va a inducir el reclutamiento de células como los neutrófilos, macrófagos, células NK y células dendríticas que a su vez van a activar el sistema inmune adaptativo. En algunos casos la infección va a poder ser eliminada por el sistema inmune y para otros se va a mantener una reacción pro-inflamatoria que puede durar años hasta desarrollar una lesión precancerosa y posteriormente el cáncer [36]. Una vez desarrollada la masa tumoral, una gran cantidad de células inmunitarias se infiltrarán en el tumor, cada célula tiene la capacidad de producir citocinas y otras moléculas que alteran el destino de las poblaciones celulares dentro de la masa tumoral. Una característica del entorno inflamatorio del tumor es el reclutamiento de leucocitos, éstos pueden encontrarse tanto en las células tumorales como en el estroma. Los neutrófilos polimorfonucleares derivados de las células progenitoras hematopoyéticas son las primeras células inmunes encontradas en el sitio de inflamación, seguidas por los monocitos. Dentro del tejido, los monocitos experimentan diferenciación hacia macrófagos o células dendríticas. Tanto los macrófagos como las células dendríticas forman la primera línea de defensa contra patógenos. Se sabe que los neutrófilos asociados a tumores tienen la capacidad de polarizar el fenotipo de otras células inmunes y alterar la composición celular del microambiente tumoral. Los neutrófilos pueden existir en un estado N1 o en un estado N2. En el estado N1, liberan compuestos citotóxicos que matan a las células tumorales, mientras que en el estado N2, promueven el desarrollo del tumor mediante la modulación del entorno de citocinas dentro del tumor. Los monocitos circulantes actúan como precursores de los macrófagos asociados a tumores (TAMs), a través de la liberación de quimiocinas. Los TAMs constituyen una proporción significativa de las células inmunitarias asociadas a tumores [37].

Todo este proceso inflamatorio hace suponer que podría haber correlación entre el infiltrado de células inflamatorias y la carcinogénesis inducida por PVH. Cabe señalar que el desarrollo de los cánceres, su crecimiento y diseminación están asociados con la inmunosupresión. El PVH produce proteínas oncogénicas que regulan la expresión de varios genes y proteínas que contribuyen a la proliferación celular, angiogénesis e impiden la muerte celular de las células infectadas mediante diferentes vías de señalización. Un sujeto inmunosuprimido (por ejemplo con desnutrición o SIDA) no será capaz de contener la infección viral, permitiendo la infección y por consiguiente que todo este mecanismo persistan de manera crónica, teniendo como desenlace el cáncer [37].

1.1.2 PROCESO INFLAMATORIO SECUNDARIO A LA RADIACIÓN

El proceso inflamatorio que ocurre en las pacientes con CaCu no sólo se debe a la enfermedad en sí misma, sino también al tratamiento oncológico. En la explicación del mecanismo de acción del cisplatino se mencionó que las células de rápido recambio son afectadas por este tipo de tratamientos; además, la radioterapia a pelvis también termina dañando estructuras que se encuentren a su paso, por lo que va a causar la muerte de células tanto tumorales como las del mismo organismo, entre ellas las del intestino. La lesión intestinal temprana se manifiesta a los pocos días e incluso horas después de haber comenzado el tratamiento con RT y es activada principalmente por la muerte celular en el epitelio de la cripta de proliferación rápida y una prolongada reacción inflamatoria aguda en la lámina propia. Se estima que entre un 60-80% de los pacientes con RT dirigida a pelvis presentan toxicidad gastrointestinal la cual se manifiesta principalmente con náusea, dolor abdominal, diarrea y fatiga [38].

Cuando la barrera mucosa se interrumpe (tal como sucede después de la exposición a la radiación), los productos bacterianos y otros agentes activadores acceden a los tejidos intestinales y estimulan una variedad de células inmunes para producir citocinas y otros mediadores proinflamatorios. Las citocinas son proteínas reguladoras de bajo peso molecular o glucoproteínas secretadas por leucocitos y otras células en el organismo en respuesta a diversos estímulos. Estas proteínas ayudan a regular el desarrollo de células inmunitarias efectoras, y algunas citocinas poseen funciones autócrinas [39]. Las citocinas regulan la intensidad y la duración de la respuesta inmunitaria al estimular o inhibir la activación, proliferación, diferenciación de diversas células, y controlar la secreción de anticuerpos y citocinas. Muchas citocinas se conocen como interleucinas debido a que los leucocitos las secretan y pueden actuar sobre otros leucocitos, otras forman parte de la familia de interferones, e importantemente, de las primeras citocinas que inician el proceso inflamatorio, el factor de necrosis tumoral [40].

En el caso del CaCu, el proceso inflamatorio causado por el tratamiento antineoplásico es muy parecido al de la enfermedad inflamatoria intestinal (IBD) pues se producen citocinas y mediadores inflamatorios que participan en la activación celular de la respuesta innata y adaptativa, hay activación de proteínas de fase aguda, se producen citocinas proinflamatorias, se induce la muerte de células epiteliales, hay reclutamiento de neutrófilos y fibroblastos, angiogénesis y secreción de metaloproteinasas de matriz extracelular (MMPs) involucradas en la ulceración y degradación de la matriz extracelular. Entre estas citocinas pro-inflamatorias se encuentran: TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-13, IL-17, IL-18, IL 21 [41-43].

Por otro lado las citocinas anti-inflamatorias que participan en la supresión de respuestas de la inmunidad innata y adquirida, inhibición de respuestas inflamatorias y activación de las células T reguladoras, células linfoides innatas (ILCs) y macrófagos M2 son: IL-37, TGF-β, IL-10 [44-46].

La disfunción endotelial inducida por radiación conduce a la pérdida de tromboresis, lo que resulta en la formación de trombina, reclutamiento y activación de neutrófilos y estimulación de células mesenquimales. Entre otros mecanismos activados se encuentran los relacionados con las células cebadas, el sistema nervioso entérico y el microbioma intestinal; éstos desempeñan un papel importante en la patogénesis de la enteropatía por radiación [38].

La patogénesis de la enteropatía tardía por radiación es compleja e implica cambios en la mayoría de los compartimentos de la pared intestinal tales como la atrofia de la mucosa, fibrosis de la pared intestinal y esclerosis microvascular, las cuales actualmente son irreversibles. Las principales características clínicas de la enteropatía retardada por radiación son el tránsito intestinal alterado, la malabsorción de nutrientes y la dismotilidad intestinal [47]. Alrededor del 12% de los pacientes fallecen a causa de la enteropatía por radiación y en otro 14% contribuye a su muerte. Por otra parte, casi el 60% de los pacientes supervivientes continúa con sintomatología, 1 de cada 3 sufren de síntomas debilitantes crónicos de enteropatía por radiación y 1 de cada 4 tienen síntomas moderados. Esto se debe a que esta condición es progresiva y carece de opciones terapéuticas disponibles [48].

Debido a que las toxicidades que presentan las pacientes que reciben QT-RT + BT pueden llegar a ser severas y de larga duración, éstas pueden causar el deterioro del estado nutricional durante y después del tratamiento como se explica a continuación.

2 ANTECEDENTES

2.1 ESTADO DE NUTRICIÓN EN LAS PACIENTES CON CÁNCER CERVICOUTERINO

En las guías de *The European Society of Clinical Nutrition and Metabolism* (ESPEN) [49], se ha hecho el esfuerzo por homogeneizar el concepto de “desnutrición” en el que se ha definido como "un estado resultante de la falta de ingesta o absorción de los nutrimentos que conduce a una alteración de la composición corporal (disminución de la masa libre de grasa) y la masa celular corporal, que conducen a la disminución de la función física y mental y deterioro del resultado clínico de la enfermedad". Para identificar a los pacientes que se encuentren "en riesgo nutricional" se debe utilizar una herramienta validada para la detección del riesgo nutricional (como la VGS-GP) y deberá ser confirmado por cualquiera de las dos siguientes condiciones [49]:

- Índice de masa corporal bajo (<18.5kg/m^2), de acuerdo con la definición de insuficiencia ponderal proporcionada por la OMS
- Pérdida de peso + IMC bajo o reducción en el índice de masa libre de grasa (dependiente del género)

De acuerdo con la ESPEN, la desnutrición en las enfermedades crónicas (como el CaCu) es aquella que está relacionada con una condición hipercatabólica en la cual la etiología es multifactorial; en el caso del cáncer, la desnutrición puede ser resultado de una respuesta inflamatoria exacerbada, por la presencia de anorexia y/o la descomposición de tejidos, además de las demandas metabólicas del tumor en sí mismo. La enfermedad es la principal causante de la inflamación, mientras que las vías inflamatorias que conducen a la anorexia, la ingesta reducida de alimentos, la pérdida de peso y el catabolismo muscular son bastante consistentes con el cáncer y otras comorbilidades que se pueden presentar de forma paralela [49].

De acuerdo con la “The Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition” (ASPEN), para considerar a un individuo como desnutrido éste deberá cumplir con al menos 2 de los siguientes 6 criterios [50]:

1. Bajo consumo de energía
2. Pérdida de peso
3. Pérdida de masa muscular
4. Pérdida de grasa subcutánea
5. Acumulación de líquido (hinchazón)
6. Pérdida de la fuerza de agarre de mano

En pacientes con cáncer se ha reportado que la incidencia de desnutrición oscila entre el 34.5% hasta el 69%, siendo los pacientes en etapas avanzadas los más afectados [51]. Aunque la desnutrición en las pacientes con CaCu localmente avanzado al momento del diagnóstico es poco frecuente, al finalizar el tratamiento se puede alcanzar una frecuencia de entre 69-81%, dependiendo de la herramienta utilizada [52]. La Valoración Global subjetiva Generada por el Paciente (VGS-GP) es una herramienta que se usa con mucha frecuencia para detectar a pacientes con desnutrición, en riesgo de desnutrición o sin desnutrición; dicha herramienta se encuentra validada para su aplicación en pacientes con cáncer,y presenta una sensibilidad del 98% y una especificidad del 82% [53]. La etiología de la desnutrición en los paciente con cáncer es multifactorial; contribuye la misma enfermedad, los efectos adversos por los tratamientos antineoplásicos, así como otras condiciones y circunstancias de los pacientes [54].

En un estudio previo realizado en el INCan se reportó que el 14.8% de las pacientes presentaban algún grado de desnutrición al momento del diagnóstico el cual se vio incrementado a lo largo del tratamiento hasta alcanzar el 81.8% (medición realizada posterior al tratamiento con QT-RT), la mediana del índice de masa corporal descendió de 27.6 kg/m^2 a 24.9 kg/m^2 y la pérdida de peso (PP) promedio fue del 7.5% (vale la pena mencionar que la media de PP en aquellos con PP grave [>5%] fue del 43%). Dentro del mismo trabajo se reportó que, de acuerdo con el Recordatorio de 24h (Rec. 24h), al momento del diagnóstico, únicamente el 9.1% de las pacientes consumía la cantidad de energía adecuada para su requerimiento; además, el consumo se vio impactado por el tratamiento, ya que la mediana inicial del consumo energético fue de 1491 kcal/día y descendió hasta 813.2 kcal/día (al término del tratamiento con QT-RT). No se mostraron cambios estadísticamente significativos en el Índice cintura cadera y hubo una mediana de reducción del porcentaje de grasa corporal del 2% medido por BIA [55].

2.1.1 ABORDAJE NUTRICIONAL EN LOS PACIENTES CON RADIOTERAPIA A PELVIS

Durante el tratamiento con RT, la pérdida de peso es un indicador temprano del declive del estado de nutrición. Ravasco Et al., reportaron que en un período de seis semanas, con una dosis de 50 Gy de RT a abdomen o pelvis, un 59% de los pacientes pueden perder un promedio del 10% de su peso inicial [56]. Sin embargo, recibir consejo nutricional individualizado, repercute positivamente en el estado de nutrición en comparación con los pacientes que sólo reciben recomendaciones generales [56, 57]. Incluso, puede llegar a disminuir hasta en un 21.7% el número de pacientes con desnutrición [58]. Por otra parte, existe evidencia en la que no se observan cambios en la calidad de vida, efectos adversos por el tratamiento antineoplásico o la aparición de deficiencias de micronutrientes [59].

DIETA BAJA EN RESIDUO

En la literatura se pueden encontrar únicamente 2 ensayos clínicos (EC) en los que se comparan diferentes intervenciones dietéticas (sin suplementos, ni medicamentos) modificadas en grasas y/o lactosa y que reporten como desenlace la toxicidad gastrointestinal en mujeres con cánceres ginecológicos bajo tratamiento con RT a pelvis. El primero en publicarse fue el de Bye A. et al., con un total de 143 mujeres bajo tratamiento con RT a pelvis, diagnosticadas con neoplasias ginecológicas. Se comparó una dieta normal contra una dieta baja en lactosa (5g por día) y grasas (40g/día), los cambios fueron medidos en la semana 6 (última semana con RT) y en la semana 12 (6 semanas posteriores al término de la RT). En los resultados se reportó que en la semana 6 el grupo experimental requirió menos medicamento para la diarrea (0.6 vs 1.1 tabletas por día, $p<0.01$) y presentó menor porcentaje de casos con diarrea comparado con el grupo con dieta normal (23% vs 48%, $p<0.01$). En la semana 12 no se mostraron diferencias en el uso de antidiarreicos ni en el porcentaje de casos con diarrea. Y, aunque no hubo diferencias estadísticamente significativas en la pérdida de peso posterior a la RT, se observó una tendencia a una mayor pérdida de peso en el grupo de intervención (2.6 kg vs 1.7 kg, $p=0.06$). En dicho estudio también se midió el estado nutricional por diferentes parámetros como pérdida de peso, circunferencia media de brazo, albúmina sérica y transferrina, sin encontrarse diferencias [60]. El segundo estudio es el de Wedlake L. et al. [61], en el que se incluyeron 117 pacientes con tumores pélvicos que recibieron RT. Se compararon 3 grupos con diferentes cantidades de grasa en la dieta: uno fue normal (40% TCL), el segundo fue modificado en grasas (20% triglicéridos de cadena larga –cubiertos con suplemento- y 20% triglicéridos de cadena media) y el tercero bajo en grasas (20% triglicéridos de cadena larga). Las mediciones de los resultados fueron realizadas a las 2 semanas, 6 semanas y al año de haber iniciado la RT. Al final del estudio no se reportaron diferencias en la toxicidad ni en la pérdida de peso entre los grupos. Los autores reportaron que una de las limitaciones fue el pobre apego, ya que la tendencia siempre fue hacia la disminución en el consumo de grasa.

La evidencia para el uso de dietas bajas en grasa y lactosa aún es escasa; sin embargo, estas recomendaciones son las que se dan como terapia nutricional durante la aplicación de la radioterapia a pelvis. Cabe agregar que en algunos estudios se ha mencionado que en sus centros oncológicos la dieta estándar para este tipo de pacientes es la dieta baja en residuo (DBR) [62, 63]. Esta dieta se caracteriza por ser baja en grasa (<25% del aporte total de energía, que va de 20 a 40 g/día), con restricción de lactosa (5 g/día) y bajo aporte de fibra (<25g) [64]. Por las características de la dieta baja en residuo (baja en fibra, disminución del consumo de leche y de productos cárnicos) ésta contribuye a reducir el volumen fecal y por ello podría ayudar con el control de la diarrea [65].

OTROS COMPONENTES DE LA DIETA

En los últimos años han surgido estudios encaminados a comprobar la funcionalidad de algunos componentes de la dieta que podría ayudar a disminuir la sintomatología de los pacientesque reciben RT a pelvis, entre los que se encuentran: probióticos, ácidos grasos poliinsaturados, antioxidantes (polifenoles) y fibra soluble.

Lácteos y probióticos

Entre los efectos colaterales de la RT se encuentra la reducción de la motilidad intestinal, ésta ocurrirá al principio del tratamiento y ocasiona el sobrecrecimiento bacteriano en el intestino, el cual es el responsable de al menos el 45% de los casos de diarrea, incremento en la permeabilidad intestinal y disminución de las defensas. Todos estos factores propician la translocación bacteriana en el intestino. Los probióticos pueden tener un papel importante en la prevención de la diarrea, ya que tienen la capacidad para modificar la flora, fortalecer la barrera intestinal, prevenir el sobrecrecimiento bacteriano, así como estimular el sistema inmune. Uno de sus mecanismos es mediante su interacción con las células epiteliales, macrófagos y células dendríticas para estimular la secreción de células anti-inflamatorias como la IL-10 o regulando la producción de citocinas como TNF-α, IFN-γ, IL-1 e IL-12 [66].

La diarrea causa pérdida de líquidos y electrolitos, que a su vez repercutirán en la hidratación y el estado de nutrición del paciente con cáncer, y consecuentemente habrá mayor número de hospitalizaciones; todo esto puede llevar a un compromiso cardiovascular y posteriormente la muerte [67].

En la literatura científica existen discrepancias entre recomendar el consumo de lácteos o su limitación debido a que se cree que el tratamiento con RT podría causar intolerancia a la lactosa y entonces incrementar el riesgo de diarrea. En respuesta a esta hipótesis, en el estudio de Stryker et al., fueron aleatorizados 64 pacientes bajo tratamiento con RT a pelvis a tres grupos diferentes: tomar dos vasos de leche entera al día, 2 vasos de leche deslactosada al día o seguir una dieta libre de lactosa durante 5 semanas. Se observó que la RT a pelvis no modificaba la habilidad del intestino para hidrolizar la lactosa ingerida, por lo que su restricción no mejoró la diarrea [68].

También hay estudios realizados con probióticos para demostrar que aun cuando el yogur tiene pequeñas cantidades de lactosa, puede ser consumido e incluso aminorar la toxicidad por el tratamiento. En un EC aleatorizado donde se comparó el consejo nutricional más el consumo de 2×10^9 Lactobacillus Acidophilus (en presentación de yogurt) contra únicamente consejo nutricional durante el tratamiento con RT. El grupo de intervención tuvo menor incidencia de diarrea comparado con el grupo control ($p<0.01$); sin embargo, con la intervención se observó un aumento en las flatulencias; no hubo diferencias estadísticamente significativas en las náuseas, vómito, dolor abdominal, pérdida de apetito o de peso [69]. En un estudio similar, se incluyeron 24 mujeres bajo tratamiento con RT a pelvis por algún tipo de cáncer ginecológico, aleatorizadas en 2 grupos: el grupo control o para recibir 150 ml de yogurt con al menos 2×10^9 Lactobacillus Acidophilus + 6.5% de lactulosa; en ambos grupos se implementó una dieta baja en residuo. La incidencia de diarrea fue más baja en el grupo de intervención ($p<0.01$), así como el número de pacientes que utilizó antidiarreicos (9% vs 60%, $p<0.05$). Se reportó que una de las pacientes del grupo

de intervención tuvo que usar laxantes. No se mostraron diferencias en la incidencia de vómito, náusea, dolor abdominal, anorexia o pérdida de peso. Nuevamente en el grupo de intervención se reportó un incremento en las flatulencias [70]. En otro EC se aleatorizaron 63 pacientes con CaCu para recibir dos veces al día 2×10^9 unidades de lactobacillus acidophilus más bifidobacterium bifidum o placebo. La intervención se inició 7 días antes de iniciar el tratamiento con RT y se continuó durante todo el tratamiento. En los resultados se observa que el 100% de las pacientes presentaron diarrea; sin embargo, aquellas con la intervención presentan con menor frecuencia diarrea grado 2 o más (9% vs 45%, p=0.002), menor frecuencia en el uso de antidiarreicos (9% vs 32%, p=0.03) y menor presencia de evacuaciones líquidas (19% vs 65%, p<0.001) comparados con el grupo placebo. No se observaron diferencias en la pérdida de peso ni en el conteo de glóbulos blancos o glóbulos rojos encontrados en las heces [71]. De acuerdo con la evidencia científica, el uso de probióticos podría disminuir la incidencia de diarrea secundaria a la RT (OR=0.44, IC95% CI=0.21-0.92), reducir el uso de loperamida (medicamento para la diarrea) (OR=0.29, IC95%=0.01-6.80) y la frecuencia de evacuaciones líquidas (OR=0.36, IC95%=0.05-2.81), así como aumentar las heces blandas (OR=2.34, IC95%=0.11-49.17); sin embargo, la evidencia no es contundente, por lo que se requieren más EC de calidad para confirmar estos hallazgos [72].

Fibra

La ingesta de fibra dietética puede ser benéfica al ayudar con el control la diarrea mediante el aumento de la masa fecal y la modulación de la motilidad. Específicamente la fibra insoluble actúa como un agente de volumen de heces debido a la incapacidad de ser digerido y la fibra soluble desempeña un papel importante en la mejora de la integridad de la microbiota intestinal; en otras palabras, la fibra contribuye con la formación fecal y el mantenimiento de la microbiota en el íleon terminal y el colon. Esto es de gran importancia debido a que la microbiota, a su vez, ejerce un papel protector y anti-inflamatorio en el intestino [73]. Otro de los beneficios de la fibra es el efecto prebiótico, es decir, los componentes no digeribles de la dieta promueven el crecimiento de la microbiota intestinal (por ejemplo bifidobacterias). Las bacterias fermentan proteínas y carbohidratos, y los productos finales son los ácidos grasos de cadena corta (AGCC) como el butirato, acetato y propionato. Estos AGCC se absorven fácimente en el intestino (~90%), cabe agregar que dicha absorción se acompaña de sodio y agua, lo que podría ayudar con el control de la diarrea asociada a mala absorción de carbohidratos [74]. Los AGCC tienen un efecto antiinflamatorio al inhibir la producción de citocina tipo Th1, Th17 y la activación de células dendríticas [75]. Al final de cuentas, la fibra dietética (en particular la fibra soluble) podría ser benéfica para los pacientes con inflamación por RT a pelvis [76].

En un EC que incluyó 130 pacientes, se comparó una dieta baja en fibra insoluble y lactosa contra una dieta normal, no se observaron diferencias en el desarrollo de toxicidad ni en la calidad de vida de los pacientes [77]. En un estudio crossover realizado en 10 pacientes con RT a pelvis, se comparó la efectividad del Fosfato de codeína contra la fibra Ispaghulahusk para el control de la diarrea, en ambos casos, la dieta baja en residuo era la manejada como estándar. Los resultados arrojaron que el Ispaghulahusk fue menos efectivo en el control de la diarrea y poco aceptado por su sabor. Además, el estudio tuvo que detenerse debido a que solo 2 de 5 pacientes presentaron beneficio con el Ispaghulahusk, mientras que con el Fosfato de codeína 4 pacientes se controlaron y 1 disminuyó el número de evacuaciones. Al hacer el cruce de tratamientos los resultados fueron muy similares, el Fosfato de Codeína

nuevamente ayudó con el control de la diarrea, mientras que con el Ispaghulahusk los pacientes tendían a descontrolarse [77].

En un ensayo clínico controlado y aleatorizado se incluyeron 51 pacientes bajo tratamiento con RT a pelvis, los cuales fueron aleatorizados para tomar o no tomar metamucil (fibra de tipo soluble), con un seguimiento que concluyó 28 días posterior al término de la aplicación de la RT, se observó que en aquellos que tomaron el metamucil hubo menor incidencia de diarrea (60 vs 83%, p=0.049), de acuerdo con la escala de diarrea de Murphy la severidad fue menor (1.8 vs 2.3 puntos, p=0.03) y se mostró una tendencia en la reducción en la frecuencia de la medicación (6.7 vs 15.1 días, p=0.062), no se observaron diferencias estadísticamente significativas en el tiempo de inicio o la duración de la diarrea [63].

Ácidos grasos omega-3

De acuerdo con las recomendaciones de la ESPEN, es necesario agregar a la dieta agentes anti-catabólicos y anti-inflamatorios, debido a que la inflamación sistémica inhibe la utilización de los nutrimentos e induce catabolismo [78]. Existe una gran variedad de alimentos con alto contenido de ácidos grasos poliinsaturados como el aceite de pescado, la chía, la liaza, entre otros (véase anexo 2), los cuales son una buena fuente de ácidos grasos de cadena larga, principalmente de omega-3. Actualmente se sugiere el consumo de este tipo de grasas para mejorar el apetito, la ingesta oral, la masa corporal magra y el peso corporal en pacientes con cáncer avanzado y en riesgo de desnutrición [79]. Los ácidos grasos omega-3 inhiben factores de transcripción como NFκ-B, lo que impide la producción de citocinas pro-infamatorias como TNF-α, IL-1 e IL-6 [75].

Los resultados de un EC aleatorizado en pacientes con cáncer colorrectal avanzado, a los que se les administraron 2 g de aceite de pescado diariamente durante las primeras 9 semanas de QT, mostraron que el tiempo hasta la progresión tumoral fue significativamente mayor para los pacientes que recibieron aceite de pescado (593 vs 330 días, p=0.04) [80]. En otro estudio, bajo exactamente las mismas condiciones, al final de la intervención se observó que la PCR se redujo en el grupo con los 2g de aceite de pescado, comparada con el incremento en el grupo control (1.46 vs 18.14mg/l, p=0.04), lo que hace suponer a los autores que esto podría impactar en el estado nutricio; sin embargo, no se observaron diferencias en los niveles de las citocinas pro/anti-inflamatorias[81]. Dos estudios con un suplemento nutricional oral completo que contiene ácidos grasos omega-3 administrado a pacientes con cáncer de pulmón mostraron una mejora en la calidad de vida y la función física [82, 83]. Aunque todavía se necesitan estudios para confirmar la mejoría en los resultados clínicos, los aceites omega-3 siguen siendo prometedores en el manejo nutricional.

En algunos tipos de patologías se han llevado a cabo intervenciones dietéticas con el objetivo de determinar si éstas logran disminuir algunos marcadores de inflamación; sin embargo, en la mayoría de los estudios se usan suplementos y no se analizan las características de la dieta de los individuos estudiados, los tiempos de seguimiento son muy variables (en algunos casos muy cortos) y, en su mayoría, los tamaños de muestran son pequeños, por lo que los estudios no son concluyentes. En la Tabla 3 se muestran algunas de las intervenciones que se han llevado a cabo.

Tabla 3: Intervenciones dietéticas y su impacto en los niveles de citocinas

AUTOR, AÑO	n	TIPO DE ESTUDIO	PATOLOGÍA	INTERVENCIÓN	Tiempo	CITOCINA BLANCO
Silva, et al., 2012. **[84]**.	18	ECA	Cáncer colorrectal (QT)	2g de aceite de pescado	9 s	TNF-α: 61.1 vs. 60.7 pg/mL (p=0.74) IL-1β: 3.6 vs. 1.2 pg/ml (p=0.19) IL-6: 81.2 vs 69.8 pg/mL (p=1.0)
Mocellin, et al. 2013 **[85]**.	11	ECA	Cáncer colorrectal (QT)	2g de aceite de pescado	9 s	TNF-α: 2.48 vs. 2.48 pg/mL (p=0.48) IL-1β: 1.57 vs. 1.57 pg/ml (p=0.93) IL-10: 2.3 vs. 2.35 pg/ml (p=0.25) IL-17A: 2.34 vs. 2.35 pg/ml (p=0.82)
Pot, et al., 2010 **[86]**	52	ECA	-Adenoma colorrectal -Colitis ulcerosa no activa -Sin macrolesiones	Salmón 300g/sem Bacalao 300g/sem Dieta normal	6 s	Calprotectina: 108 vs 92 vs 87 mg/kg (p>0.05)
Finocchiaro, et al., 2012 **[87]**.	27	ECA doble ciego	Cáncer de pulmón (QT)	4.25g de Ω-3 por día (cápsulas)	9.4 s	IL-6: 2 vs 14 pg/mL **(p<0.05)** TNF-α: 1 vs 15 pg/mL (p>0.05)
Sánchez-Lara, et al., 2014 **[88]**.	92	ECA	Cáncer de pulmón (QT)	2.2 g de EPA + 0.9g DHA (fórmula polimérica)	6 s	IL-6: 17.5 vs 14.9 pg/mL (p=0.602) TNF-α: 58.7 vs 67.2 pg/mL (p=0.541)
Faber, et al., 2013 **[89]**.	38	ECA	Varios tipos de cáncer (RT)	3.6g de Ω-3 por día (2 fórmulas poliméricas)	1 s	IL-1β: 1408 vs 1263 pg/ml (p>0.05) TNF-α: 3996 vs 3616 pg/mL (p>0.05) IFN-γ: 679 vs 696 pg/mL (p>0.05) IL-10: 638 vs 545 pg/ml (p>0.05)
Sunpaweravong, et al., 2013 **[90]**.	71	ECA	Cáncer de esófago (QT-RT)	Fórmula inmunomoduladora (Ω-3) vs fórmula estándar	4 s	TNF-α: 0.84% vs 1.21% **(p=0.01)** IL-6: 1.06% vs 1.69% (p=0.105) IL-10: 1.0% vs 1.05% (p=0.749) IFN-γ: 1.17% vs 1.24% (p=0.706)
Gómez-Candela, et al., 2011 **[91]**.	40	ECA	Varios tipos de cáncer y tratamientos	1.5g EPA (2 fórmulas poliméricas)	4 s	TNF-α: 2.88 vs 3.12 pg/mL (p>0.05) IL-1: 0.46 vs 0.59 pg/ml (p>0.05) IL-6: 19.23 vs 17.2 pg/ml (p>0.05) IFN-γ: 0.65 vs 2.2 pg/ml **(p<0.05)**

QT, quimioterapia; RT, radioterapia; ECA, ensayo clínico aleatorizado; EPA, eicosapentaenoico.

Polifenoles

Los polifenoles son un tipo de antioxidantes presentes en futas, verduras y plantas que les otorgan sus colores característicos a estos alimentos; estos antioxidantes se diferencian por presentar uno o más anillos fenólicos, de ahí que su nombre sea polifenoles [92]. Entre los beneficios que se les atribuye se encuentra su poder antioxidante, anticancerígeno y anti-inflamatorio sin mostrar eventos adversos en humanos [93]. Algunos polifenoles pueden disminuir la expresión de citocinas pro-inflamatorias y moléculas de adhesión en células endoteliales y monocitos. También previenen el crecimiento del tumor al inhibir la angiogénesis mediante la supresión de la expresión de IL-8 y la modulación de la molécula de adhesión celular cadherina [94].

Un compuesto que ha sido ampliamente estudiado, dentro del grupo de polifenoles, es el epigalocatequin-3-galato (EGCG), que es el componente principal del té verde. Se le han atribuido propiedades anti-inflamatorias y anticancerígenas, su mecanismo consiste en la inhibición de la producción de TNF-α, al bloquear la activación de NF-κβ [94]. La fisetina, la quercetina, la curcumina y el resveratrol son otros tipos de polifenoles que tienen actividad antioxidante al inhibir la producción de especies reactivas de oxígeno (ROS) e inhibir la activación de las células dendríticas para la producción de TNF-α, IL-1 e IL-6 [75].

Para el caso particular de las pacientes con cáncer cervicouterino, en estudios in vitro se ha sugerido el uso de los polifenoles como un agente terapéutico quimiopreventivo ya que además de actuar como antioxidantes, los polifenoles muestran una amplia variedad de funciones biológicas que incluyen la inducción de la apoptosis, la detención del crecimiento tumoral, la inhibición de la síntesis de ADN y la modulación de las vías de transducción de señales. Pueden interferir con cada etapa de iniciación, promoción y progresión de la carcinogénesis para prevenir el desarrollo del cáncer. También se cree que los polifenoles podrían modular las vías a través de las cuales el VPH induce la cancerogénesis. Al actuar en pasos específicos de la cascada de transformación viral, se ha demostrado que los polifenoles inhiben selectivamente el crecimiento de células tumorales y pueden ser una herramienta terapéutica prometedora para el tratamiento del cáncer de cuello uterino [95].

Propiedades antiinflamatorias de la dieta

Cada día va en aumento la evidencia sobre los alimentos y sus diferentes propiedades de manera aislada. Sin embargo, la realidad es que la dieta se compone de múltiples alimentos, algunos pueden ser benéficos y otros no tanto, así que el efecto debería ser considerado desde un punto global y no como una unidad [75]. En el año 2009 Cavichia et al. [96] crearon el índice inflamatorio de la dieta (DII, por sus siglas en inglés) con el objetivo de determinar si la dieta de un individuo es pro- o antiinflamatoria. Para la creación de este índice se llevó a cabo una búsqueda en la literatura para identificar componentes de la dieta que pudieran modificar marcadores de inflamación. A cada artículo se le dio cierto peso de acuerdo con el nivel de la evidencia tomando como mayor calidad a los EC y menor calidad a los estudios celulares. Posteriormente se obtuvo la fracción de artículos con efecto pro-inflamatorio, anti-inflamatorio o sin efecto y finalmente al efecto anti-inflamatorio se le extrajo el valor del efecto proinflamatorio. Derivado de esto se obtuvieron los índices para cada elemento de la dieta. En el año 2014 Shivappa et al. [97] llevaron a cabo una actualización del DII bajo la misma metodología que llevaron a cabo Cavicchia et al.

En esta actualización se reportaron las medias poblacionales y desviaciones estándar globales. Para obtener el DII de un individuo se debe contar con alguna herramienta para recabar información sobre la dieta, ya sea una frecuencia de consumo de alimentos, recordatorio de 24h, etc. Una vez que se cuenta con estos datos se calcula un score-z, se hace la conversión a percentiles, se hace la multiplicación por el índice reportado en las tablas y se suman todos los valores para determinar el DII del individuo [97]. En la tabla 4 se muestran los componentes de la dieta potencialmente pro- y anti-inflamatorios.

Tabla 4. Componentes incluidos en el índice inflamatorio de la dieta.

Componentes pro-inflamatorios	Componentes anti-inflamatorios	
Vitamina B12	Alcohol	Selenio
Carbohidratos	Vitamina B6	Tiamina
Colesterol	β-caroteno	Cúrcuma
Energía	Cafeína	Vitamina A
Grasa total	Eugenol	Vitamina C
Hierro	Fibra	Vitamina D
Proteínas	Ácido fólico	Vitamina E
Grasas saturadas	Ajo	Zinc
Grasas trans	Jengibre	Té verde/negro
	Magnesio	Flavon-3-ol
	Ácidos grasos monoinsaturados	Flavonas
	Niacina	Flavonoles
	Ácidos grasos omega-3	Flavononas
	Ácidos grasos omega-6	Antocianidinas
	Cebolla	Isoflavonas
	Ácidos grasos poliinsaturados	Pimienta
	Riboflavina	Orégano
	Azafrán	Romero

PRIMER CONSENSO NACIONAL DE NUTRICIÓN ONCOLÓGICA EN PACIENTES QUE RECIBEN QUIMIO-RADIOTERAPIA CONCOMITANTE EN LA REGIÓN PÉLVICA

En el INCan se llevó a cabo un consenso al que asistieron un grupo de expertos en nutrición, oncología médica y radioterapia oncológica, con la finalidad de establecer las recomendaciones para una dieta adecuada en pacientes que reciben RT a pelvis. La intervención nutricional que se sugiere en el presente trabajo está basada en las recomendaciones de dicho consenso.

De acuerdo con la evidencia científica, la recomendación de lípidos para estos pacientes es de 30-40% del valor calórico total, considerando que el mayor aporte debe provenir de ácidos grasos monoinsaturados, con un énfasis en mantener un índice omega-3/omega-6 elevado, y en menor proporción de ácidos grasos saturados. La restricción de lípidos debe considerarse sólo cuando se presenta malabsorción de lípidos [98]. Al considerar un aporte alto de grasas estamos asegurando un mayor consumo de energía en una

porción pequeña, esto se debe a que 1g de lípidos aporta 9 kcal, comparado con las 4 kcal que aporta 1 g de proteínas o 1g de hidratos de carbono.

Para la distribución de macronutrientes, Tarlovsky et al. recomiendan que **para pacientes con metabolismo normal** se calcule una ingesta de 25 a 30 kcal/kg/día y de 1 a 1.5 g/kg/día de proteínas. Cuando **el paciente presenta hipercatabolismo** se recomiendan de 30 a 35 kcal/kg/día y de 1.5 a 2.5/kg/día de proteínas [55]. Para las pacientes con sobrepeso se recomiendan de 21 a 26 kcal/kg/día [64, 99].

Si bien un cambio en la distribución de los macronutrientes impacta en el funcionamiento del organismo, este efecto se ve potenciado particularmente por un grupo de alimentos conocidos como “alimentos funcionales”[49]. En el consenso del INCan 2016 se llegó al acuerdo de que el uso de alimentos que contengan glutamina, omega-3, antioxidantes que provengan de la dieta (como los polifenoles), prebióticos y probióticos resultan benéficos para los pacientes con RT a pelvis, y reducen los síntomas asociados al tratamiento [100].

Debido a la evidencia sobre el beneficio de la intervención nutricional y su asociación con la disminución del proceso inflamatorio, planeamos tratar a las pacientes con CaCu de forma individualizada, proporcionándoles un plan de alimentación basado en las recomendaciones del Consenso ya mencionado, que cubra sus requerimientos y sea modificado para incluir alimentos con propiedades anti-inflamatorias, que se adecúe a sus preferencias y que considere que la dieta sea accesible para la paciente.

3 PLANTEAMIENTO DEL PROBLEMA

Alrededor del 14.8% de las pacientes con CaCu debutan con desnutrición al momento del diagnóstico; sin embargo, debido al tratamiento antineoplásico este porcentaje puede incrementar progresivamente hasta un 81.4% finalizado el tratamiento con RT.

Entre el 60% y el 80% de las pacientes con CaCu desarrollan enteritis por el tratamiento con radiación, dichas pacientes tendrán problemas de absorción de nutrimentos y tenderán a desnutrirse aún más. Clínicamente se sabe que estas pacientes presentan inflamación, pero ésta no se ha evaluado a nivel molecular en nuestra población de pacientes.

Actualmente no existe una intervención dietética específica para los pacientes con RT a pelvis; sin embargo, la dieta baja en residuo es la más aceptada e implementada. Aunque la dieta baja en residuo no ha demostrado disminuir la severidad de la diarrea, también limita el consumo de alimentos con propiedades anti-inflamatorias (debido a que la mayoría de los alimentos son cocidos), limita el consumo de fibra (por lo que sus consecuentes beneficios sobre la flora intestinal se ven limitados), y limita el consumo de lípidos.

En nuestro Instituto las pacientes con CaCu reciben recomendaciones dietéticas con alimentos permitidos y no permitidos, promoviendo el consumo de alimentos astringentes. En nuestra experiencia, dichas recomendaciones son restrictivas, con instrucciones confusas y limitadas en opciones de alimentos; además, se asume que todas las pacientes presentan diarrea a lo largo del tratamiento y no consideran a las que presentan estreñimiento.

Entre las intervenciones descritas en la literatura se observa que el objetivo primario siempre es la toxicidad gastrointestinal y que la pérdida de peso se usa como indicador nutricional, aunque de acuerdo con la ESPEN, el peso es uno de los indicadores del estado nutricional mas no el único para hacer un adecuado diagnóstico.

Debido a que la dieta baja en residuo al momento ha sido la más aceptada y ha demostrado disminuir la severidad de la diarrea secundaria al tratamiento con RT, y a que los estudios muestran resultados contradictorios, esta dieta es la que se usará como comparador del presente estudio.

4 JUSTIFICACIÓN

El CaCu es una de las neoplasias más frecuentes en la población femenina y, aunque en la actualidad han incrementado las investigaciones que van dirigidas al desarrollo de nuevos tratamientos antineoplásicos que están prolongando la respuesta al tratamiento y supervivencia de las pacientes, aún es alto el porcentaje de mujeres que desarrollan efectos adversos a corto y a largo plazo, lo que pone en riesgo el estado nutricional de las pacientes.

A pesar de que la dieta baja en residuo es la más aceptada a nivel mundial, se han realizado diversos estudios en pacientes con RT a pelvis en los que se observa que se ha limitado el consumo de la fibra, los lácteos y las grasas sin suficiente sustento científico. De hecho, se ha identificado que algunos de estos componentes tienen propiedades antiinflamatorias que podrían ser benéficos durante el tratamiento oncológico.

Derivado de la evidencia científica, y considerando el consenso de nutrición para pacientes con RT a pelvis, se propone el patrón dietario que lleva por nombre “dieta anti-inflamatoria”. Este patrón consiste en recomendar una mayor proporción de grasas en la dieta y el consumo de alimentos con propiedades anti-inflamatorias. Dichas recomendaciones podrían ayudar a que las pacientes presenten menor inflamación intestinal, por lo que esperaríamos que disminuyera la toxicidad gastrointestinal y, como consecuencia, prevenir la desnutrición. Además de que podría ser más fácil cubrir los requerimientos energéticos con una mayor proporción de grasas, lo cual es muy importante en estas pacientes dada la alta toxicidad gastrointestinal por el tratamiento.

Esta investigación nos ayudará a probar si una dieta con propiedades anti-inflamatorias o una DBR es la más adecuada para pacientes con CaCu que reciben QT/RT concomitante.

5 PREGUNTA DE INVESTIGACIÓN

¿Cuál es el efecto de una dieta anti-inflamatoria, en comparación con una dieta baja en residuo, sobre el estado de nutrición y la expresión de citocinas a nivel sistémico y local en el intestino en pacientes con cáncer cervicouterino localmente avanzado?

6 OBJETIVOS

6.1 OBJETIVO GENERAL

Evaluar el efecto de una dieta anti-inflamatoria, en comparación con una dieta baja en residuo, sobre el estado de nutrición y niveles de citocinas a nivel sistémico y local en el intestino, en las pacientes con CaCu localmente avanzado (IB2-IVA).

6.2 OBJETIVOS ESPECÍFICOS

— Comparar el estado de nutrición de las pacientes antes, durante y después del tratamiento antineoplásico bajo una dieta anti-inflamatoria *versus* una dieta baja en residuo.

— Determinar la expresión de citocinas pro- y anti-inflamatorias en suero de pacientes que reciban una dieta anti-inflamatoria y compararlas con las que reciban una dieta baja en residuo.

6.3 OBJETIVOS SECUNDARIOS

— Evaluar las toxicidades gastrointestinales de las pacientes que reciban una dieta anti-inflamatoria y compararlas con las que reciban una dieta baja en residuo.

7 HIPÓTESIS

- Las pacientes con CaCu que llevan una dieta anti-inflamatoria presentan 21.7% menos desnutrición, menor expresión de citocinas pro-inflamatorias y mayor expresión de citocinas anti-inflamatorias a nivel sistémico, comparadas con las pacientes que llevan una dieta baja en residuo.

8 CONCEPTUALIZACIÓN Y OPERACIONALIZACIÓN DE VARIABLES

VARIABLES DEPENDIENTES			
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**TIPO DE VARIABLE**
IL-17	Familia de citocinas producida por los linfocitos T cooperadores tipo Th17. Se han identificado 6 moléculas diferentes que se denominan IL-17A, IL-17B, IL-17C, IL-17D, IL-17E y IL-17F. La IL-17A participa en los procesos de autoinmunidad, inflamación e inmunidad [101].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-18	También conocida como factor inductor de IFN-γ. Es una citocina proinflamatoria que es producida por los macrófagos y otras células e induce la activación de células NK y linfocitos T citotóxicos, además incrementa el efecto de la IL-12 [102].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-21	Interleucina que tiene potentes efectos reguladores sobre las células del sistema inmunológico, incluyendo las células NK y las células T citotóxicas que pueden destruir a células con infección intracelular y células transformadas [103].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-37	Interleucina antiinflamatoria que participa en la supresión de respuestas innatas, inhibición de respuestas inflamatorias y activación de las células T reguladoras Treg. Incrementa a la par de la progresión del tumor [44].	Tipo de citocina medida en plasma	Cuantitativa continua
TGF-β	Esta citocina es secretada por las células Treg principalmente, macrófagos, y otros tipos de células. Entre sus funciones están inhibir la proliferación de células T y las funciones efectoras; inhibe la activación de células B; promueve el cambio de isotipo a IgA; inhibe activación de macrófagos [45].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-10	Interleucina anti-inflamatoria que participa en la supresión de respuestas innatas, inhibición de respuestas inflamatorias y activación de las células Treg, por lo que favorece el crecimiento tumoral [46].	Tipo de citocina medida en plasma	Cuantitativa continua

VARIABLES DEPENDIENTES			
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**TIPO DE VARIABLE**
TNF-α	Citocina también conocida como caquectina liberada por una gran variedad de células, principalmente por macrófagos. Su liberación produce activación local del endotelio vascular, liberación de óxido nítrico con vasodilatación y aumento de la permeabilidad vascular que conduce al reclutamiento de las células inflamatorias, liberación de inmunoglobulinas y activación del complemento, provocando la activación de los linfocitos T, B, NK y células de la inmunidad innata [104].	Tipo de citocina medida en plasma	Cuantitativa continua
IFN-γ	Es un tipo de citocina producida por los linfocitos Th1, células $CD8^+$ y asesinas naturales (NK) cuya función más importante es la activación de los macrófagos y las células dendríticas, participa en las respuestas inmunes innatas y en las respuestas celulares adaptativas, su actividad quimioatrayente interviene en el reclutamiento de monocitos de la circulación. También aumenta la capacidad fagocítica de células APC (presentadoras de antígeno), la expresión de moléculas de MHC clase I y II; e incrementa la presentación de antígeno [105].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-1β	Citocina que participa primordialmente en la activación del inflamosoma, genera respuestas sistémicas y locales a la infección, lesiones y desafíos inmunológicos y es la causa principal de la inflamación crónica y aguda. Se ha demostrado que el complejo multiproteico del inflamosoma induce la muerte celular por piroptosis [106].	Tipo de citocina medida en plasma	Cuantitativa continua
IL-12	Interleucina que es producida por células dendríticas, macrófagos, neutrófilos y células β-linfoblastoides humanas en respuesta a la estimulación antigénica. Tiene efecto sobre las células NK y modifica la inmunidad adaptativa (promueve la respuesta de tipo Th1) [107].	Citocina medida en plasma	Cuantitativa continua
IL-13	Interleucina secretada por muchos tipos de células, pero especialmente las células Th2, es un mediador de la inflamación y respuesta principalmente contra parásitos [108].	Citocina medida en plasma	Cuantitativa continua

VARIABLES DEPENDIENTES				
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**ESCALA**	**TIPO DE VARIABLE**
Estado Nutricio	Situación en la que se encuentra una persona en relación con la ingesta y adaptaciones fisiológicas que tienen lugar tras el ingreso de nutrientes. [49].	Desnutrición: presencia de 2 o más de los siguientes signos: • VGS-GP B o C • Ingesta de energía <75% del requerimiento. • Pérdida de peso severa (>5% en 1 mes). • IMC <18.5 kg/m^2. • Edema generalizado (que puede enmascarar la pérdida de peso). • Fuerza de agarre <5to Percentil para grupo de edad y sexo. Estado adecuado de nutrición cuando se cumplan los siguientes signos: • VGS-GP A. • Ingesta de energía: 95-105% del requerimiento. • %Peso ideal (PI): 95-105. • IMC: 18.5-24.9 kg/m^2. • Fuerza de agarre > valor del 5to Percentil por grupo de edad y sexo.	• Desnutrición • Estado adecuado de nutrición	Dicotómica

VARIABLES DEPENDIENTES			
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**TIPO DE VARIABLE**
Toxicidad	Todos los trastornos que resultan del uso de fármacos [23].	El CTCAE clasifica la toxicidad por grados. Grado se refiere a la gravedad del evento adverso. Los grados 1 a 5 tienen descripciones clínicas únicas de gravedad de cada efecto adverso y se dividen con base en esta norma general: • Grado 1: leve; asintomáticos o síntomas leves; sólo observaciones clínicas o de diagnóstico; intervención no indicada. • Grado 2: moderado; mínima, indicación de intervención local o no invasiva; limita el uso de instrumentos de la vida diaria adecuados a la edad *. • Grado 3: severa o médicamente significativa, pero no inmediatamente peligrosa para la vida; se indica hospitalización o prolongación de ésta; incapacitante; limita las actividades de la vida diaria para el auto cuidado**. • Grado 4: consecuencias potencialmente mortales; indicación de intervención urgente. • Grado 5: muerte relacionada con los efectos adversos. **Actividades de la Vida Diaria:** * Se refiere a la preparación de las comidas, la compra de alimentos o ropa, el uso del teléfono, la administración del dinero, etc. ** Autocuidado se refieren a bañarse, vestirse y desvestirse, alimentarse uno mismo, ir al baño solo, tomar medicamentos, y no postrado en cama.	Ordinal

VARIABLE INDEPENDIENTE			
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**TIPO DE VARIABLE**
Tipo de dieta	Alimentos y bebidas habitualmente consumidos por una persona a lo largo de un día [21].	Intervención: dieta anti-inflamatoria. Con una distribución de 20% de proteínas, 30-40% de lípidos y 40-50% de hidratos de carbono. Además de recomendaciones para promover el consumo de alimentos anti-inflamatorios. Control: dieta baja en residuo (5g lactosa, 20% grasas, 20 g fibra). Con una distribución de 20% de proteínas, 20% de lípidos y 60% de hidratos de carbono.	Cualitativa Nominal

VARIABLES ANTECEDENTES			
VARIABLE	**DEFINICIÓN CONCEPTUAL**	**DEFINICIÓN OPERACIONAL**	**TIPO DE VARIABLE**
Edad	Tiempo que una persona ha vivido [109].	Número de años reportado en el expediente clínico.	Cuantitativa Continua
Estado funcional	La escala ECOG valora la evolución de las capacidades del paciente en su vida diaria, así como el impacto que la enfermedad va teniendo en el mismo.	— 0: asintomático. — 1: presenta síntomas que le impiden realizar trabajos arduos. — 2: no es capaz de desempeñar ningún trabajo. — 3: el paciente necesita estar encamado más de la mitad del día por la presencia de síntomas. — 4: el paciente permanece encamado el 100% del día y necesita ayuda para todas las actividades de la vida diaria. — 5: muerte.	Cualitativa Ordinal
Etapa clínica de la enfermedad	Sistema empleado para definir el avance de una enfermedad. El sistema FIGO (específico para el CaCu) se basa en la localización del tumor, su extensión y dimensiones. Dicha clasificación debe ser confirmada por algún estudio de imagen [12].	Sistema FIGO I: carcinoma cervical confinado al cuello uterino. II: el carcinoma cervical invade más allá del útero, pero no a la pared pélvica o al tercio inferior de la vagina. III: e l tumor se extiende a la pared pélvica y/o involucra el tercio inferior de la vagina y/o causa hidronefrosis o riñón no funcional. IV: el tumor invade la mucosa de la vejiga o del recto y / o se extiende más allá de la pelvis verdadera (el edema ampolloso no es suficiente para clasificar un tumor como T4).	Cualitativa Ordinal
Histología	Estudio de la estructura de varios tejidos de organismos a nivel microscópico [11].	— Carcinoma de células escamosas o epidermoide — Adenocarcinoma — Carcinoma adenoescamoso — Carcinoma de células vidriosas	Cualitativa Nominal

9 MATERIALES Y MÉTODOS

9.1 DISEÑO DEL ESTUDIO

El presente estudio es un ensayo clínico aleatorizado, controlado y abierto.

- **Estado basal** de las pacientes: Mujeres con cáncer cervicouterino en etapas localmente avanzadas.
- **Maniobra:** Dieta anti-inflamatoria *versus* dieta baja en residuo.
- **Desenlace:** Estado de nutrición, niveles de citocinas y toxicidad.

9.2 LUGAR Y TIEMPO

El estudio se realizó en el INCan, en el consultorio 010 de Nutrición de CaCu (Programa MICAELA). El reclutamiento de las pacientes para este estudio se llevó a cabo entre enero 2019 y abril 2021. El reclutamiento de pacientes en el Instituto continuará hasta completar la muestra calculada.

9.3 TAMAÑO DE LA MUESTRA

Dado que se tienen 2 objetivos específicos, se realizó el cálculo del tamaño de muestra para determinar el impacto de la dieta sobre los niveles de citocinas y el estado de nutrición. A continuación, se presenta el cálculo que arrojó un mayor número de pacientes.

	TNF-α[110]	**TGF-β[110]**	**IFN-γ[91]**	**Estado nutricional[55]**
Fórmula	2 medias	2 medias	2 medias	2 proporciones
α	5%	5%	5%	5%
β	80%	80%	80%	80%
p1	-12.32 ± 3.97	-25.95 ± 8.61	0.65 ± 0.92	81.4%
p2	-1.72 ± 5	-7.28 ± 5.95	2.2 ± 3.19	59.7%
n total	8	8	67	130
+ 20%	**10**	**10**	**80**	**156**

Se utilizó un cálculo de tamaño de muestra para 2 proporciones, con un error alfa del 5% y un poder del 80%. En un estudio previo se reportó una incidencia del 81.4% de desnutrición al término del tratamiento en las pacientes con CaCu [55], por lo que se consideró una p_1=0.814 y debido a que se ha demostrado que una intervención nutricional en pacientes con RT a pelvis puede prevenir hasta en un 21.7% la desnutrición [58], se consideró una p_2=0.597.

Considerando un 20% de pérdidas, **el resultado es una n de 156 pacientes.**

9.4 CRITERIOS DE INCLUSIÓN

1. Habilidad de entender la naturaleza del estudio y de dar un informe de consentimiento por escrito.
2. Edad ≥ 18 años.
3. Estado de funcionamiento ECOG: 0-2.
4. Tener la voluntad y ser capaz de cumplir con las visitas programadas, el algoritmo nutricional propuesto, el plan de tratamiento y las pruebas de laboratorio.
5. Clasificadas con estadio clínico IB2-IVA.
6. Candidatas a recibir el tratamiento estándar de QT-RT concomitante seguida de BT.
7. Que se les indique el Cisplatino o Gemcitabina como radiosensibilizador.
8. Pacientes sin tratamiento previo a base de QT-RT.
9. Hemoglobina ≥ 10 g/dL.
10. Leucocitos ≥ 4000/mm 3.
11. Plaquetas ≥ 100 000/mm 3.
12. Función hepática adecuada: Bilirrubina total hasta 1.5 veces el valor normal, albumina igual o mayor a 2, TGP y TGO menor o igual a 1.5 veces al límite superior normal.
13. Adecuada función renal: tasa de filtrado glomerular ≥ 90 ml/min.

9.5 CRITERIOS DE EXCLUSIÓN

1. Pacientes en tratamiento nutricional o que ingieran algún suplemento alimenticio.
2. Pacientes portadoras de enfermedades intercurrentes incluyendo infecciones activas que contraindiquen la QT: insuficiencia cardíaca congestiva sintomática, angina de pecho inestable, arritmia cardíaca, diabetes, hipertensión, enfermedad renal, VIH/SIDA, etc., así como enfermedades psiquiátricas.
3. Pacientes en tratamiento concomitante con alguna droga experimental.
4. Pacientes con fístulas vesicovaginales o vesicorectal al diagnóstico
5. Pacientes con malignidad previa o concomitante excepto carcinoma de piel no melanoma.

9.6 CRITERIOS DE ELIMINACIÓN

1. Pérdida del seguimiento por más de 21 días posterior a la primera o segunda evaluación.
2. Evidencia de progresión de la enfermedad.
3. Pérdida de peso severa (≥5% en 1 mes o ≥2% en 1 semana), con baja ingesta de energía y reducción de la fuerza de mano, y que optaran por suplementarse.
4. Si el médico tratante considera que un cambio de terapia podría beneficiar a la paciente.
5. Si la paciente solicita la descontinuación.
6. Por toxicidad que a criterio del investigador se considere no manejable.
7. Por embarazo o si la paciente se reúsa continuar con la utilización de los métodos anticonceptivos indicados por el médico tratante.

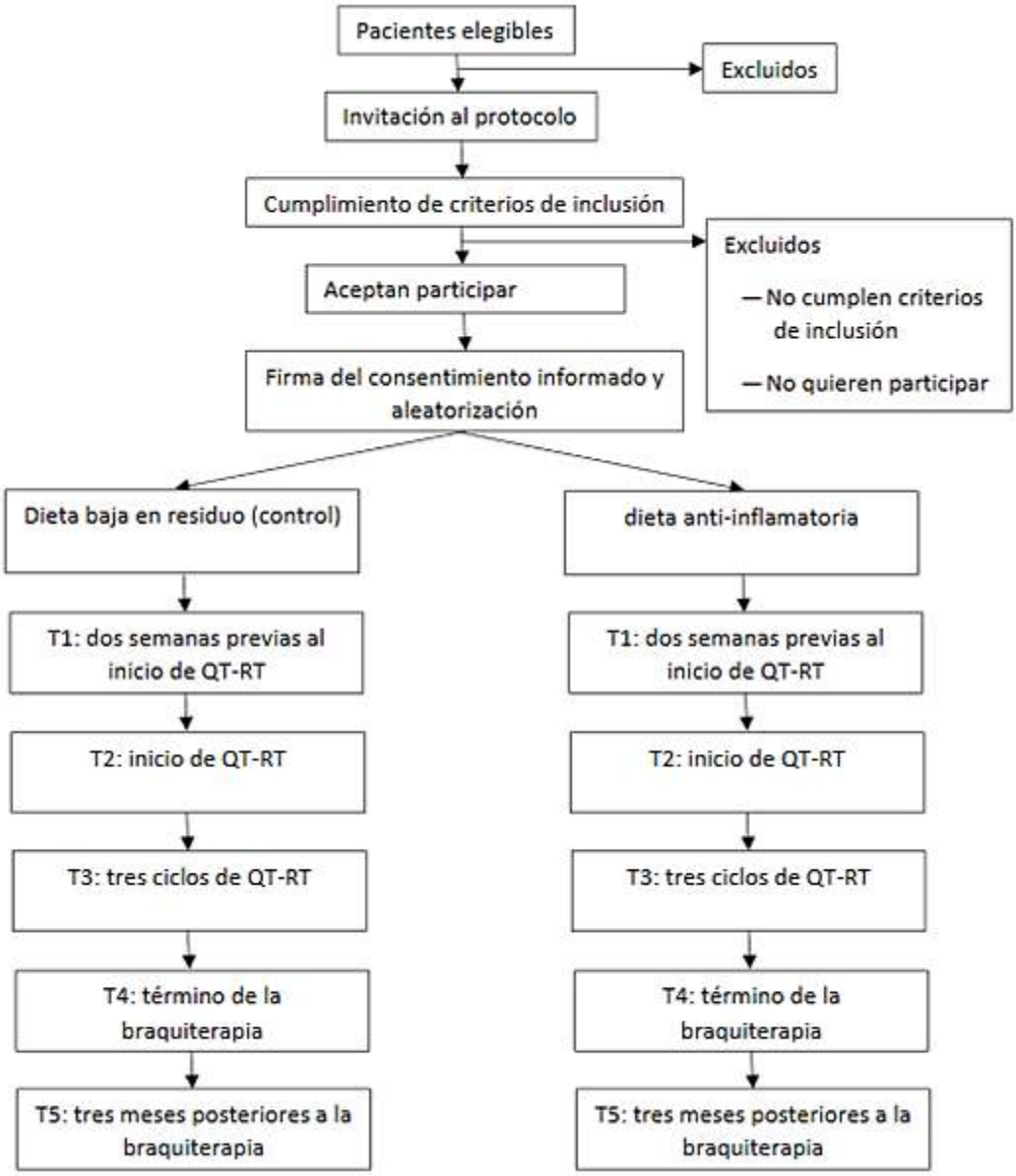
*Las pacientes que salgan del estudio fueron consideradas en el análisis estadístico a menos que no contaran con al menos las primeras 3 evaluaciones.

9.7 RECOLECCIÓN DE DATOS

Las pacientes se aleatorizaron para recibir DBR o DAI, con una distribución de 1:1. Se creó una lista con el programa random.org para la asignación del brazo según el bloque (con comorbilidades o sin comorbilidades).

9.8 INTERVENCIÓN

Una vez verificados los criterios de selección, las pacientes que aceptaron participar firmaron un formato de consentimiento informado y se aleatorizaron. El seguimiento de las pacientes se llevó a cabo de la siguiente manera:



1. **Grupo Experimental:** El grupo de intervención fué DAI. La dieta se indicó dos semanas antes del inicio de la QT-RT y seguida hasta 3 meses después de haber concluido la braquiterapia.
   1.1. A las pacientes se les calculó un consumo de energía de 28 a 31 kcal/kg/día. Distribución de macronutrientes: 20-30% proteína, 30-40% de grasas y 40-50% de hidratos de carbono.
   1.2. A todas las pacientes del grupo experimental se les instruyó para que consumieran alimentos ricos en fibra soluble, ácidos grasos monoinsaturados y omega-3, polifenoles y fuentes de probióticos (para algunos ejemplos, véanse anexos 1-3). Esta recomendación, al mismo tiempo, se basó en los equivalentes que se manejan en el Sistema Mexicano de Alimentos Equivalentes (SMAE) debido a que resultaba más sencillo de manejar por las pacientes [111]. Además, a las pacientes se les proporcionaron:

   -30 sobres con 1.5g de té verde: Tomar 1 sobre al día.

   -150g de jengibre molido: Tomar como té o en el agua natural del día.

   -150g de cúrcuma molida: Agregar a los alimentos o tomar en té.

   -340g de chía: Ingerir diariamente 5 cucharaditas en el agua natural del día.

En el anexo 4 se observa el formato utilizado para implementar la dieta de cada paciente.

2. **Grupo Control:** Recibieron DBR. La dieta se indicó dos semanas antes del primer día de la QT-RT hasta 3 meses después de haber concluido la braquiterapia.
   2.1. A las pacientes se les calculó un consumo de energía de 28 a 31 kcal/kg/día. Distribución de nutrimentos: 20% de grasas, 20% de proteínas y 60% de hidratos de carbono.

- La dieta tenía un máximo de 5g de lactosa y 20g de fibra. A todas las pacientes del grupo control se les instruyó para evitar el consumo excesivo de fibra, grasas y lactosa a través del manejo de equivalentes del SMAE.

En el anexo 5 se observa el formato utilizado para implementar la dieta de cada paciente.

EVALUACIONES

Para realizar el diagnóstico nutricional se requerirá de la evaluación antropométrica y dietética, y se tomará en cuenta la definición operacional ya mencionada para los siguientes diagnósticos:

- Desnutrición
- Adecuado estado nutrición
- Sobrepeso
- Obesidad
- Sobrepeso u obesidad sarcopénica

Aunque los criterios de inclusión sólo admiten a pacientes con adecuado estado de nutrición, sobrepeso y obesidad, éste puede verse modificado a lo largo del tratamiento.

Evaluación antropométrica

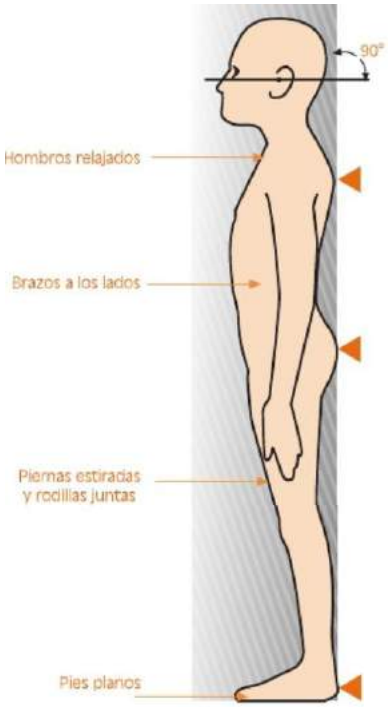
Las medidas de peso, talla y circunferencia de cintura se realizarán bajo las "Normas Internacionales para la Valoración Antropométrica" [112].

Durante las mediciones, para la comodidad del evaluador, éste debería poder moverse con facilidad alrededor del sujeto, para ello el espacio debe ser amplio. Además, debe pedírsele a la evaluada que se presente con la menor cantidad de ropa posible para que las mediciones sean más precisas.

- Peso: la medición se realizará en una báscula digital.
    1. El sujeto se para en el centro del platillo sin sostenerse, con el peso distribuido por igual sobre ambos apoyos, de frente al medidor y mirando hacia un punto fijo frente a él como se muestra en la Imagen 1.
    2. Se debe anotar el peso del sujeto en Kg, con al menos, una décima de kilogramo.

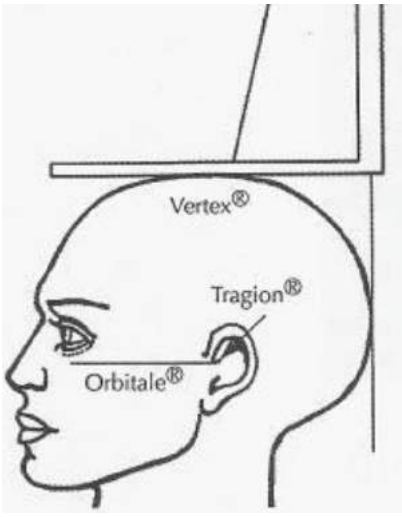
- Talla: la medición se realizará a través de la técnica de la estatura estirada con estadiómetro.
    1. El sujeto debe estar parado con los pies juntos y los talones, nalgas, y parte superior de la espalda apoyados sobre el estadiómetro.
    2. La cabeza debe colocarse en el plano de Frankfort, como se muestra en la Imagen 2.

Imagen 1. Posición del sujeto para realizar la medición del



El sujeto debe colocarse de frente al medidor, con los hombros relajados, brazo s a los costados, talones juntos y puntas de los pies ligeréate separadas.

Imagen 2. Plano de Frankfort.

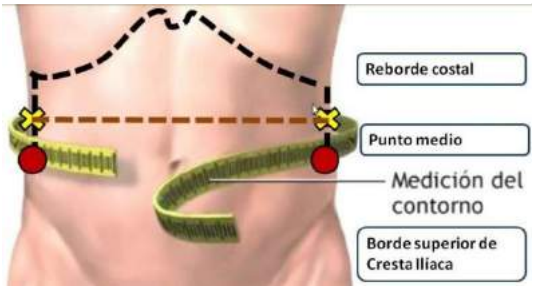


El plano de Frankfort se obtiene cuando el Orbitale® (el borde más bajo del hueco del ojo), está en el plano horizontal del Tragion® (muesca superior del trago de la oreja). Cuando se alinean, el Vertex® es el punto más alto sobre el cráneo.

3. El sujeto es instruido para tomar una respiración profunda y, mientras mantiene la cabeza en el plano Frankfort, el medidor aplica una leve presión de estiramiento fuerza hacia arriba desde el proceso mastoideo.
4. El anotador ubica el plano firmemente sobre el Vertex®, aplastando el pelo tanto como sea posible y toma la medición.

- Circunferencia de cintura: se realizará con una cinta antropométrica. La cinta se mantiene en ángulo recto al segmento o miembro que se está midiendo y la tensión de la cinta debe ser constante. Una constante tensión se logra asegurando que no se deforme la piel, manteniendo la cinta sobre el lugar a medir.
    1. El sujeto asume una posición relajada, de pie con los brazos cruzados en el tórax.
    2. El medidor debe ubicar la región más estrecha entre la décima costilla y el borde de la cresta iliaca. Si el punto más estrecho no puede identificarse la medida es tomada sobre el punto medio entre la última costilla (10ª) y el borde de la cresta iliaca como se muestra en la Imagen 3.

Imagen 3. Medición correcta de la



    3. El medidor se para frente al sujeto pasa la cinta alrededor del abdomen. El extremo y la caja de la cinta son sostenidas en la mano derecha mientras el medidor utiliza su mano izquierda para ajustar el nivel de la cinta en la espalda sobre el sitio más estrecho de la región. El medidor retoma el control del extremo de la cinta con la mano izquierda y usa la técnica de manos cruzadas para ubicar la cinta al frente en el nivel buscado.
    4. Se le pide al sujeto que baje sus brazos hasta una posición relajada. La cinta se ajusta luego como sea necesario para asegurarse que no se deslice pero que tampoco esté excesivamente tensionada sobre la piel.
    5. El sujeto respira normalmente y la medición es registrada al final de una expiración normal.
- Fuerza de agarre por dinamometría: la posición que deberán adoptar los sujetos se describe a continuación:
    1. Sujeto de pie confortablemente.
    2. Con los pies separados a la altura de sus hombros.
    3. Hombros aducidos y sin rotación.
    4. Brazos a los costados en posición neutra.
    5. Muñeca en posición neutra (En extensión entre 0-30° y con una desviación ulnar de 0-15°) [113].
    6. Se le pide al sujeto que presione con la mano dominante y con la mayor fuerza posible por 5 segundos.
    7. Se toma la lectura.
    8. Se repite el procedimiento 3 veces y se toma la lectura más alta.

Evaluación dietética y apego al tratamiento:

- Recordatorio de 24 horas de pasos múltiples: este método consiste en interrogar al sujeto para conocer todo lo que ingirió el día anterior. Incluye tres listas de alimentos para ayudar al entrevistado a recordar, la primera es una lista rápida que contiene bebidas y alimentos, la segunda lista contiene alimentos que se olvidan comúnmente y la entrevista se cierra con una descripción detallada de todo lo que se consumió [114]. Los pasos para el recordatorio de 24h se describen a continuación [115]:
    1. Lista rápida de alimentos y bebidas: se le pregunta al individuo sobre todos los alimentos que consumió el día anterior (24 horas) y se hace una lista general.
    2. Lista de alimentos olvidados: mediante una lista preelaborada, que contiene alimentos específicos, se le pregunta al individuo si olvidó mencionar alguno de la lista y se palomea. Estos son los alimentos que frecuentemente se olvidan:
        - Café, té, leche, atole
        - Jugo, agua de sabor, refresco
        - Cerveza, vino, tequila, cóctel
        - Dulce, caramelo, chicloso, chicle
        - Galletas, pasteles, chocolates
        - Gelatina, nieve, helado, flan
        - Cacahuates, nueces, pistaches
        - Papas, totopos, palomitas
        - Frutas frescas o deshidratadas
        - Jícamas, zanahorias, pepinos
        - Cereal, pan, tortilla
        - Aceite, mantequilla, crema
        - Aderezo, salsa, aguacate
        - Queso, yogurt
        - Tocinos, crutones
    3. Tiempo y ocasión: de manera más específica, se le cuestiona al individuo sobre sus tiempos de comida, cómo los llama y la información se empieza a ordenar de manera cronológica y por ocasión.
    4. Detalle y revisión: se detalla la cantidad, los ingredientes y el modo de preparación de cada comida y bebida:
    5. Revisión final: se confirma la información recabada y se registran cualquier dato omitido en los 4 pasos anteriores.

En todos los casos se utilizan réplicas de alimentos para cuantificar de manera precisa los equivalentes referidos por las pacientes.

El recordatorio de 24h fué analizado de acuerdo con el SMAE [111]. Los alimentos identificados como fuente de probióticos, omega 3 y polifenoles también se contabilizaron como equivalentes. Para el caso de la fibra, ésta se contabilizó por gramos según el contenido del alimento [116, 117].

Valoración Global Subjetiva Generada por el Paciente

La valoración global subjetiva generada por el paciente (VGS-GP) es un cuestionario que comprende 7 secciones: peso, Ingesta, síntomas, capacidad funcional, enfermedad y su relación con los requerimientos nutricionales, demanda metabólica y la evaluación física (anexo 6). Las primeras 4 preguntas las responde el individuo y las 3 últimas el evaluador. El evaluador definirá de manera subjetiva a cuál de los siguientes tres grupos pertenece la paciente:

A: bien nutrido.
B: moderada o sospechosamente mal nutrido.
C: severamente malnutrido.

Determinación de citocinas.

Se determinaron las siguientes citocinas en suero: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, TNF-α, GM-CSF. Pasos:

1. En las visitas 2, 3 y 5, a cada paciente se le tomó una muestra de sangre periférica por venopunción. Las muestras fueron centrifugadas a 2500 rpm por 10 minutos para separar el suero. El suero se almacenó a -40°C hasta su procesamiento.
2. El procesamiento de las muestras se realizó al final del estudio. Se realizó un análisis MUTIPLEX para la determinación de los marcadores.

   Procesamiento:

   2.1. Tapizado del pocillo con el anticuerpo.
   2.2. Adición de la muestra con la mezcla de antígenos.
   2.3. Unión del antígeno específico al anticuerpo tapizado en el pocillo.
   2.4. Lavado del pocillo para eliminar el exceso de antígeno no unido.
   2.5. Adición del anticuerpo secundario marcado con la enzima.
   2.6. Unión del anticuerpo secundario al antígeno.
   2.7. Lavado del pocillo para eliminar el exceso de enzima no unida.
   2.8. Adición del substrato.
   2.9. Unión del substrato a la enzima.
   2.10. Desarrollo del color.
   2.11. Lectura semicuantitativa de la concentración de las citocinas en el lector de ELISA.

Evaluación de la toxicidad.

Para evaluar la toxicidad, se utilizó el Cuestionario CTCAE V.5 (anexo 9).

10 ANÁLISIS ESTADÍSTICO

Se llevó a cabo un análisis por protocolo y otro por intención a tratar. Para el análisis por protocolo, se incluyeron únicamente las pacientes con al menos un 70% de apego a la intervención. En el anexo 10 se encuentra el formato para calcular el apego: para cada elemento de la dieta se registra el indicado en el tiempo 1 y posteriormente se registra lo consumido con su respectivo porcentaje de apego. Al final se hace un promedio de apego para cada tiempo y otro promedio general.

Se determinó la distribución de las **variables cuantitativas** (como edad, peso, citocinas, macronutrimentos, etc.) por medio de la prueba Kolmogorov Smirnov. Para aquellas con distribución normal se reportó media ± desviación estándar o mediana con sus respectivos percentiles 25 y 75 para las variables con libre distribución.

Las **variables categóricas** (como el estado de nutrición, estado funcional, etapa clínica de la enfermedad, histología, grado de toxicidad, etc.) fueron dicotomizadas y los resultados se reportaron como proporciones.

Las siguientes pruebas se utilizaron para determinar si existían cambios estadísticamente significativos a través de los 5 tiempos:

- La prueba estadística ANOVA de medidas repetidas (bondad de ajuste por Bonferroni), para variables con distribución normal.
- La prueba de Friedman para las variables con libre distribución.
- Q de Cochrane para variables dicotómicas.

Las siguientes pruebas se utilizaron para determinar si existían cambios estadísticamente significativos entre los 5 tiempos:

- T pareada para variables cuantitativas con distribución normal.
- Wilcoxon para variables con libre distribución.
- Mc Nemar para variables dicotómicas.

Las siguientes pruebas se utilizaron para determinar si existían diferencias entre grupos:

- T de student para variables cuantitativas con distribución normal (cuando en la prueba de Leven se obtenga una $p>0.05$ se asumirán varianzas iguales).
- U de Mann Whitney para variables cuantitativas con libre distribución.
- Prueba exacta de Fisher (cuando había un recuento menor a 5 en alguna de las casillas) o chi cuadrada (cuando todas las casillas tenían un recuento ≥5) para variables dicotómicas.

Para todas las pruebas se tomó como significancia estadística una $p\leq0.05$.

El análisis fué realizado con el paquete estadístico SPSS v23© (IBM Corp., Armonk, NY).

11 SEGURIDAD Y BIOÉTICA

El estudio se llevó a cabo bajo los acuerdos en la Declaración de Helsinki y siguiendo los lineamientos de las buenas prácticas clínicas. De acuerdo con el artículo 17 del Reglamento de la Ley General de Salud en Materia de Investigación para la Salud, la participación de las voluntarias en este estudio conlleva un riesgo mayor al mínimo.

El protocolo fue sometido a revisión por los comités de Investigación (018/023/ICI) y de Ética en Investigación (CEI/1247/18) del INCan y se registró en la página de Clinical Trials (NCT03994055). En el anexo 11 se encuentra el consentimiento aprobado para consentir a las pacientes del estudio.

Durante el reclutamiento, a cada paciente se le explicó a través de una presentación en qué consistía el estudio, los riesgos, así como los beneficios que esta investigación podía producirles. Se firmó un consentimiento informado y se entregó una copia a las pacientes que aceptaron participar en el estudio (Anexos 5 y 6). A cada participante se le proporcionará la información explícita del estudio y los datos (teléfono y dirección) del investigador principal para poder disolver futuras dudas sobre el protocolo.

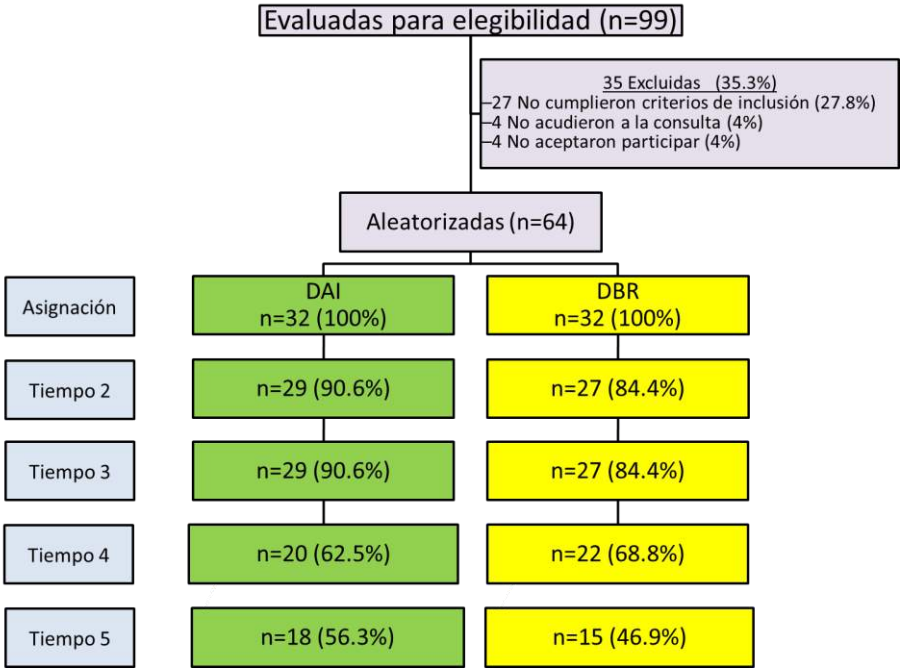
12 CRONOGRAMA DE ACTIVIDADES REALIZADAS

ACTIVIDAD	LUGAR	2017-2	2018-1	2018-2	2019-1	2019-2	2020-1	2020-2	2021-1
Revisión de la literatura	INCan								
Elaboración y cambios en el protocolo	INCan								
Someter protocolo a los comités del INCan	INCan								
Reclutamiento	INCan								
Seguimiento de pacientes	INCan								
Examen de candidatura	UNAM								
Procesar muestras de sangre y heces	HIMFG								
Análisis de datos	INCan								
Escritura de artículos científicos	INCan								
Enviar artículos a publicación	INCan								
Finalización de la tesis	INCan								

13 RESULTADOS

Un total de 99 pacientes fueron candidatas al estudio de las cuales 35 no cumplieron con los criterios de inclusión. En la Figura 1 se muestran los motivos de no inclusión. Finalmente, se aleatorizaron 64 pacientes, 32 en el brazo DAI y 32 en el brazo DBR. Se eliminaron del estudio a 8 pacientes, 3 del brazo DAI (2 pérdidas de seguimiento y 1 por cambio de tratamiento oncológico) y 5 del brazo DBR (2 por progresión de la enfermedad, 1 pérdida de seguimiento, 2 abandonaron el tratamiento oncológico). Estas pacientes no se incluyeron en el análisis debido a que se aleatorizaron, pero ya no fue posible realizar la primera evaluación.

Figura 1. Reclutamiento de las pacientes y aleatorización.



Las pacientes que no se incluyeron en el estudio también recibieron orientación nutricional y se invitaron a continuar bajo seguimiento nutricional.

En el T1, T2 y T3 se analizaron 56 pacientes, en el T4 42 pacientes y en el T5 33 pacientes. En el brazo DAI 6 pacientes salieron luego del T3 (3 por desnutrición, 1 pérdida de seguimiento, 1 defunción y 1 por cambio de tratamiento oncológico); para el T4 3 pacientes y para el T5 2 pacientes no habían sido evaluadas, pero continuan en seguimiento bajo protocolo. En el brazo DBR 2 pacientes salieron posterior al T3 (1 por desnutrición, 1 por toxicidad no manejable) y 4 pacientes salieron posterior al T4 (2 por desnutrición y 2 por pérdida de seguimiento); adicionalmente, en el T4 2 pacientes y en el T5 4 pacientes no alcanzaron a evaluarse, pero continúan en seguimiento bajo protocolo. Cabe agregar que una paciente en el brazo DBR perdió su visita en el T4 por motivos personales, pero retomó su evaluación en el T5. No se observaron diferencias en el número de visitas concluidas entre los grupos de estudio (p=0.666).

En la tabla 1 se muestran las características de toda la población y por grupos. No se observaron diferencias estadísticamente significativas entre los grupos en ninguna de las mediciones basales.

La media para la edad fue de 47.4 ± 12 años. El 55.4% (n=31) de la población presentaba alguna comorbilidad: 23.2% (n=13) obesidad, 12.5% (n=7) hipertensión, 10.7% (n=6) diabetes y 14.2% (n=7) eran geriátricas. El 48.2% (n=27) de las pacientes se diagnosticaron en etapas clínicas IIIB o IIIC1, el 39.3% (n=22) en etapas IIA o IIB y 12.5% (n=7) en etapas IB2 o IB3 del CaCu. La histología más común fue la Epidermoide con el 71.4% de los casos (n=40), seguida del adenocarcinoma con el 25% (n=14). Todas las pacientes presentaban adecuado estado funcional medido por la escala ECOG.

Tabla 1. Características basales de la población.

Variable		Todas	DAI (n=29)	DBR (n=27)	P
Edad (años)		47.4 ± 12	49.7 ± 13.6	44.7 ± 9.5	0.116
Pacientes con comorbilidades, n (%)		31 (55.4)	16 (55.2)	15 (55.6)	0.977
Etapa clínica, n (%)	**I**	7 (12.5)	5 (17.2)	2 (7.4)	0.199
	II	22 (39.3)	12 (41.4)	10 (37)	
	III	27 (48.2)	12 (41.4)	15 (55.6)	
Histología, n (%)	**Epidermoide**	40 (71.4)	20 (69)	20 (74.1)	0.738
	Adenocarcinoma	14 (25)	8 (27.6)	6 (22.2)	
	Adenoescamosa	2 (3.6)	1 (3.4)	1 (3.7)	
ECOG, n (%)	**0**	27 (48.2)	15 (51.7)	12 (44.4)	0.589
	1	29 (51.8)	14 (48.3)	15 (55.6)	

DAI: dieta antiinflamatoria; **DBR:** Dieta baja en residuo; **IMC:** índice de masa corporal; **ECOG:** *Eastern Cooperative Oncology Group* (sigla en inglés). Pruebas estadísticas: t de student y Prueba exacta de Fisher. Media ± DE.

En la Tabla 2 se reporta el tratamiento oncológico que recibieron las pacientes. El 91.1% (n=51) recibieron el Cisplatino como radiosensibilizador, la mediana de ciclos de QT recibidos fue de 4.5 (RIQ: 4-5), con una mediana de dosis de RT de 50.4 Gy (RIQ: 40-50.4), el 86% (n=37) recibieron BT de alta tasa y una mediana de dosis de BT de 28 Gy (RIQ: 26-28). No se observaron diferencias estadísticamente significativas entre grupos.

Tabla 2. Carácterísticas del tratamiento oncológico.

Variable		Todas	DAI (n=29)	DBR (n=27)	P
Radiosensibilizazor, n (%)	**Cisplatino**	51 (91.1)	25 (86.2)	26 (96.3)	0.353
	Gemcitabina	5 (8.9)	4 (13.8)	1 (3.7)	
Ciclos de quimioterpia		4.5 (4-5)	4 (4-5)	5 (4-5)	0.075
Dosis total de Radioterapia (Gy)		50.4 (45-50.4)	50.4 (45-50.4)	50.4 (45-50.4)	0.482
Dosis total de braquiterapia (Gy)		28 (26-28)	28 (26-28)	28 (26-28)	0.799
Tipo de braquiterapia, n (%)	**Baja tasa**	6 (14)	3 (15)	3 (13)	1
	Alta tasa	37 (86)	17 (85)	20 (87)	

Mediana (Rango intercuartilar). Pruebas estadísticas: Prueba exacta de Fisher y U de Mann Whitney.

En la tabla 3 se observan las características del consumo dietario por grupos. En el T1 no se observaron diferencias entre grupos. En el T2 el grupo DAI consumió más fibra total (p=0.003), fibra soluble (p=0.041), lactosa (p=0.003), equivalentes de omega 3 (p=0.023), equivalentes de probióticos (p=0.001) y equivalentes de polifenoles (p<0.0001). En el T3 el grupo DAI consumió más energía (p=0.029), proteína (p=0.027), fibra total (p=0.003), fibra soluble (p=0.013), lactosa (p=0.001), equivalentes de probióticos (p<0.0001) y equivalentes de polifenoles (p<0.0001).

Tabla 3. Consumo dietario por grupos.

Variables dietéticas	Brazo	T1 (n=56)	T2 (n=56)	T3 (n=56)	T4 (n=42)	T5 (n=33)	p
Energía (kcal/kg)	DAI	19.6 (14.1-26.4)	19 (15.6-24.6)	16.9 (10.6-21.6)	18.6 (10.1-27.1)	20.1 (15.5-31.7)	0.793
	DBR	18.9 (14.5-27.2)	17.9 (13.3-26)	12.9 (8.8-16.6)	17 (10.9-19.9)	22 (18.5-25.8)	**0.002**†¬‡°+^
	p	0.799	0.629	**0.029**	0.351	0.929	
Proteínas (g/kg)	DAI	0.75 (0.58-0.89)	0.96 (0.76-1.22)	0.77 (0.45-1)	0.75 (0.41-1.58)	0.96 (0.53-1.36)	0.4
	DBR	0.69 (0.55-0.89)	0.98 (0.7-1.1)	0.43 (0.34-0.81)	0.6 (0.38-0.91)	0.96 (0.82-1)	**0.011***†‘‡°+^
	p	0.329	0.476	**0.027**	0.257	0.957	
Proteína (%)	DAI	16.5 (12.5-22.6)	20.1 ± 4.2	18.1 ± 6.2	17.3 ± 6.6	17.8 ± 4.5	**0.026***
	DBR	15.6 (13.2-17.4)	18.6 ± 4.9	17.4 ± 6.1	16.2 ± 8.1	17.3 ± 2.5	**0.007***‘#
	p	0.496	0.222	0.642	0.65	0.715	
Lípidos (%)	DAI	27.1 ± 10.9	28.4 ± 8.35	21 (12.7-28.3)	23.1 ± 9.7	25.1 ± 13.1	0.554
	DBR	28.9 ± 9.8	25.3 ±9.45	21.4 (12.5-26.1)	22.3 ± 11.4	25.4 ± 7.7	0.454
	p	0.514	0.196	0.496	0.805	0.949	
Carbohidratos (%)	DAI	55.7 ± 13.5	51.4 ± 10.5	59.9 ± 14.3	59.5 ± 14	56.9 ± 17.7	**0.041**°
	DBR	55 ± 10.1	55.9 ± 12.1	62.6 ± 12.6	61.7 ± 16.6	57.2 ± 8.2	0.554
	p	0.816	0.138	0.46	0.644	0.95	
Agua (L)	DAI	1.25 (1-2)	1.62 (1.37-2)	1.5 (1.5-2.3)	1.75 (1.37-2)	1.5 (1.37-2.1)	0.108
	DBR	1.5 (1-2)	1.5 (1.42-2)	1.5 (1-2)	1.25 (1-2)	1.5 (1-2)	0.698
	p	0.218	0.913	0.881	0.446	0.817	
Fibra total (g)	DAI	23 (12.8-28.5)	25.7 (20.2-31.1)	21.2 (12.4-28.4)	26.3 ± 14.6	31.4 ± 18.9	**0.028**‡+^‘
	DBR	17.3 (9.6-24.7)	19.1 (12.1-24)	10.3 (8.2-16.2)	13.3 ± 7.1	19.8 ± 8	0.063‡°+^†¬‘
	p	0.161	**0.003**	**0.003**	**0.005**	**0.036**	
Fibra soluble (g)	DAI	0.54 (0.03-1.51)	5.4 (4-7.5)	4.3 (2.6-5.6)	5.3 ± 3.6	6.6 ± 4.35	0.618*†¬‘
	DBR	0.99 (0.36-1.74)	4 (2.3-6.3)	2.4 (1.6-4.4)	2.7 ± 2	4.54 ± 1.69	**0.018**‡°^*†¬‘
	p	0.366	**0.041**	**0.013**	**0.007**	0.074	
Lactosa (g)	DAI	0 (0-0.235)	2 (0-5)	2 (0-2.7)	0.25 (0-3.2)	0 (0-3.3)	0.606
	DBR	0 (0-1)	0 (0-1.3)	0	0 (0-0.35)	0.5 (0-2.5)	0.471
	p	0.375	**0.003**	**0.001**	0.134	1	
Omega 3 (equivalentes)	DAI	1 (0-2)	2 (1-3)	1 (0.25-2)	1 (0-1.6)	0.75 (0-3)	0.144*
	DBR	1 (0-2)	1 (0-2)	0 (0-2)	0.5 (0-3)	0.15 (0-2.2)	0.466
	p	0.876	**0.023**	0.051	0.925	0.656	
Probióticos (equivalentes)	DAI	0	1 (0-1.1)	0.5 (0-1)	0 (0-0.5)	0 (0-0.5)	0.051#*†
	DBR	0	0 (0-0.25)	0	0 (0-1)	0 (0-0.1)	0.349
	p	0.463	**0.001**	**<0.0001**	0.08	0.464	
Polifenoles (equivalentes)	DAI	4 (2-6)	7.1 ± 2.8	5.9 ± 2.8	5.6 ± 3.3	7.55 ± 3.1	0.239*†¬‘
	DBR	3 (1-6)	4 ± 2	3.2 ± 2.1	3.7 ±2.3	4.1 ± 2.3	0.622
	p	0.476	**<0.0001**	**<0.0001**	**0.039**	**0.02**	

DAI: dieta antiinflamatoria; **DBR:** Dieta baja en residuo. **P<0.05:** *T1-T2, †T1-T3, ¬T1-T4, ‘T1-T5, ‡T2-T3, °T2-T4, ~T2-T5, #T3-T4, +T3-T5, ^T4-5. Pruebas estadísticas: t de student, U de Manwithnney, t pareada, Wilcoxon, ANOVA de medidas repetidas (ajuste Bonferrroni), Friedman.

En el T4 el grupo DAI consumió más fibra total (p=0.005), fibra soluble (p=0.007) y equivalentes de polifenoles (p=0.039). En el T5 el grupo DAI consumió más fibra total (p=0.036) y equivalentes de polifenoles (p=0.02). Durante las evaluaciones el grupo DAI tuvo variaciones significativas en el porcentaje de proteínas (p=0.007), porcentaje de hidratos de carbono (p=0.041) y fibra total (p=0.037). Mientras que el grupo DBR presentó variaciones significativas en el consumo de energía (p=0.002), gramos/kg de proteína (p=0.011), porcentaje de proteínas (p=0.007), fibra total (p=0.011) y fibra soluble (p=0.018).

En la tabla 4 se presentan los resultados de las variables antropométricas y el diagnóstico nutricional. Al comparar ambos grupos, no se observan diferencias en la pérdida de peso, porcentaje de pacientes con baja fuerza de agarre, índice cintura/talla, IMC ni desnutrición medida por la VGS-GP. Al medir el estado nutricional a través de todas las variables anteriores, no se observaron diferencias en la proporción de pacientes con y sin desnutrición. Cabe destacar que, en el T3, durante el tratamiento, es cuando las pacientes consumen menos alimentos y pierden la mayor cantidad de peso; sin embargo, todas las pacientes del grupo DAI recuperaron su estado nutricional y el 13.3% (n=2) de las pacientes del grupo DBR persistieron con desnutrición.

Tabla 4. Indicadores antropométricos y del estado nutricional.

Variable	Brazo	T1 (n=56)	T2 (n=56)	T3 (n=56)	T4 (n=36)	T5 (n=31)	p
Pacientes con	DAI	18 (62.1)	21 (72.4)	24 (82.8)	15 (75)	10 (55.6)	0.421
baja ingesta de	DBR	17 (63)	15 (55.6)	25 (92.6)	19 (86.4)	7 (46.7)	**0.012†‡+^**
energía, n (%)	p	0.945	0.188	0.424	0.445	0.611	
Pérdida de	DAI	2.5 (0-7.7)	0.52 (0-1.4)	5.7 (3.8-9.4)	2.5 (0-4.8)	0	**<0.0001'‡#+^**
peso (%)	DBR	4.3 (0-5.6)	0.49 (0-1.9)	3.8 (2.9-5.8)	2.8 (0-8.2)	0 (0-1.3)	**0.019*‡°+**
	p	0.987	0.473	0.341	0.172	0.211	
Pacientes con	DAI	14 (48.3)	13 (44.8)	13 (44.8)	15 (75)	13 (81.3)	**0.017**
baja fuerza de	DBR	14 (51.9)	13 (48.1)	12 (44.4)	11 (50)	11 (73.3)	0.07
agarre, n (%)	p	0.789	0.803	0.977	0.096	0.598	
Índice	DAI	0.59 ± 0.08	0.58 ± 0.08	0.56 ± 0.08	0.55 (0.5-0.59)	0.56 ± 0.07	**0.001*† ¬'‡°**
cintura/talla	DBR	0.62 ± 0.08	0.61 ± 0.08	0.59 ± 0.09	0.57 (0.52-0.6)	0.59 ± 0.1	**<0.0001†¬‡°#**
(cm/cm)	p	0.169	0.099	0.204	0.465	0.263	
IMC (kg/m^2)	DAI	27.7 ± 4.8	27.4 ± 4.7	25.8 ± 4.8	25.6 ± 4.3	26.1 ± 4.2	**<0.0001†¬'‡°~#^**
	DBR	30.2 ± 6.4	30.2 ± 6.2	28.5 ± 6.4	26.7 ± 4.2	28.3 ± 7.4	**<0.0001*†¬'‡°~#^**
	p	0.103	0.067	0.084	0.413	0.312	
Pacientes con	DAI	7 (24.1)	8 (27.6)	24 (82.8)	12 (60)	1 (5.3)	**<0.0001†‡+^**
VGS-GP B o C,	DBR	5 (18.5)	4 (14.8)	20 (74.1)	12 (54.5)	2 (13.3)	**<0.0001†¬‡°+**
n (%)	p	0.609	0.244	0.429	0.721	0.439	
Pacientes con	DAI	-	-	10 (34.5)	5 (25)	0	**0.021+**
desnutrición,	DBR			5 (18.5)	6 (27.3)	2 (13.3)	0.368
n (%)	p			0.178	0.867	0.11	

DAI: dieta antiinflamatoria; **DBR:** Dieta baja en residuo. **P<0.05: *** T1-T2, **†** T1-T3, ¬T1-T4, **'** T1-T5, **‡** T2-T3, **°** T2-T4, **~** T2-T5, #T3-T4, **+** T3-T5, **^** T4-5. Pruebas estadísticas: t de student, U de Manwithnney, t pareada, Wilcoxon, ANOVA de medidas repetidas (ajuste Bonferrroni), Friedman, prueba exacta de Fisher o chi cuadrada, Q de Cochran, McNemar.

En la Tabla 5 se muestran los resultados del desarrollo de toxicidad. En el T5 el grupo DBR presentó una mayor proporción de pacientes con xerostomía grado 1 o más (p=0.033). El grupo DAI presentó variaciones importantes en el desarrollo de náuseas (P=0.004), xerostomía (p=0.03), diarrea (p=0.001) y dolor abdominal (p=0.05). El grupo de DBR presentó mayor variación en el desarrollo de anorexia (p=0.002) y saciedad temprana (p=0.015).

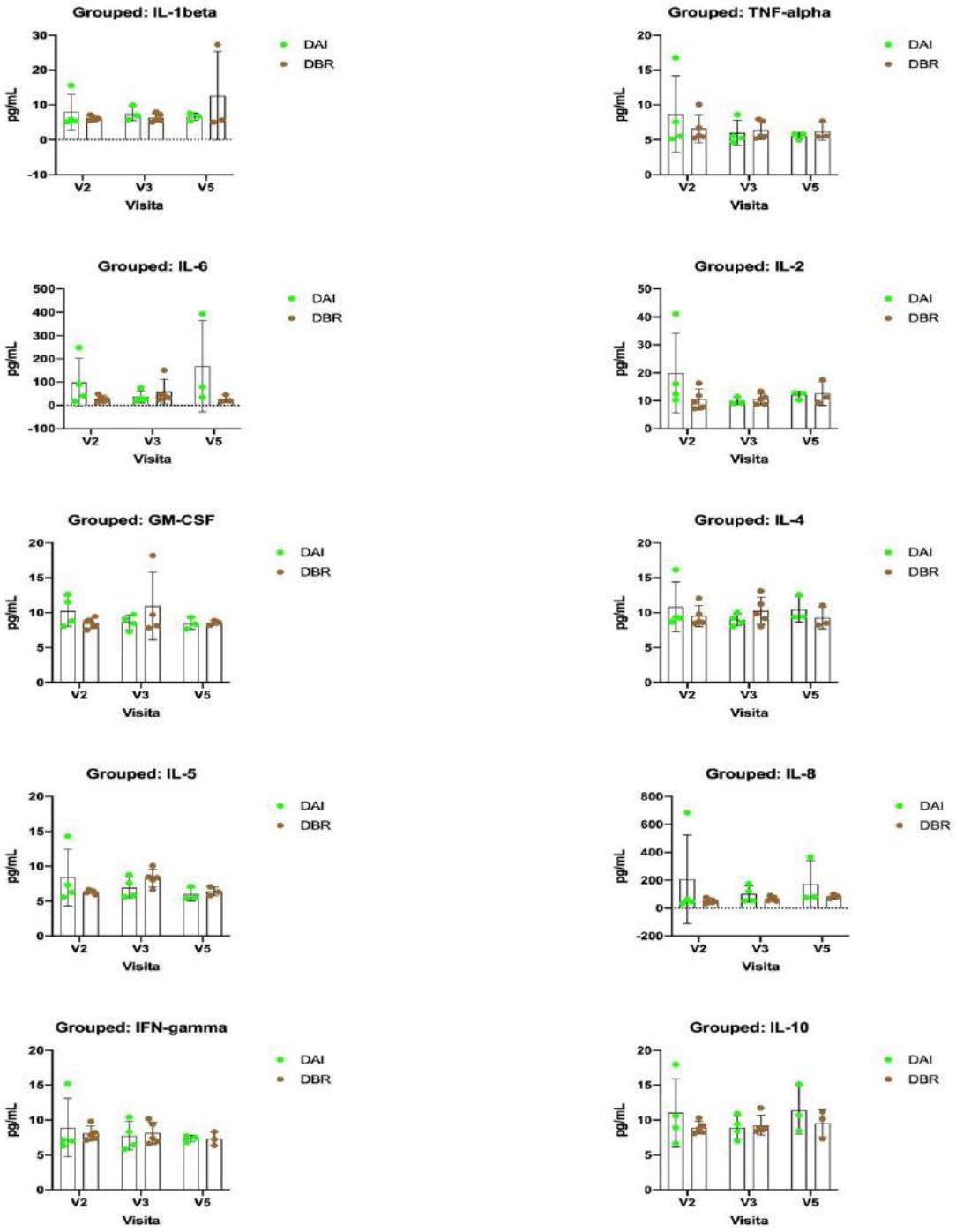
Tabla 5. Toxicidad gastrointestinal.

Toxicidad	Brazo	T3 (n=56)	T4 (n=43)	T5 (n=33)	p
Náuseas grado ≥ 2, n (%)	DAI	13 (44.8)	5 (25)	0	**0.004**+
	DBR	10 (37)	10 (45.5)	1 (6.7)	0.115
	p	0.55	0.167	0.454	
Vómito grado ≥ 1, n (%)	DAI	9 (31)	2 (10)	1 (5.6)	0.156
	DBR	8 (29.6)	6 (27.3)	1 (6.7)	0.472
	p	0.909	0.243	1	
Anorexia grado ≥ 1, n (%)	DAI	12 (41.4)	4 (20)	5 (27.8)	0.307
	DBR	16 (59.3)	6 (27.3)	1 (6.7)	**0.002**+
	p	0.18	0.723	0.186	
Disgeusia grado ≥ 1, n (%)	DAI	3 (10.3)	2 (10)	1 (5.6)	0.779
	DBR	7 (25.9)	4 (18.2)	1 (6.7)	0.549
	p	0.171	0.665	1	
Disfagia grado ≥ 1, n (%)	DAI	1 (3.4)	1 (5)	0	1
	DBR	1 (3.7)	2 (9.1)	1 (6.7)	0.368
	p	1	1	0.455	
Xerostomía grado ≥ 1, n (%)	DAI	10 (34.5)	6 (30)	0	**0.03**
	DBR	12 (44.4)	9 (40.9)	4 (26.7)	0.565
	p	0.446	0.461	**0.033**	
Diarrea grado ≥ 1, n (%)	DAI	21 (72.4)	4 (20)	4 (22.2)	**0.001**#+
	DBR	17 (63)	7 (31.8)	4 (26.7)	0.097
	p	0.449	0.384	1	
Estreñimiento grado ≥ 1, n (%)	DAI	9 (31)	8 (40)	7 (38.9)	0.472
	DBR	9 (33.3)	7 (31.8)	4 (26.7)	1
	p	0.854	0.58	0.458	
Distensión abdominal grado ≥ 1, n (%)	DAI	15 (51.7)	7 (35)	7 (38.9)	0.301
	DBR	10 (37)	10 (45.5)	7 (46.7)	0.135
	p	0.269	0.491	0.653	
Dolor abdominal grado ≥ 1, n (%)	DAI	14 (48.3)	4 (20)	6 (33.3)	**0.05**
	DBR	11 (40.7)	10 (45.5)	7 (46.7)	0.607
	p	0.571	0.081	0.435	
Saciedad temprana, n (%)	DAI	10 (34.5)	7 (35)	4 (22.2)	0.236
	DBR	14 (51.9)	7 (31.8)	2 (13.3)	**0.015**+
	p	0.189	0.827	0.665	

DAI: dieta antiinflamatoria; **DBR:** Dieta baja en residuo. **P<0.05:** #T3-T4, **+**T3-T5, **^**T4-5. Pruebas estadísticas: prueba exacta de Fisher o chi cuadrada, Q de Cochran, McNemar.

En la Figura 2 se muestra un experimento de la expresión de citocinas con muestras de suero de 4 pacientes del brazo DAI y 5 pacientes del brazo DBR. No se observaron diferencias significativas entre grupos.

Figura 2. Expresión de citocinas en suero.

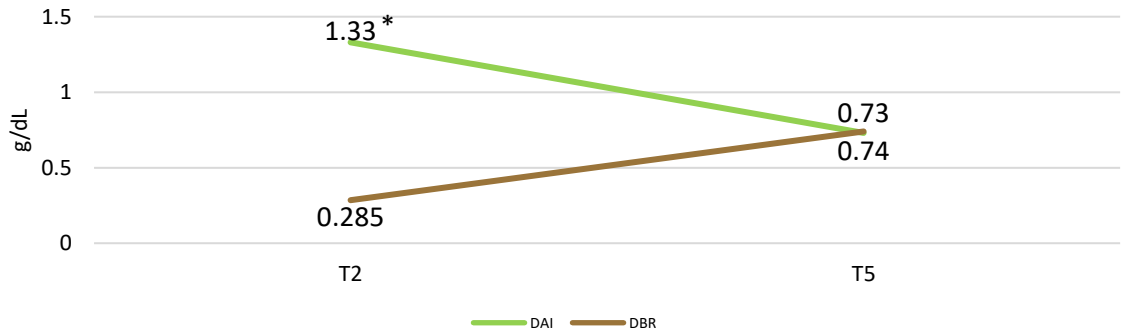


Esta figura muestra las medianas de expresión de citocinas en suero de 4 pacientes del brazo DAI y 5 pacientes del brazo DBR. No se observaron diferencias entre grupos. **V:** tiempo; **DAI:** Dieta antiinflamatoria; **DBR:** Dieta baja en residuo.

El 31% (n=9) de las pacientes en el grupo DAI y el 25.9% (n=7) de las pacientes en el grupo DBR presentaron un buen apego y terminaron las 5 evaluaciones nutricionales. De acuerdo con el análisis por protocolo, no se observaron diferencias en las características basales ni en el tratamiento oncológico. En las Figuras 3 a la 6 se pueden observar los resultados del análisis por protocolo del consumo dietario, presencia de desnutrición, parámetros inflamatorios y toxicidad gastrointestinal.

En la figura 3 se muestran las medianas de PCR en 7 pacientes del brazo DAI y 6 pacientes del brazo DBR. Las pacientes con DAI presentaban valores de PCR más altos en el T2 que las del grupo DBR (p=0.035). Dichas diferencias se pierden para el T5 (p=0.836).

Figura 3. Niveles de proteína C reactiva de las pacientes con buen apego a las intervenciones nutricionales.



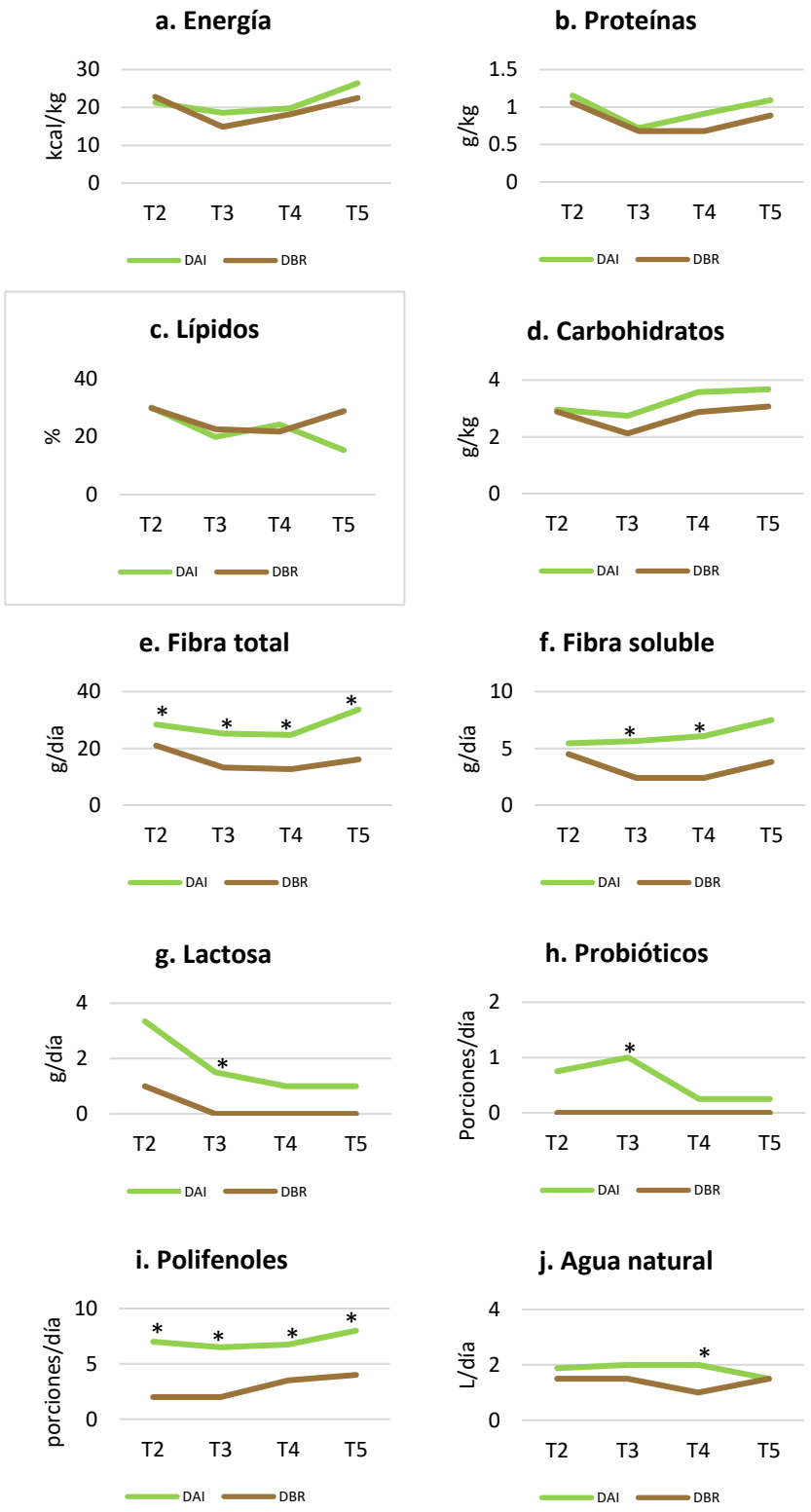
Esta figura muestra las medianas de PCR en las pacientes con buen apego del grupo DAI (n=7) y del grupo DBR (n=6). En el T2 la mediana del grupo DAI fue mayor que la del grupo DBR (p=0.035); sin embargo, para el T5 el grupo DAI tendió a disminuir (p=0.063) y el grupo DBR a aumentar (p=0.144), de tal manera que se perdieron las diferencias entre grupos (p=0.836) en el T5. **DAI:** Dieta antiinflamatoria; **DBR:** Dieta baja en residuo.

En la figura 4 se muestran los elementos dietarios en los que se observaron diferencias significativas entre grupos. El grupo DAI presentó un mayor consumo de fibra total, fibra soluble, lactosa, probióticos, polifenoles y agua natural.

En la Figura 5 se muestra el desarrollo de desnutrición a lo largo del tratamiento nutricional. En el grupo DAI las pacientes desarrollaron más desnutrición en el T3 que el grupo DBR (33.3% vs 0%, p=0.016). Sin embargo, hubo una mejor recuperación en en el T5 para el grupo DAI que en el grupo DBR.

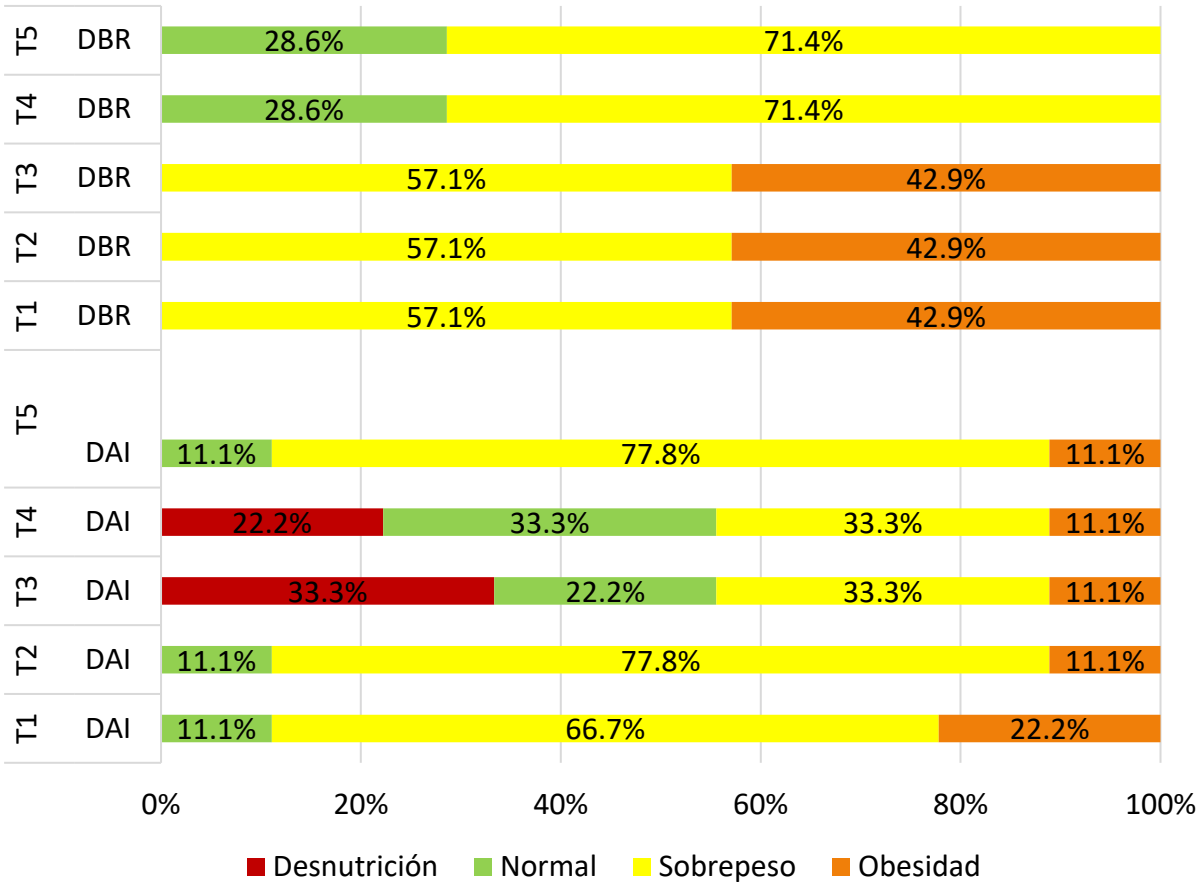
En la Figura 6 se observa el desarrollo de diarrea, estreñimiento y xerostomía a lo largo de los 5 tiempos. Para el caso de las primeras 2 toxicidades no hubo diferencias entre grupos. En el caso de la xerostomía se observó una diferencia significativa en el T5 (p=0.036). Para el caso de las náuseas, vómito, disgeusia, disfagia, anorexia, saciedad temprana, dolor y distensión abdominal, los resultados fueron similares entre grupos.

Figura 4. Consumo dietario de las pacientes con buen apego a las intervenciones nutricionales.



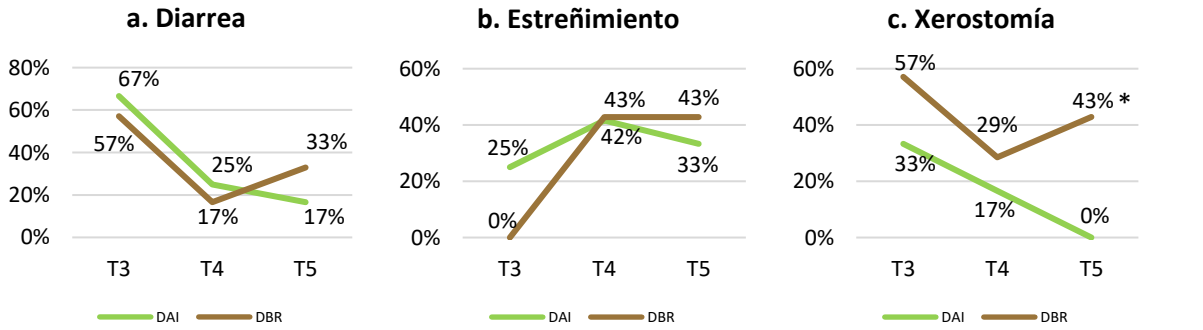
Esta figura muestra los elementos dietarios como energía, macronutrimentos y los componentes dietéticos que mostraron diferencias significativas entre grupos en las pacientes con buen apego a las dietas. En las **Figuras a, b, c y d** no hubo diferencias entre grupos. En la **Figura e** se observa que en los 5 tiempos el grupo DAI presentó un mayor consumo de fibra. En la **Figura f**, en los T3 y T4, el grupo DAI presentó un mayor consumo de fibra soluble. En la **Figura g**, en el T3, el grupo DAI presentó un mayor consumo de lactosa. En la **Figura h**, en el T3, el grupo DAI presentó un mayor consumo de probióticos. En la **Figura i** se muestra que, en los 5 tiempos, el grupo DAI presentó un mayor consumo de polifenoles. En la **Figura j**, en el T3, el grupo DAI presentó un mayor consumo de agua natural. **DAI:** Dieta antiinflamatoria; **DBR:** Dieta baja en residuo. ***p<0.05.**

Figura 5. Desarrollo de desnutrición en las pacientes con buen apego.



Esta figura muestra el desarrollo de desnutrición a lo largo del tratamiento nutricional. Se analizaron 9 pacientes del brazo DAI y 7 pacientes del grupo DBR. Durante el T3 en el brazo DAI 3 pacientes (33.3%) presentaron desnutrición vs 0 pacientes (0%) del grupo DBR (p=0.027). Durante los T1, T2, T4 y T5 no se mostraron diferencias significativas entre grupos. Para el T5 no se observaron pacientes con desnutrición. **DAI:** Dieta antiinflamatoria; **DBR:** Dieta baja en residuo. *p<0.05.

Figura 6. Desarrollo de toxicidades en las pacientes con buen apego.



En las figuras a y b se muestran el desarrollo diarrea y el de estreñimiento por grupos; en ambos casos no hubo diferencias significativas. En el caso de la xerostomía, a lo largo de los T3 y T4 no se mostraron diferencias, pero durante el T5 el grupo DAI no presentó pacientes con xerostomía (0%) comparado con 3 pacientes (42.9%) del grupo de DBR (p=0.036). **DAI:** Dieta antiinflamatoria; **DBR:** Dieta baja en residuo. *p<0.05.

Adicionalmente, se realizó un análisis para comparar a los grupos con buen apego (DAI y DBR) y sin apego. En el T2 el grupo DAI consumía más proteína (1.1 vs 0.89 g/kg, p=0.013), fibra (28 vs 20.5g, p=0.041), lactosa (4 vs 0g, p=0.004), probióticos (1 vs 0 equivalentes, p=0.013), polifenoles (8 vs 5 equivalentes, p=0.087) y omega 3 (3 vs 1 equivalentes, p=0.001), además de un menor porcentaje de carbohidratos (48.5 vs 58.7%, p=0.047). Estas diferencias se mantuvieron para la fibra en el T3 (27.5 vs 13g, p=0.018), T4 (24.5 vs 13.3g, p=0.029) y T5 (32.4 vs 22.7g, p=0.036), la lactosa en el T4 (1 vs 0g, p=0.021), probióticos en el T3 (1 vs 0 equivalentes, p=0.061), T4 (0.5 vs 0 equivalentes, p=0.107) y T5 (0.5 vs 0 equivalentes, p=0.069) y polifenoles en el T3 (7 vs 4.8 equivalentes, p=0.008), T4 (5.5 vs 4.2 equivalentes, p=0.058) y T5 (7.5 vs 5 equivalentes, p=0.134). En el T2 el grupo de DBR consumió una mayor cantidad de proteína (1 vs 0.89g, p=0.091), pero menor cantidad de polifenoles que el grupo sin apego (2 vs 5 equivalentes, p=0.003). No se observaron diferencias significativas para el resto de los componentes de la dieta. En el análisis de los indicadores nutricionales, no se observaron diferencias en el porcentaje de pacientes con baja ingesta de energía, porcentaje de pérdida de peso, porcentaje de pacientes con baja fuerza de agarre o IMC; sin embargo, en el T5 se observó una tendencia a que las pacientes sin apego presentaran mayor riesgo de desnutrición o desnutrición medida por la VGS-GP comparadas con las pacientes que sí se apegaron a alguna de las dietas (20 vs 0 vs 0%, p=0.074). En cuanto a los análisis de toxicidades gastrointestinales, aunque no hubo diferencias significativas, en el T5 el grupo DBR tendía a tener más xerostomía, estreñimiento, náuseas, disgeusia, disfagia y dolor abdominal; el grupo DAI tendía a tener más anorexia y el grupo sin apego tendía a tener más diarrea, vómito y saciedad temprana. Finalmente, no hubo diferencias en los niveles de PCR entre el grupo DAI o DBR y las pacientes sin apego.

14 DISCUSIÓN DE RESULTADOS

Tradicionalmente, DBR se ha indicado a los pacientes que reciben RT a pelvis con el objetivo de aminorar la severidad de la diarrea; sin embargo, poco se ha estudiado sobre los efectos de esta dieta en el estado nutricional y la respuesta inflamatoria. En el presente estudio se propuso comparar DBR *versus* una intervención totalmente diferente en componentes dietarios, la intervención DAI. Se realizó un enfoque hacia el estado nutricional, parámetros inflamatorios y la toxicidad gastrointestinal durante aproximadamente 6 meses posteriores al inicio del tratamiento oncológico. De acuerdo con los resultados preliminares, no se observaron diferencias significativas en el estado de nutrición entre grupos; sin embargo, el grupo DAI desarrolló más desnutrición, pero menos xerostomía. Dichas diferencias en desnutrición podrían ser explicadas por la presencia de valores de PCR más elevados en el grupo DAI que en el grupo DBR.

El primer estudio que se realizó sobre una dieta baja en grasa y lactosa fue el de Bye A. et al. [60]. En dicho estudio se indicaron 5g/día de lactosa y 40g/día de grasas vs una dieta normal en mujeres con RT a pelvis diagnosticadas con algún cáncer ginecológico. En la última semana de la RT se observó que el grupo experimental requirió menor dosis de antidiarreicos y presentó una menor incidencia de diarrea comparado con el grupo control. Para la semana 12 estas diferencias dejaron de ser significativas. Los indicadores nutricionales como pérdida de peso, circunferencia media de brazo, albúmina sérica y transferrina no mostraron diferencias significativas entre grupos. En el estudio de Wedlake et al. [61] en el que se compararon 3 dietas con diferente contenido de grasas (baja, alta y modificada en grasas) durante el tratamiento con RT a pelvis, no se observaron diferencias en la incidencia de diarrea. Los autores reportaron que, aunque sí hubo diferencias significativas entre grupos en el consumo de grasas, se observó que los pacientes tendían a consumir menor cantidad de grasa de la indicada en el protocolo. En el mismo artículo se menciona que el pobre apego podría atribuirse al mensaje que se difunde actualmente sobre que “una dieta baja en grasa es más saludable” o al género, ya que en su estudio se observó que las mujeres tenían menor apego que los hombres. En el presente estudio se observó un comportamiento similar, en el T2 las pacientes DAI incrementaban su consumo de lípidos, pero durante el tratamiento lo volvían a disminuir; en ninguno de los casos se reportó que esta disminución fuera por intolerancia. Lo que las pacientes llegaron a mencionar fue que “las grasas son malas” o que “las grasas pueden causar diarrea”.

En el estudio de Stryker et al., un grupo de pacientes bajo tratamiento con RT a pelvis se aleatorizó para tomar dos vasos de leche entera al día, 2 vasos de leche deslactosada al día o seguir una dieta libre de lactosa durante 5 semanas; con dicho estudio se observó que la RT a pelvis no modificaba la habilidad del intestino para hidrolizar la lactosa ingerida, por lo que su restricción no mejoró la diarrea [68]. Actualmente sabemos que aproximadamente el 15% de los pacientes bajo tratamiento con RT a pelvis podrían desarrollar intolerancia a la lactosa [118]. Por lo que no habría justificación para restringir su consumo en aquellos pacientes que indiquen buena tolerancia. Las pacientes del presente estudio manifestaron que limitaban su consumo de lácteos porque estos “causan diarrea”. Dicha creencia se ha difundido tanto en pacientes como entre médicos tratantes, lo que dificulta la educación del paciente que está en tratamiento.

Se han llevado a cabo varias intervenciones con suplementos de fibra en pacientes con RT a pelvis. Los resultados han sido variados, ya que en algunos se observa que la suplementación aminora la severidad de la diarrea [63, 70, 77, 119], pero en otros se observa un incremento o nulo efecto [62, 120]. Wedlake et al. llevaron a cabo el primer EC aleatoriazado en el que se evaluó el consumo de una dieta alta, normal o baja en fibra en pacientes con RT a pelvis. Los pacientes recibieron recomendaciones para llegar a las metas de fibra a base de alimentos. Al igual que en nuestro estudio, no se encontraron diferencias entre grupos en la toxicidad gastrointestinal al término de la RT o en el nadir durante la RT; no obstante, sí se observaron diferencias a favor de un consumo alto de fibra en el cuestionario de toxicidad intestinal IBDQ 1 año después del tratamiento. Dicho hallazgo respalda el hecho de que no se justifica la reducción del consumo de fibra ya que se restringe a los pacientes de los beneficios que este componente de la dieta ofrece [121].

Para el caso de los polifenoles, al momento solamente se han llevado a cabo 2 intervenciones en pacientes con RT a pelvis. El primer estudio es el de Ahmad et al. [122] en el que se aleatorizaron 42 pacientes con cáncer de próstata, un grupo tomó 200mg de isoflavonas provenientes de la soya y el otro grupo un placebo. Entre los beneficios, luego de 6 meses de tratamiento, se encontró menor frecuencia de calambres/diarrea y menor dolor al defecar en el grupo de intervención que en el grupo placebo. El segundo estudio es el de Emami et al.[123], en el que se aleatorizaron 42 pacientes al grupo con tabletas de 450mg de té verde o placebo. El resultado mostró que el consumo de las tabletas de té verde reducía la frecuencia y severidad de la diarrea a partir de la semana 3 posterior al inicio del tratamiento. En el presente estudio, a las pacientes del grupo DAI se les indicó tomar 1 taza de té verde al día, aún así no se observó diferencia en el número de evacuaciones. Este resultado puede deberse a que la dosis del té es mucho menor a la ingerida a través de las tabletas.

Este es el primer estudio de una intervención dietética que mide el efecto de DBR sobre diversos parámetros nutricionales, además de que se enfoca en 11 diferentes toxicidades gastrointestinales y no únicamente en la diarrea, y en parámetros inflamatorios sistémicos e intestinales. Cabe agregar que, aunque el hecho de no cuantificar el consumo de polifenoles, omega 3 y probióticos podría ser una limitación, también podría considerarse como una fortaleza, ya que son más representativos del consumo real de la población. Entre las debilidades del estudio se encuentran que al momento del análisis aún no se concluía el tamaño de la muestra calculada para el objetivo principal, las limitaciones que en sí mismas presentan las herramientas como el Recordatorio de 24h y las mediciones antropométricas, que por motivos de costos no fue posible medir los parámetros inflamatorios en todas las pacientes y el bajo apego a las intervenciones.

Estudios de intervenciones con dietas y suplementos durante la RT a pelvis han reportado que el porcentaje de individuos que logran un buen apego va desde 30% hasta un 85% [124-127]. En el caso de nuestro estudio, el bajo apego podría estar relacionado con el nivel socioeconómico y nivel de estudios de las pacientes. Cabe resaltar que, a pesar de que a las pacientes DAI se les proporcionaron algunos alimentos, éstas refieren que no los consumen porque se les olvida, no les gusta el sabor o por falta de interés. En el caso del grupo DBR se observa que, como se les permite el consumo de alimentos dulces y procesados, las pacientes tienden a centrar su consumo en

alimentos poco saludables (por ejemplo: azúcar, gelatina, pan, etc.) y, en otros casos, les cuesta trabajo dejar los alimentos como fruta y verdura fresca o las tortillas.

Lejos de tener beneficios, se ha llegado a decir que una dieta baja en residuo podría ser nutricionalmente inadecuada, ya que representa un riesgo debido a la falta de los efectos potencialmente benéficos de la fibra dietética, propiciando, por ejemplo, el estreñimiento [128]. De hecho, se llevó a cabo un EC aleatorizado doble ciego, de prebióticos (inulina y fructooligosacáridos) contra placebo en pacientes con RT pelvis. Al final de la RT se observó un descenso en Lactobacillus y Bifidobacterium en ambos grupos; no obstante, a las 3 semanas, mediante un análisis de cultivos, el grupo de intervención presentó un mayor recuento que el grupo control, lo que sugiere que los pacientes con dietas altas en fibra podrían recuperarse más rápidamente de las toxicidades gastrointestinales [129]. En un estudio similar, no se observaron diferencias en el desarrollo de diarrea, pero sí en la consistencia de las heces a favor del grupo de intervención [120].

Actualmente son bien conocidos los mecanismos a través de los cuales diversos componentes de la dieta inhiben la producción de especies reactivas de oxígeno (debido a su capacidad antioxidante), inducen la producción de citocinas antiinflamatorias como IL-10 o T reguladoras, inhiben la activación de citocinas tipo Th1 o Th17 (disminuyendo la producción de citocinas proinflamatorias) o inhiben la activación de factores de transcripción como NFκ-B [75]. Además de que hay una basta información acerca de su efecto sobre diversas citocinas [97] e incluso su efecto en poblaciones más específicas como lo son los pacientes con comorbilidades [130]. Aunque en el presente estudio no se logró ver el efecto de la dieta sobre las citocinas, esto se puede deber a que las pacientes analizadas no fueron necesariamente las del mejor apego. En cuanto a la PCR, en el T2 se observaba más alta en el grupo DAI que en el grupo DBR, pero posteriormente los grupos se emparejaron y dejaron de verse diferencias, dicha disminución en el grupo DAI podría atribuirse al efecto de la dieta. Hace falta incrementar el tamaño de la muestra y esperar que la aleatorización equilibre a los grupos o hacer un análisis estratificado. Cabe agregar que el deterioro del estado nutricional de las pacientes del grupo DAI podría explicarse por los niveles de PCR. Si bien estas pacientes aún no tenían desnutrición, se sabe que la inflamación es un indicador de un incremento en las necesidades energéticas, y consecuentemente un factor de riesgo para el desarrollo de desnutrición [49, 131]. En cuanto a los resultados del T5, si la dieta realmente fue la responsable de la modulación de la PCR en el grupo DAI y los resultados continuan bajo el mismo patrón, podríamos lograr la recuperación del estado nutricional de la mayoría de las pacientes que presenten alteraciones de la PCR previas al tratamiento.

En cuanto al desarrollo de la xerostomía, ésta puede deberse a que las pacientes en el brazo DBR en el T4 presentaban una menor ingesta de agua natural que podrían haber sido persistente por varias semanas más; asimismo, recordar que esta dieta limita el consumo de frutas y verduras (por la fibra), lo que estaría reduciendo la ingesta del agua presente en las mismas, e incrementa el consumo de cereales, cuyo contenido de agua es más bajo [132].

Hace falta incrementar el tamaño de la muestra para confirmar lo hallazgos del presente estudio. Es necesario mejorar el apego en ambos brazos, pero principalmente el de las pacientes de DBR que presenten elevación de la PCR para observar el comportamiento del estado nutricional, así como el

desarrollo y recuperación de las toxicidades gastrointestinales. Se requieren intervenciones dietéticas más largas que permitan conocer el efecto de la dieta sobre el desarrollo de toxicidades tardías como la proctopatía por radiación; en dichas intervenciones sería conveniente considerar marcadores inflamatorios desde el proceso de aleatorización para obtener mejores resultados. Además, sería importante considerar la medición de la composición corporal y la calidad de vida antes, durante y después del tratamiento. Aunque ya hay estudios que exploran los cambios en la microbiota durante el tratamiento con RT, sería importante explorar más a profundidad la capacidad de la dieta para aminorar aquellos cambios que impactan negativamente.

15 CONCLUSIONES

De acuerdo con los resultados del presente estudio, la DBR ayuda a prevenir la desnutrición; sin embargo, se observó con mayor frecuencia la persistencia de las toxicidades gastrointestionales meses después de haber finalizado el tratamiento oncológico. Además, había una tendencia a incrementar la inflamación medida por PCR. Por otra parte, aunque en el grupo DAI se observó una mayor incidencia de desnutrición en el T3, para el T5 todas las pacientes se recuperaron, un mínimo porcentaje presentó toxicidades gastrointestinales y se observó una tendencia a disminuir la inflamación. Por todo lo anterior, se puede concluir que la intervención con una DAI podría ayudar a modular parámetros inflamatorios como la PCR y a aminorar las toxicidades gastrointestinales. El consumo de altas cantidades de fibra a lo largo de todo el tratamiento y después del mismo no impactan sobre el desarrollo de diarrea o alguna otra toxicidad gastrointestinal, por lo que la DAI es benéfica y segura para su uso antes, durante y después del tratamiento oncológico.

Cabe agregar que el apego a las intervenciones nutricionales es crucial para prevenir la desnutrición de las pacientes bajo tratamiento con QT/RT.

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17 ANEXOS

ANEXO 1: ALIMENTOS CON ALTO CONTENIDO DE FIBRA SOLUBLE

CONTENIDO DE FIBRA EN 100g DE DIFERENTES ALIMENTOS

FRUTAS	FIBRA SOLUBLE	FIBRA INSOLUBLE	FIBRA TOTAL
Aguacate	1.25	5.48	6.72
Ciruela	1.12	1.76	2.87
Ciruela pasa	4.5	3.63	8.13
Durazno con piel	1.31	1.54	2.85
Durazno sin piel	0.84	1.16	2
Fresas	0.6	1.7	2.30
Guayaba	1.54	11.81	12.72
Kiwi	0.8	2.61	3.39
Mandarina	0.4	1.4	1.8
Mango	0.69	1.08	1.76
Manzana	0.67	1.54	2.21
Manzana sin cáscara	0.6	1.29	1.89
Melocotón	0.84	1.16	2
Naranja	1.37	0.99	2.35
Nectarina	0.98	1.06	2.04
Papaya	0.89	0.9	1.8
Pasas	0.9	2.17	3.07
Pera	0.92	2.25	3.16
Piña	0.04	1.42	1.46
Plátano	0.58	1.21	1.79
pomelo	0.58	0.32	0.89
Sandía	0.13	0.27	0.4
Uvas verdes	0.58	0.32	0.9

Fuente: Li, B. W., Andrews, K. W., & Pehrsson, P. R. (2002). Individual sugars, soluble, and insoluble dietary fiber contents of 70 high consumption foods. Journal of food composition and analysis, 15(6), 715-723.

ANEXO 1: ALIMENTOS CON ALTO CONTENIDO DE FIBRA SOLUBLE

CONTENIDO DE FIBRA EN 100g DE DIFERENTES ALIMENTOS

VEGETALES COCIDOS	**FIBRA SOLUBLE**	**FIBRA INSOLUBLE**	**FIBRA TOTAL**
Brócoli	1.85	2.81	4.66
Chícharos verdes	0.94	2.61	3.54
Ejotes	1.85	2.81	4.66
Habas verdes	1.02	4.21	5.23
Maíz amarillo	1.58	2.29	3.87
Nopal	0.82	2.68	3.5
Zanahorias	1.58	2.28	3.87
VEGETALES CRUDOS			
Brócoli	0.44	3.06	3.5
Berenjena	1.3	5.3	6.6
Cebolla	0.71	1.22	1.93
Col	0.46	1.79	2.24
Coliflor	0.47	2.15	2.62
Espinacas	0.77	2.43	3.2
Lechuga	0.1	0.88	0.98
Nopal	0.6	2.4	3
Pepino con cáscara	0.2	0.94	1.14
Pimiento verde	0.53	0.99	1.52
Tomate rojo	0.15	1.19	1.34
Tomate verde	0.1	1	1.1
Zanahoria	0.49	2.39	2.88

Fuentes: Spiller, G. A. (Ed.). (2001). CRC handbook of dietary fiber in human nutrition. CRC Press. Méndez, L.P., Flores, F.T., Martín, J.D., Rodríguez-Rodríguez, E.M., Romero, C.D., Physicochemical characterization of cactus pads from Opuntia dillenii and Opuntia ficus indica, Food Chemistry (2015)

ANEXO 1: ALIMENTOS CON ALTO CONTENIDO DE FIBRA SOLUBLE

CONTENIDO DE FIBRA EN 100g DE DIFERENTES ALIMENTOS

CEREALES Y TUBÉRCULOS	**FIBRA SOLUBLE**	**FIBRA INSOLUBLE**	**FIBRA TOTAL**
Amaranto	4.86	10.33	15.2
Avena	3.8	6.5	10.3
Arroz cocido	0	0.7	0.7
Camote	1.1	1.89	3
Papas hervidas	0.99	1.06	2.05
Papas horneadas	0.61	1.7	2.31
Tortilla	0.03	5.89	5.92
SEMILLAS			
Almendras	1.1	10.1	11.2
Cacahuate tostado	0.5	7.5	8
Chía	6.5	33.8	40.3
Linaza	12.18	10.15	22.18
Nueces	1.8	7.19	9

Fuentes: Spiller, G. A. (Ed.). (2001). CRC handbook of dietary fiber in human nutrition. CRC Press. Reyes-Caudillo, E., Tecante, A., & Valdivia-López, M. A. (2008). Dietary fibre content and antioxidant activity of phenolic compounds present in Mexican chia (Salvia hispanica L.) seeds. Food Chemistry, 107(2), 656-663.

ANEXO 2: ALIMENTOS CON ALTO CONTENIDO DE ÁCIDOS GRASOS POLIINSATURADOS

ALIMENTO	AGPI n-6		AGPI n-3		
	AL (18L:2)	AA (20:4)	ALN (18L:3)	EPA (20:5)	DHA (20.6)
Atún			-	0.1	0.4
Bacalao			<0.05	0.1	0.1
Margarina	5.2	0	0.34	0.36	0.52
Yema de huevo	3.5	0.4	0.10	0.01	0.11
Sardina	0.05	0	0.02	0.12	0.57
Salmón	0.22	0.26	0.13	0.67	1.96
Aceite de bacalao	2.2	1.2	1.5	6.89	10.9
Aguacate	1.67	0	0.1	0	0
Aceite de canola	19.2	0	7.9	0	0
Aceite de cártamo	74.1	0	0	0	0
Aceite de girasol	65.7	0	0	0	0
Aceite de maíz	58	0	0.7	0	0
Aceite de oliva	7.9	0	0.6	0	0
Aceite de soya	51	0	6.8	0	0
Ajonjolí	23.2	0	2.0	0	0
Almendras	12.21	0	0	0	0
Cacahuate	15.7	0	0.003	0	0
Chía	5.8	0.7	16.3		
Linaza	4.3	0	18.1	0	0
Nuez de castilla	38		9		
Pistache	14		0.26		

AGPI= ácido graso poliinsaturado
AL=ácido linoleico
AA=ácido araquidónico
ALN= ácido alfa linolénico
EPA= ácido graso eicosapentaenoico
DHA=ácido graso docosahexaenoico

Mataix J. Lípidos alimentarios. en Libro Blanco de los omega-3 Mataix J, Gil A editores 2004; Ed. Panamericana:14-32.

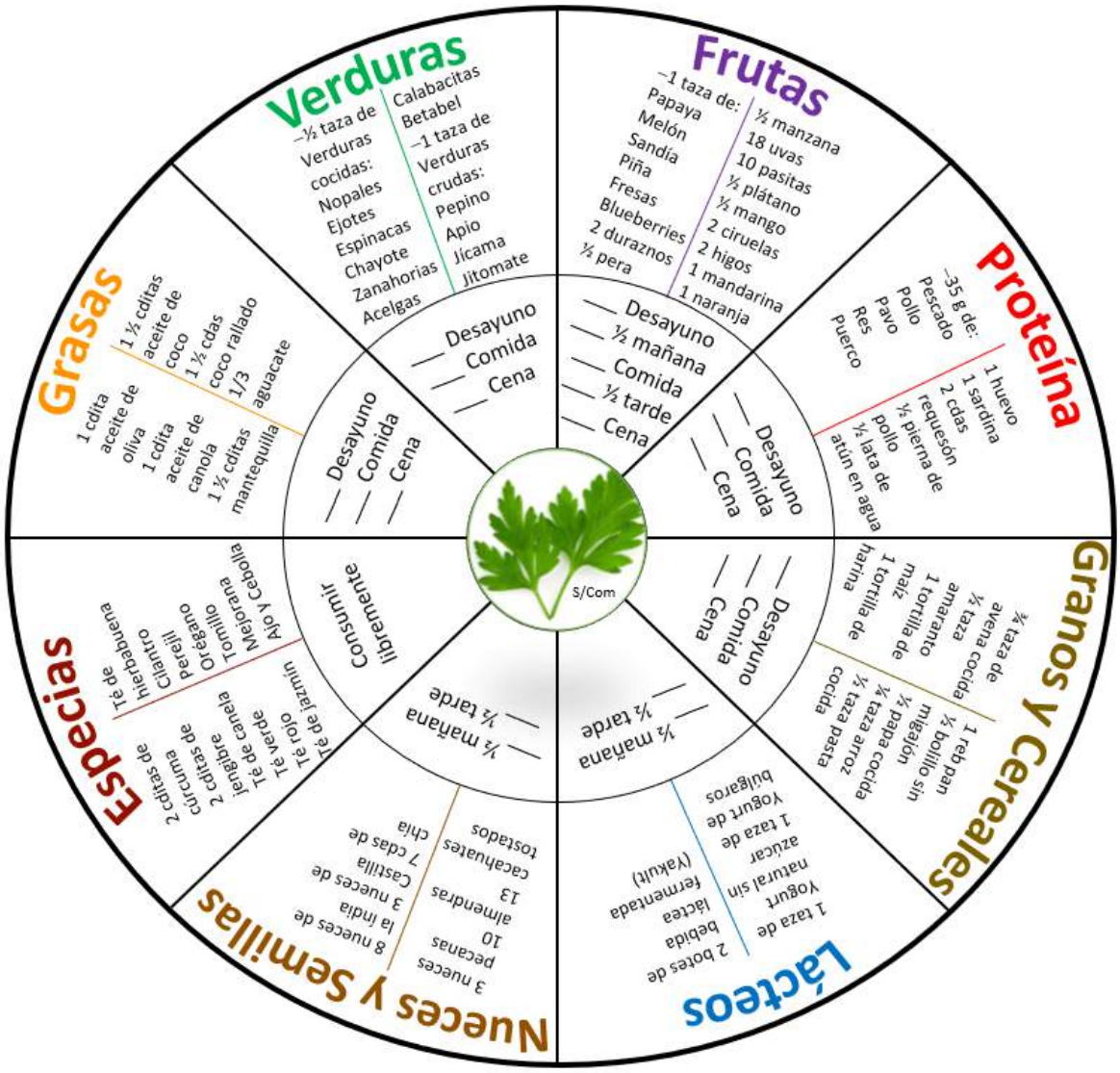
ANEXO 3: ALIMENTOS CON ALTO CONTENIDO DE FLAVONOIDES (POLIFENOLES)

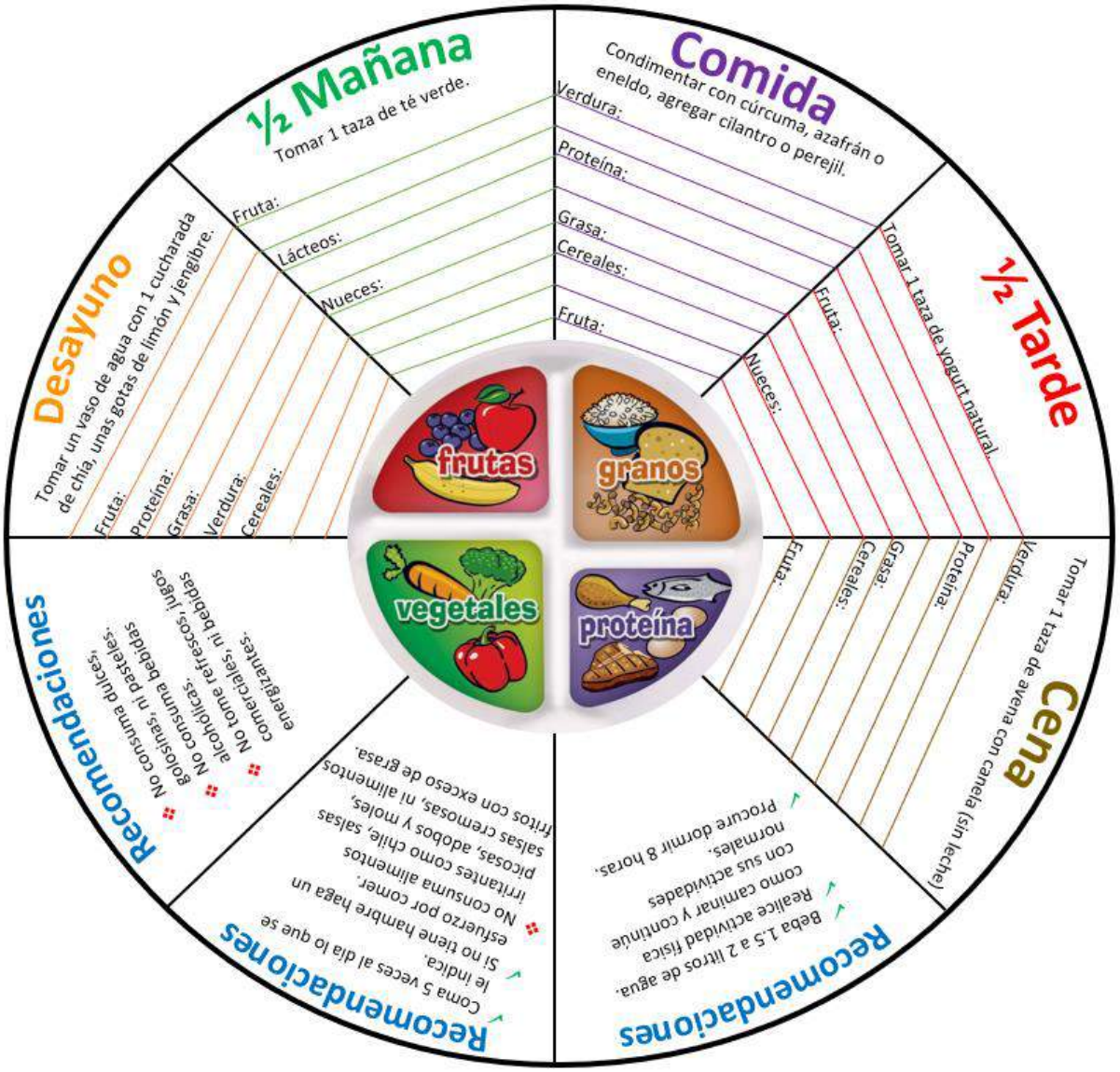
ALIMENTO	mg/100g	Flavanonas	Flavonas	Flavonoles	Antocianidinas	Flavan-3-ols	Isoflavonas
ESPECIAS Y YERBAS							
Alcaparras (lata)	303.89			303.89			
Alcaparras	493.01			493.01			
Azafrán	205.48			205.48			
Cebollín	17.11	0	0	17.11			
Eneldo	112.68	0	0	112.68			
Estragón	27	0	1	26			
Menta fresca	58.13	40.08	18.05	0			
Orégano fresco	34.5	0	25.1	9.4			
Orégano seco	1504.79	417.33	1045.46	42			
Perejil seco	4854.49		4523.25	331.24			
Romero fresco	27.41	24.86	2.55	0			
Tomillo	47.75	0	47.75	0			
FRUTAS							
Aceitunas verdes enlatadas	0.56		0.56			0	
Arándanos	246.35			4.13	242.22		
Chabacano	10.67		0	2.26		8.41	
Ciruela Davidson	48.96				48.96		
Ciruela Illawara	558.19				558.19		
Ciruela Roja	9.82		0.02	1.81	7.99		
Ciruela morada	25.33			2.19	23.14		
Ciruela negra diamante	69.72	0	0.6	13.07	56.05		
Ciruela Prunus spp.	14.42	0	0	0.9	5.94	7.58	
Durazno	11.1	0	0	0.88	1.92	8.3	
Frambuesas	55.57	0	0	1.11	48.63	5.83	
Frambuesa molucca	94.24				94.24		
Frambuesas negras	683.79				683.79		
Frambuesas rojas congeladas	25.39		0.03	1.14	24.22		
Fresas	33.52	0.26	0	1.65	27.01	4.6	
Jugo de limón	21.12	20.73	0	0.39		0	
Jugo de naranja	14.56	14.26	0	0.3	0		
Lima	46.8	46.4	0.4				
Limón sin cáscara	52.83	49.26	1.9	1.67			
Mandarinas	17.96	17.96	0	0			
Mango	0						
Manzana fuji	19.86	0	0.01	2.36	0.81	16.68	
Manzana gala	13.23	0	0	3.8	1.22	8.21	
Manzana golden	9.74	0	0	3.69	0	6.05	
Manzana malus doméstica	15.15	0	0.12	4.15	1.59	9.29	
Manzana red delicious	18.21	0	0.01	0.87	5	12.33	
Mora	147.63	0	0	4.52	100.61	42.5	
Mora azul	174.13	0	0.2	10.63	163.3		
Mora azul congelada	103.56		1.81	7.5	94.25		
Naranja	43.49	42.57	0.19	0.73		0	

Pomelo	33.12	33.12					
Uva blanca	21.98	21.98	0	0			
Uva blanca o verde	7.11		0	1.4		5.71	
Uva Concord	125.35			3.11	120.1	2.14	
Uva roja	52.42		1.3	1.05	48.04	2.03	
Uva rosa y roja	33.94	32.99	0.6	0.35	0	0	
Uva negra	24.02		0	2.39		21.63	
VERDURAS							
Acelga suiza roja	25.6		18.9			6.7	
Acelga suiza blanca	12.6			11.1		1.5	
Alcachofas	22.28	12.5	9.78				
Arúgula	47.11		0	47.11	0		
Berngena cruda	85.73		0	0.04	85.69	0	
Berros	53.05	0	0.03	53.02			
Berros de jardín	14	0	0	14			
Brócoli crudo	11.96	0	0.8	11.16	0	0	
Cebolla blanca	6.66		0	6.66	0		
Cebolla blanca cocida	10.55			10.55			
Cebolla morada	56.61		0.4	46.65	9.56		
Cilantro	52.9	0	0	52.9			
Col morada cocida	39.38				39.38		
Col morada cruda	210.67		0.16	0.56	209.95	0	
Col rizada	22.9		0	22.9			
Corazones de apio verde	22.6		22.6				
Cúrcuma	6.96			6.96			
Endivia	10.1		0	10.1		0	
Espárragos cocidos	15.15			15.15			
Espárragos crudos	20.07			20.07			
Espinaca fresca	11.44		0.74	10.7			
Jengibre	33.6			33.6			
Lechuga de hoja roja	11.72	0	0.95	7.63	3.14	0	
Habas verdes cocidas	20.63					20.63	
Habas verdes crudas	67.47		0	4.6		62.87	
Hinojo	84.5		0.1	84.4			
Lechuga orejona cruda	22.51			22.51			
Perejil fresco	233.16	0	216.55	16.61			
Rábano	63.96	0	0	0.83	63.13	0	
NUECES Y SEMILLAS							
Cacahuate						0.66	0.26
Chía	30.72			30.72			
Nueces pecanas	34.01	0	0	0	18.02	15.99	
Pistaches	15.64	0	0	1.46	7.33	6.85	
Linaza							0
BEBIDAS							
Cocoa en polvo	54.76			2.03		52.73	
Té blanco	69.45					69.45	
Té frutal	10.25					10.25	
Té negro preparado	57.19		0	4.51		52.68	
Té verde	137.93		0.3	4.82		132.81	0.05
Té verde descafeinado	62.05			4.77		57.28	
LEGUMINOSAS							
Frijoles				2.92	0.06		0

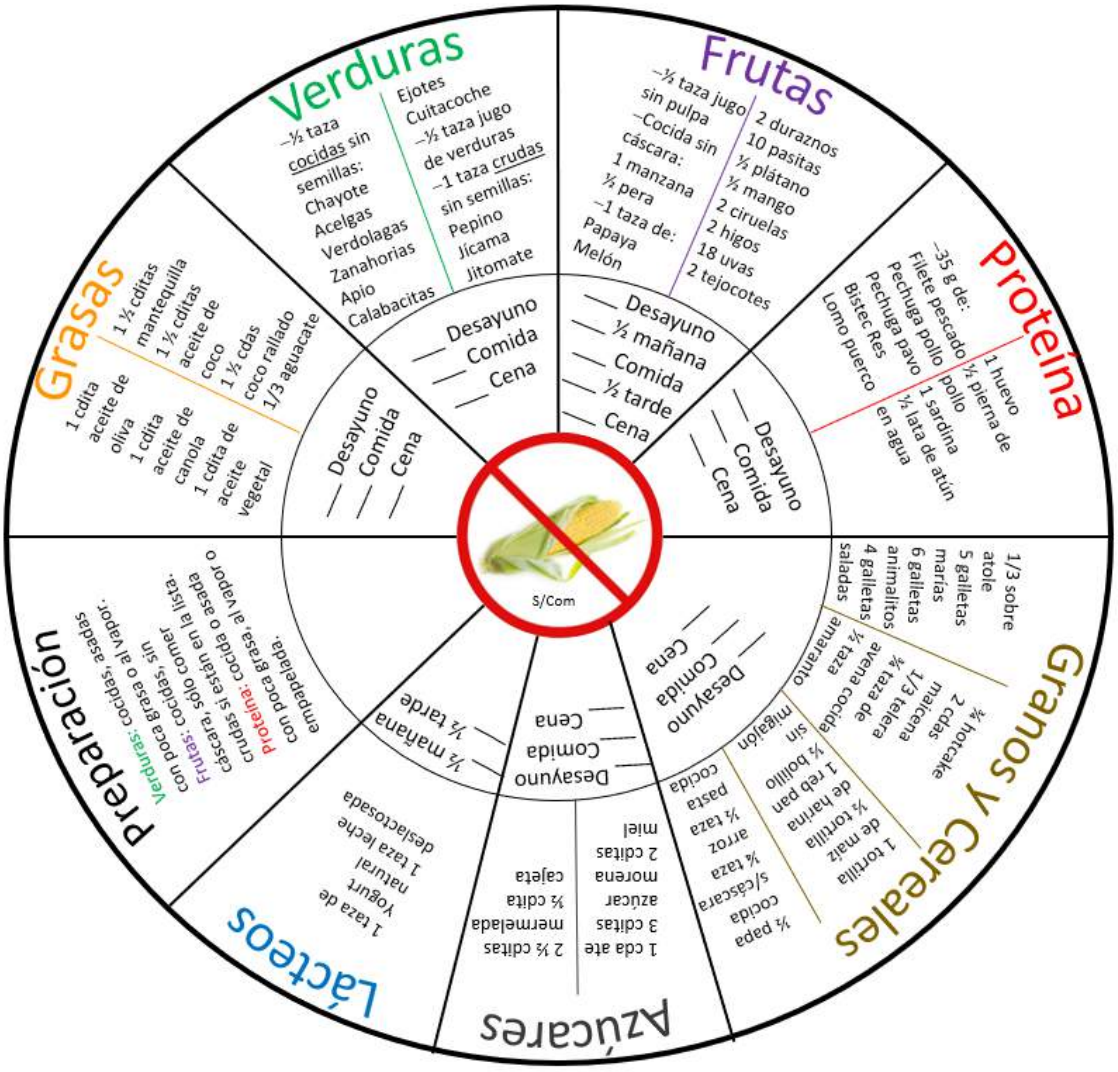
Fuente: Bhagwat, S., Haytowitz, D. B., & Holden, J. M. (2011). USDA database for the flavonoid content of selected foods, Release 3.1. *Beltsville: US Department of Agriculture*, 03-1. United States Department of Agriculture. "USDA-Iowa State University Database on the Isoflavone Content of Foods, Release 1.4-2007." (2007).

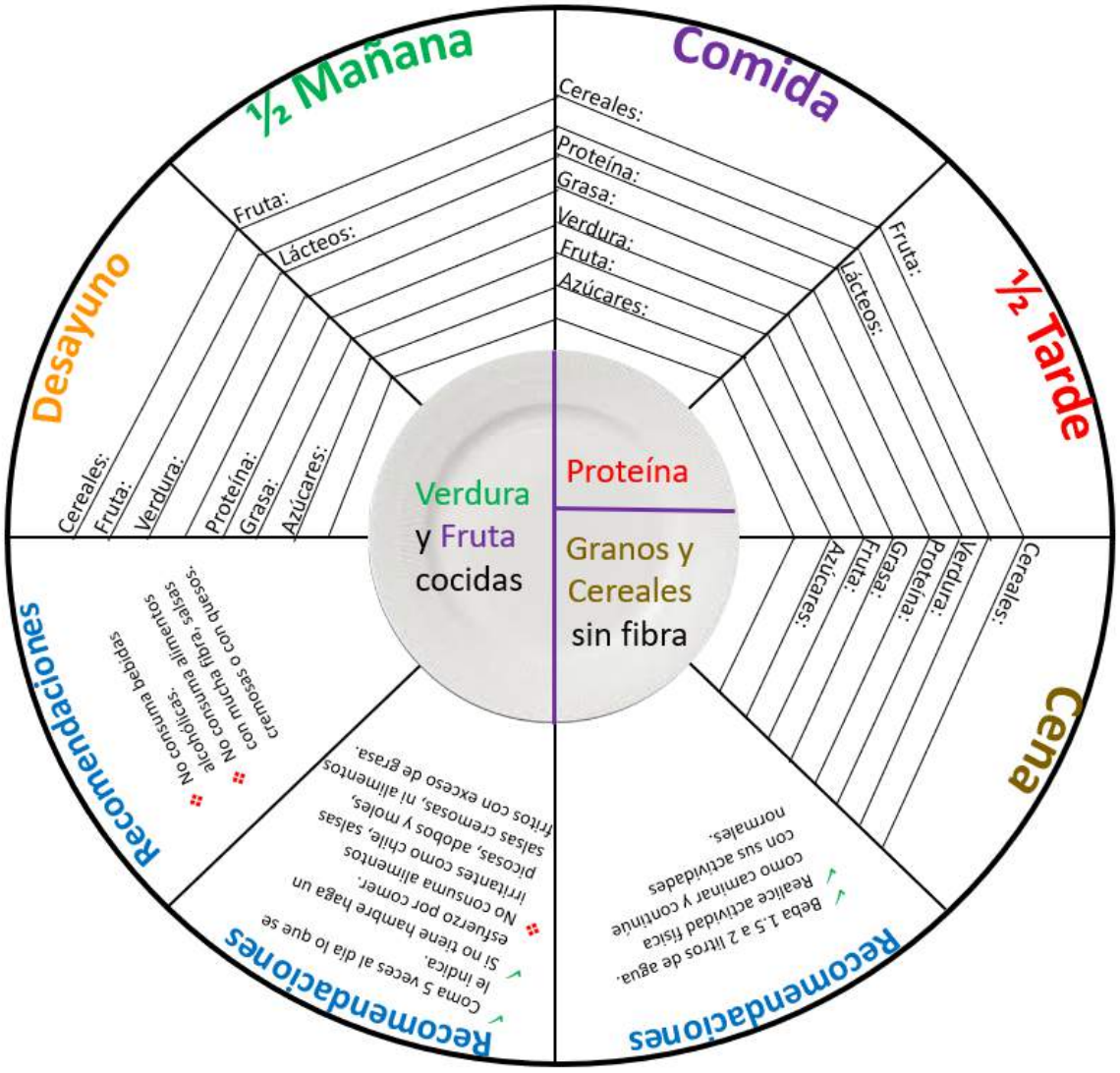
ANEXO 4: FORMATO PARA EL PLAN DE ALIMENTACIÓN DE LA DIETA ANTI-INFLAMATORIA




½ Mañana
Tomar 1 taza de té verde.
Fruta:
Lácteos:
Nueces:
Comida
Condimentar con cúrcuma, azafrán o eneldo, agregar cilantro o perejil.
Verdura:
Proteína:
Grasa:
Cereales:
Fruta:
½ Tarde
Tomar 1 taza de yogurt natural.
Fruta:
Nueces:
Cena
Tomar 1 taza de avena con canela (sin lecher
Verdura.
Proteína.
Grasa.
Cereales.
Fruta.
Desayuno
Tomar un vaso de agua con 1 cucharada de chía, unas gotas de limón y jengibre.
Fruta:
Proteína:
Grasa:
Verdura:
Cereales:
frutas
granos
vegetales
proteína
Recomendaciones
Beba 1.5 a 2 litros de agua.
Realice actividad física como caminar y continúe con sus actividades normales.
Procure dormir 8 horas.
Recomendaciones
Coma 5 veces al día lo que se le indica.
Si no tiene hambre haga un esfuerzo por comer.
No consuma alimentos irritantes como chile, salsas picosas, adobos y moles, salsas cremosas, ni alimentos fritos con exceso de grasa.
Recomendaciones
No consuma dulces, bolosinas, ni pasteles.
No consuma bebidas alcohólicas.
No tome refrescos, jugos comerciales, ni bebidas energéticantes.

ANEXO 5: FORMATO PARA EL PLAN DE ALIMENTACIÓN DE LA DIETA BAJA EN RESIDUO




½ Mañana
Comida
½ Tarde
Cena
Recomendaciones
Recomendaciones
Recomendaciones
Desayuno
Cereales:
Proteína:
Grasa:
Verdura:
Fruta:
Azúcares:
Fruta:
Lácteos:
Cereales:
Fruta:
Verdura:
Proteína:
Grasa:
Azúcares:
Fruta:
Lácteos:
Cereales:
Verdura:
Proteína:
Grasa:
Azúcares:
Verdura y Fruta cocidas
Proteína
Granos y Cereales sin fibra
Beba 1.5 a 2 litros de agua.
Realice actividad física como caminar y continúe con sus actividades normales.
Coma 5 veces al día lo que se le indica.
Si no tiene hambre haga un esfuerzo por comer.
No consuma alimentos irritantes como chile, salsas picosas, adobos y moles, salsas cremosas, ni alimentos fritos con exceso de grasa.
No consuma bebidas alcohólicas.
No consuma alimentos con mucha fibra, salsas cremosas o con quesos.

ANEXO 6: VALORACIÓN GLOBAL SUBJETIVA GENERADA POR EL PACIENTE

VALORACION GLOBAL SUBJETIVA GENERADA POR EL PACIENTE

Por favor, conteste al siguiente formulario escribiendo los datos que se le piden o señalando la opción correcta, cuando se le ofrecen varias

Nombre y Apellidos ____________________

Edad ____ años

Fecha / /

PESO actual ________kg
Peso hace 3 meses ________kg

ALIMENTACIÓN respecto hace 1 mes:
- como más
- como igual
- como menos

Tipo de alimentos:
- dieta normal
- pocos sólidos
- sólo líquidos
- sólo preparados nutricionales
- muy poco

ACTIVIDAD COTIDIANA en el último mes:
- normal
- menor de lo habitual
- sin ganas de nada
- paso más de la mitad del día en cama o sentado

DIFICULTADES PARA ALIMENTARSE:
- SÍ
- NO

Si la respuesta era SÍ, señale cuál / cuáles de los siguientes problemas presenta:
- falta de apetito
- ganas de vomitar
- vómitos
- estreñimiento
- diarrea
- olores desagradables
- los alimentos no tienen sabor
- sabores desagradables
- me siento lleno enseguida
- dificultad para tragar
- problemas dentales
- dolor. ¿Dónde? ____________________
- depresión
- problemas económicos

Muchas gracias. A partir de aquí, lo completará su Médico

ENFERMEDADES: ____________________

TRATAMIENTO ONCOLÓGICO: ____________________

OTROS TRATAMIENTOS: ____________________

ALBÚMINA antes de tratamiento oncológico:
_____ g/dl

PREALBÚMINA tras el tratamiento oncológico:
_____ mg/dl

EXPLORACIÓN FÍSICA:

Pérdida de tejido adiposo:
- SÍ. Grado ________
- NO

Pérdida de masa muscular:
- SÍ. Grado ________
- NO

Edemas y/o ascitis:
- SÍ. Grado ________
- NO

Úlceras por presión: SÍ NO

Fiebre: SÍ NO

VALORACIÓN GLOBAL, teniendo en cuenta el formulario, señale lo que corresponda a cada dato clínico para realizar la evaluación final:

DATO CLÍNICO	A	B	C
Pérdida de peso	<5%	5-10%	>10%
Alimentación	Normal	deterioro leve-moderado	deterioro grave
Impedimentos para ingesta	NO	leves-moderados	graves
Deterioro de actividad	NO	leve-moderado	grave
Edad	65	>65	>65
Úlceras por presión	NO	NO	SI
Fiebre / corticoides	NO	leve / moderada	elevada
Tto. antineoplásico	bajo riesgo	medio riesgo	alto riesgo
Pérdida adiposa	NO	leve / moderada	elevada
Pérdida muscular	NO	leve / moderada	elevada
Edemas / ascitis	NO	leve / moderados	importantes
Albúmina (previa al tto)	>3,5	3'0-3,5	<3,0
Prealbúmina (tras tto)	>18	15-18	<15

VALORACIÓN GLOBAL,

A: buen estado nutricional

B: malnutrición moderada o riesgo de malnutrición

C: malnutrición grave

ANEXO 9: Criterios de terminología común para los eventos adversos V.5

EFECTO ADVERSO	1	2	3	4	5
1.-Náusea*	Pérdida del apetito sin alteración en el consumo de alimentos.	Disminución del consumo de alimentos, sin pérdida de peso significativa, deshidratación o malnutrición.	Inadecuado consumo de líquidos o alimentos. Alimentación por sonda, NPT u hospitalización.		
2.-Vómito*	Sin indicación de intervención.	Indicación de hidratación IV; intervención médica indicada.	Alimentación por sonda, NPT u hospitalización.	Consecuencias en las actividades de la vida diaria.	MTE
3.-Anorexia*	Pérdida del apetito sin alteración en el consumo de alimentos.	Pérdida del apetito con alteración en el consumo de alimentos. Sin pérdida significativa de peso o desnutrición. Indicar suplementación.	Asociado con pérdida significativa de peso o desnutrición. Indicación de alimentación por sonda o NE.	Consecuencias peligrosas para la vida; intervención urgente indicada.	MTE
4.-Disgeusia*	Alteración del sentido del gusto sin cambios en la alimentación.	Alteración del sentido del gusto con cambios en la alimentación; sabor nocivo o desagradable; pérdida del gusto.			
5.-Disfagia	Sintomático, capaz de consumir una dieta normal.	Sintomático, con alteraciones en el consumo de alimentos y la habilidad para tragar.	Alteraciones severas en el consumo de alimentos y la habilidad para tragar; indicación de alimentación por sonda, NPT u hospitalización.	Consecuencias peligrosas para la vida; intervención urgente indicada.	MTE
6.-Xerostomía*	Sintomático sin alteración en el consumo de alimentos.	Síntomas moderados, alteración del consumo de alimentos.	Incapaz de alimentarse por vía oral. Indicación de alimentación por sonda o NE.		
7.-Diarrea*	Incremento de hasta 3 evacuaciones al día sobre la basal.	Incremento de 4 a 6 evacuaciones al día sobre la basal. Leve aumento en la producción de ostomía respecto al valor basal.	7 o más evacuaciones al día sobre la basal; aumento grave de la salida de ostomía respecto al valor basal. Indicación de hospitalización.	Consecuencias en las actividades de la vida diaria.	MTE

8.-Estreñimiento*	Con síntomas y uso de medicamentos de manera ocasional.	Síntomas persistentes, con uso regular de laxantes o enemas.	Estreñimiento con evacuación manual indicada.	Requiere intervención urgente. Consecuencias en actividades de la vida diaria.	MTE
9.-Distensión abdominal*	Asintomático, sólo observaciones clínicas o de diagnóstico; la intervención no se indica.	Sintomático.	Severo disconfort.		
10.- Dolor abdominal*	Dolor leve.	Dolor moderado.	Dolor severo.		
11.-Saciedad temprana*	Sensación de estar lleno antes de lo normal.				

MTE: Muerte.

*Adaptado de “Common Terminology Criteria for Adverse Event” (CTCAE) V.5.

ANEXO 10: APEGO A LA DIETA

	T1	T2		T3		T4		T5	
	Indicación	Consumido	%	Consumido	%	Consumido	%	Consumido	%
Energía (kcal)									
Proteínas (g)									
Lípidos (g)									
H de C (g)									
Agua (L)									
Fibra (g)									
Lactosa (mg)									
AG Ω3 (porción)									
Probiótico (porción)									
Polifenoles (porción)									
Apego promedio									

ANEXO 11: CONSENTIMIENTO INFORMADO

INFORMACIÓN Y CONSENTIMIENTO INFORMADO PARA EL PACIENTE QUE PARTICIPA EN EL PROTOCOLO DE INVESTIGACIÓN

Título: Efecto de una dieta anti-inflamatoria sobre el estado de nutrición y expresión de citocinas en pacientes con cáncer cervicouterino localmente avanzado: Ensayo clínico aleatorizado.

1. **Datos del investigador.**

Nombre: Dra. Angel Denisse Castro Eguiluz
Teléfono: Celular 044 55 41940650
Ubicación: Cubículo 1, Edificio "La Herradura." Instituto Nacional de Cancerología. Av. San Fernando, número 22, delegación Tlalpan México, D.F.
Correo: angeldenisse@gmail.com

En caso de tener dudas sobre sus derechos por participar en un estudio de investigación, puede contactar al Comité de Ética en Investigación con la Dra. Myrna Candelaria Hernández y/o Dra. Alejandra Monroy, Presidente y Secretario respectivamente, al tel. 56280400, extensión 37015.

2. **Participación voluntaria.**

Por medio de este documento se expresa que su participación en el presente estudio es totalmente voluntaria y el negarse a participar no influirá en su tratamiento al que tiene derecho como paciente del INCan. Asi mismo, la paciente recibirá respuesta a cualquier pregunta, duda u aclaración acerca de los procedimientos, riesgos, beneficios y otros asuntos relacionados con la investigación y el tratamiento.

Es posible que el presente formulario de consentimiento contenga palabras o información con las que no está familiarizada. Por favor solicite al doctor del estudio o al personal del mismo, que le explique cualquier palabra o información que no comprenda con claridad. Puede llevar consigo una copia, sin firmas, de este formato de consentimiento para leerlo con más detenimiento y considere su participación, así como conversar con su familia o amigos antes de tomar una decisión.

Cabe señalar el compromiso de proporcionarle información actualizada obtenida durante el estudio.

Su médico le ha diagnosticado con cáncer cervicouterino. Le estamos invitando a participar en una investigación para saber si una dieta "anti-inflamatoria" puede ayudar a las pacientes con cáncer cervicouterino a mejorar su nutrición, disminuir algunos síntomas de toxicidades gastrointestinales (causadas por el tratamiento para combatir el cáncer) como la diarrea o el estreñimiento, y que su calidad de vida sea mejor.

Esta dieta anti-inflamatoria es una dieta que consiste en cubrir todas las necesidades de energía y nutrientes que cada paciente necesita, en forma personal, para evitar que pierda peso o se desnutra; además se recomendarán alimentos que tienen propiedades que se sabe que ayudan a disminuir la inflamación (pero que no se han hecho estudios como este para comprobarlo) y a mejorar la salud del intestino, como por ejemplo la fibra y las vitaminas, con el propósito de disminuir los síntomas intestinales para que se sientan mejor, puedan comer lo que necesitan y para que no se desnutran, y además toleren mejor el tratamiento.

Se espera que participen 156 mujeres con cáncer cervicouterino. Su participación es absolutamente voluntaria y no afectará su atención médica.

3. Justificación y propósito del estudio.

Debido a que el tratamiento para el cáncer no es selectivo, algunas partes del cuerpo se pueden dañar, como por ejemplo el intestino; al ocurrir esto se pueden dar malestares como náuseas, diarrea, estreñimiento, inflamación, dolor, y otros síntomas que en conjunto son conocidos como toxicidad gastrointestinal, que además podrían impactar la calidad con la que hace sus actividades del día a día (calidad de vida). Nosotros creemos que la dieta anti-inflamatoria, al incluir alimentos con propiedades nutritivas y anti-inflamatorias, podría ayudar a que esa inflamación intestinal no sea tan intensa, otro de los beneficios de esta dieta es su alto contenido de fibra soluble, esta fibra es particularmente especial porque al entrar en contacto con el agua forma una especie de gel, por lo que al consumirla podría ayudar a disminuir tanto la diarrea como el estreñimiento, en caso de que se presentara alguno.

La dieta anti-inflamatoria se va a comparar con una dieta baja en residuo. La dieta baja en residuo consiste en disminuir la cantidad de grasas, fibra y lactosa (que es el azúcar de la leche), para evitar la diarrea. Con esta dieta también se van a cubrir las necesidades de energía y nutrientes que cada paciente necesita.

Nuestro objetivo principal es evaluar el efecto de la dieta anti-inflamatoria, en comparación con la dieta baja en residuo, en el estado de nutrición, malestares de toxicidad intestinal, y la cantidad de algunas proteínas que se producen cuando hay inflamación y que se miden en sangre y en heces (o popó), en pacientes con cáncer cervicouterino localmente avanzado.

Se van a incluir 78 pacientes en el grupo de dieta anti-inflamatoria y vamos a comparar con 78 pacientes que reciban la dieta baja en residuo. Cabe aclarar que el grupo al que usted será asignada se elige mediante el azar, por lo que no le podemos asegurar que le toque una u otra dieta.

4. Datos propios del procedimiento.

Cada paciente será evaluada en 5 visitas:

1. Dos semanas antes del inicio del tratamiento del cáncer.
2. Al inicio del tratamiento del cáncer.
3. En el tercer ciclo de quimioterapia.
4. Al finalizar la braquiterapia.
5. A los 3 meses de haber concluido el tratamiento del cáncer.

Durante estas visitas se le harán preguntas y mediciones para conocer su estado de nutrición. Se van a realizar mediciones del peso, la estatura, la cintura, y la fuerza de mano; además de que se le preguntará acerca de su alimentación y los malestares de toxicidad gastrointestinal que llegue a presentar.

Se le van a aplicar los siguientes cuestionarios:

1. Cuestionario de Valoración Global Subjetiva Generada por el Paciente. Este cuestionario se le va a aplicar para conocer si ha tenido cambios en su peso, en su alimentación y en sus hábitos, con el propósito de evaluar si usted se encuentra en riesgo de desarrollar desnutrición. La aplicación dura 10 minutos.
2. Cuestionario de calidad de vida EORTC QLQ-CX24. Este cuestionario se le va a aplicar para saber si ha tenido diferentes síntomas específicos del cáncer cervicouterino y del tratamiento que está recibiendo, que afecten su vida y le impidan hacer las actividades que normalmente hace. La aplicación dura de 10-15 minutos
3. Cuestionario de calidad de vida EORTC QLQ-C30. Este cuestionario se le va a aplicar para conocer si se han afectado sus actividades de día a día, y si ha tenido molestias o dificultades que le impidan hacer las cosas que regularmente hace. La aplicación dura de 10-15 minutos.

En las visitas 1, 3 y 5, se le tomará una muestra de sangre para medir algunas proteínas (llamadas citocinas) que el cuerpo produce cuando hay inflamación, y una muestra de heces (popó), para medir algunas proteínas que el intestino produce cuando hay inflamación.

En este estudio no se recolectarán y por ende no se analizarán muestras de tumores, por lo que tampoco serán empleadas para líneas celulares permanentes o inmortales.

¿Qué molestias causan estos procedimientos?

Las mediciones de peso, estatura, cintura y fuerza de mano no causan ninguna molestia.

La obtención de la muestra de sangre por punción venosa puede causar dolor, enrojecimiento, sangrado momentáneo y moretones en el sitio del piquete. En casos raros puede haber mareo o desmayo, en pocos casos llegan a haber infecciones de la piel.

La obtención de la muestra de heces (popó) se hará cuando vaya a defecar por la mañana y no causa ninguna molestia.

Tratamiento.

Una vez que su médico decida que va a recibir su tratamiento para el cáncer, que el investigador determine que usted puede participar en el estudio porque cumple con los requisitos, y si usted así lo consiente, iniciará con una evaluación de su estado de nutrición por parte del nutriólogo investigador.

¿En qué consiste el tratamiento del estudio?

El tratamiento consistirá en llevar una dieta anti-inflamatoria. El nutriólogo investigador le va a entregar su dieta por escrito, que va a estar diseñada específicamente para sus necesidades de energía y nutrientes. El nutriólogo platicará con usted para saber qué alimentos le gustan y qué alimentos puede conseguir, y anotará en su dieta escrita, varias opciones de alimentos que debe incluir, dentro de los que usted puede conseguir, que tienen propiedades nutritivas y que evitan la inflamación.

En caso de llevar la dieta baja en residuo, el nutriólogo también le entregará una dieta por escrito, diseñada para cubrir sus necesidades de energía y nutrientes, donde consumirá alimentos que tengan muy poca fibra, poca grasa y que no tengan leche, ni productos derivados de la leche.

En ambas dietas, se cubrirán los requerimientos y necesidades personales de cada paciente y serán calculados de la misma forma. El grupo al que usted será asignada se elige mediante el azar, por lo que no le podemos asegurar que le toque una u otra dieta.

La dieta debe comenzarla desde dos semanas antes de iniciar su tratamiento para el cáncer, y continuarla hasta 3 meses después de haber terminado su tratamiento para el cáncer.

5. Riesgos de participar en el estudio.

La dieta conlleva un riesgo mínimo. Solamente pudiera llegar a presentarse diarrea o estreñimiento, ablandamiento de heces y en algunas ocasiones gases en menos del 10% de las pacientes.

6. Beneficios por participar en este estudio.

A todas las pacientes del presente estudio se les indicará una dieta adecuada para conservar y/o mejorar el estado de nutrición, y se harán ajustes en la dieta de acuerdo con los síntomas que usted manifieste a lo largo del tratamiento.

¿Cuáles son los costos?

No habrá costos para usted por su participación en el estudio y tampoco pagará por las visitas al nutriólogo. En la dieta escrita que se le entregue, se recomendarán alimentos que se consumen frecuentemente por los mexicanos, que son accesibles y de bajo costo.

7. Procedimientos alternativos.

En caso de que decida no participar en este estudio, usted seguirá recibiendo su tratamiento para el cáncer que su médico oncólogo considere adecuado para usted. En caso de que llegue a presentar toxicidad gastrointestinal que le impida comer o desnutrición, su médico le indicará que haga una cita con la nutrióloga, dicha consulta no será parte del protocolo de investigación.

Además, usted o su representante legal será informado de manera oportuna si se dispone de nueva información que pueda ser relevante para su decisión de continuar participando en este estudio.

8. Responsabilidades del paciente.

Al firmar el consentimiento informado, usted se compromete a realizar todas las visitas estipuladas en el mismo, seguir la dieta propuesta, así como proporcionar información verídica de lo que se le solicite con el fin de obtener resultados reales de esta investigación. Finalmente, si usted firma el consentimiento y posteriormente decide ya no participar, tendrá la responsabilidad de informar al investigador principal o a uno de los colaboradores para cancelar su próxima cita y poder agendar a otra paciente.

Usted no debe participar en este estudio si está embarazada o pudiera estarlo. Es necesario realizar una prueba de embarazo antes de iniciar el estudio en todas las mujeres que pudieran quedar embarazadas. Usted deberá utilizar un método anticonceptivo efectivo en caso de estar en edad fértil.

9. Confidencialidad.

Toda la información que se genere de este estudio permanecerá confidencial. El grupo de investigadores, así como el monitor, auditor y las autoridades reguladoras, tendrán acceso a su expediente clínico, para la verificación de los procedimientos y datos del estudio. Los resultados serán capturados en una base de datos, donde usted no podrá ser identificado. Nadie conocerá los datos relativos a usted, sólo los resultados. Podremos publicar los resultados del estudio o presentarlos en reuniones profesionales, pero su nombre no se divulgará, ni se mencionará en ningún informe o publicación. No es posible que terceras personas, amigos, o allegados suyos sepan de su enfermedad y conozcan otras cosas únicas acerca de su edad, sexo o enfermedad que pudieran identificarlo a usted en una publicación.

Si tiene cualquier pregunta o inquietud acerca de sus derechos a la privacidad, contacte a la Dra. Myrna Gloria Candelaria Hernández, Presidente del Comité de Ética en Investigación al teléfono 01 (55) 5628-0400, extensión 37015.

No obstante, los Comités de Ética e Investigación del Instituto Nacional de Cancerología, así como las autoridades sanitarias (COFEPRIS) podrán revisar los documentos originales y su expediente con el fin de verificar la veracidad y calidad de la información.

10. Compensación.

Usted no recibirá remuneración alguna por su participación. En caso de tener algún efecto secundario al tratamiento administrado, recibirá tratamiento médico sin costo para usted.

11. Indemnizaciones y pago de eventos adversos.

El Instituto Nacional de Cancerología no cubrirá los gastos médicos de las lesiones no relacionadas con el tratamiento del estudio o que fueran atribuibles al desarrollo natural de cualquier enfermedad subyacente. El Instituto Nacional de Cancerología no proporcionará ningún otro tipo de indemnización. Si usted sufre algún efecto dañino o lesión, debe contactar a su doctor de inmediato.

12. Terminación del estudio.

Su participación en el estudio va a concluir en la quinta visita, que es 3 meses después de finalizada la braquiterapia, con una duración aproximada de 5 a 6 meses. Si usted o el investigador consideran necesario que usted salga del estudio, su participación podría durar menos.
Deberá informar al investigador si a lo largo del tratamiento resulta embarazada.

13. Contactos.

Mediante la firma del presente consentimiento y al aceptar participar en este estudio de investigación, usted no renuncia a ninguno de los derechos legales que de otra manera tendría como sujeto de una investigación. La firma del presente consentimiento no implica renunciar a alguno de sus derechos legales en virtud de la legislación mexicana. Si tiene dudas o preguntas acerca de sus derechos, puede ponerse en contacto con el Presidente del Comité de Ética en Investigación del Instituto Nacional de Cancerología, Dra. Myrna Gloria Candelaria Hernández, al teléfono 01 (55) 56280400, extensión 37015.

En caso de tener dudas acerca de este estudio o si se enferma durante o como resultado del producto de investigación, deberá llamar inmediatamente a la Dra. Lucely Cetina Pérez, al Instituto Nacional de Cancerología, teléfono 01 (55) 56280400 extensión 56101.

Si tiene dudas sobre sus derechos como un sujeto de estudio de investigación, puede llamar al Comité de Ética en Investigación del Instituto Nacional de Cancerología; al teléfono 01 (55) 56280400 extensión 37015. El Comité de Ética en investigación es un grupo de profesionales que evalúan los estudios de investigación y aseguran que su derechos y seguridad estén protegidos. Las leyes mexicanas tienen como requisito que un Comité de Ética en investigación revise y apruebe todas las investigaciones que implican la participación de seres humanos. La revisión y aprobación del estudio debe hacerse antes de que éste inicie. El estudio también será evaluado continuamente mientras se desarrolla.

Consentimiento.

Mediante la firma del presente formulario de consentimiento, estoy indicando que he leído y comprendo la información que se incluye en el mismo. He recibido respuestas aceptables a todas mis preguntas. Consiento voluntariamente mi participación en el proyecto **"Efecto de una dieta anti-inflamatoria sobre el estado de nutrición y expresión de citocinas en pacientes con cáncer cervicouterino localmente avanzado: Ensayo clínico aleatorizado."**

Comprendo que recibiré una copia del presente formulario de consentimiento con firma y fecha. Confirmo que he recibido un duplicado firmado de la información para el sujeto de investigación y el formulario de consentimiento.

5 Efecto de una dieta anti-inflamatoria sobre el estado de nutrición y expresión de citocinas en pacientes con cáncer cervicouterino localmente avanzado. Ensayo clínico aleatorizado, Versión 1, en español, con fecha del 1 de marzo de 2018.

Nombre del paciente en letra de imprenta

Firma de la paciente

Fecha

Testigos:

Nombre del testigo imparcial en letra de imprenta

Parentesco

Firma del testigo

Fecha

Dirección del testigo

Nombre del testigo imparcial en letra de imprenta

Parentesco

Firma del testigo

Fecha

Dirección del testigo

Certifico que, a mi leal saber y entender, la sujeto que firma el presente formulario de consentimiento ha recibido una explicación completa y cuidadosa de la investigación, y que comprende con claridad la naturaleza, riesgos y beneficios de la participación.

Nombre de la persona a cargo de la explicación del consentimiento en letra de imprenta

Firma de la persona a cargo de la explicación

Fecha del consentimiento

6 Efecto de una dieta anti-inflamatoria sobre el estado de nutrición y expresión de citocinas en pacientes con cáncer cervicouterino localmente avanzado. Ensayo clínico aleatorizado. Versión 1, en español, con fecha del 1 de marzo de 2018.

18 PUBLICACIONES DERIVADAS DE LA LÍNEA DE INVESTIGACIÓN

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

Journal of Human Nutrition and Dietetics

RESEARCH PAPER

Deterioration of nutritional status of patients with locally advanced cervical cancer during treatment with concomitant chemoradiotherapy

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Keywords
cancer cachexia, cervical cancer, malnutrition.

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Abstract

Background: In Mexico, 80% women with cervical cancer are diagnosed at locally advanced stages and are treated with concomitant chemoradiotherapy. The treatment modality and catabolic state confer a nutritional risk. The present study aimed to thoroughly evaluate the nutritional status and change in body composition of locally advanced cervical cancer (LACC) patients throughout treatment.

Methods: An observational prospective study, carried out at the Mexican National Cancer Institute, included 55 LACC patients. Nutritional status was evaluated before, during and after treatment, using anthropometric, dietary and biochemical measurements. Body composition was analysed using computed tomography images obtained at the time of diagnosis and approximately 4 months after treatment completion. Clinical outcomes were associated with changes in body composition.

Results: At the time of diagnosis, no patients were clinically malnourished, although 33.3% presented sarcopenia and most were overweight; by the end of treatment, 69% became clinically malnourished and 58% were sarcopenic. Average weight loss was 7.4 kg ($P = 0.001$). Adequacy of energy intake was reduced to 54%, obtained predominantly from carbohydrates. By the week 9, 62.8% patients became anemic and 34.5% had low albumin levels. Body composition analysis revealed that patients lost both, muscle and adipose tissues, although 27% patients were muscle depleted by the end of treatment. Patients who lost ≥10% skeletal muscle presented a higher tumour recurrence (hazard ratio = 2.957, $P = 0.006$) and a tendency towards diminished overall survival (hazard ratio = 2.572, not significant).

Conclusions: The nutritional status of cervical cancer patients deteriorates during treatment with concomitant chemoradiotherapy and, most importantly, muscle loss impacts the clinical outcome of patients.

Introduction

Cervical cancer is the third most frequently diagnosed cancer amongst women worldwide and the second amongst women in Mexico [(1)]. Eighty percent of women with cervical cancer arrive at the Mexican National Cancer Institute (INCan) with locally advanced stages. Concomitant treatment with cisplatin chemotherapy and radiotherapy followed by brachytherapy is the standard treatment [(2)] and this results in several symptoms that

confer a risk of malnutrition, including nausea, diarrhoea, tenesmus, abdominal cramps, urgency, mucus discharge, faecal urgency, loss of appetite and bleeding [3].

Several studies have proved an association of the patients' nutritional status with their quality of life and medical complications [4,5]. Unfortunately, most of these studies include heterogeneous groups regarding the type of tumour, treatment and nutritional evaluation tools used to determine the nutritional status. Most studies have used anthropometric and body composition measurements; however, different measurements, including anthropometric, dietary and biochemical evaluations, have not been used in conjunction to provide a complete nutritional diagnosis.

Malnutrition in cancer patients has a negative impact on their quality of life, response to treatment and overall survival [6–9]. Particularly, sarcopenia (and more so in the context of overweight and obesity) has been associated with higher toxicity to cancer treatment, shorter time to tumour progression and survival [10–14]. Recently, the body composition of cervical cancer patients using computed tomography (CT) images was reported, indicating an association of lower skeletal muscle index (SMI) and acute dose limiting toxicity, and with SMI loss during treatment being associated with worse overall survival [13,15,16].

In Mexico, 75.6% of the adult women population is overweight and obese [17]; therefore, it is most likely that a high proportion of LACC patients arrive at the INCan overweight and obese. These women may present sarcopenia masked with high adiposity and the combined effect of visceral adiposity derived inflammation and concomitant chemoradiotherapy may worsen the nutritional status and outcome of these patients. The fact that sarcopenic obesity is not clinically detectable because patients do not appear to be emaciated, poses an additional challenge to identify patients at higher risk of toxicity, complications and poor clinical outcome.

In this context, a systematic evaluation and nutritional intervention should be routine practice for all cancer patients. The INCan provides dietary recommendations of astringent foods to LACC patients during and after treatment with concomitant chemoradiotherapy, with the purpose of controlling gastrointestinal toxicity, and with particular attention to diarrhoea. This is a restrictive diet that may pose an additional risk to the development of malnutrition and nutrient deficiencies.

As far as we know, in Mexican LACC patients, a thorough nutritional evaluation, including body composition analysis, has not been assessed in response to concomitant treatment, nor has its impact on tumour recurrence and overall survival. Accordingly, to perform a complete nutritional evaluation, the present study considered that validated tools must be used and interpreted together to obtain a more precise and integral nutritional diagnosis.

The present study aimed to evaluate the nutritional status and body composition of LACC patients before, during and after treatment and identify the change in nutritional status and its impact on tumour recurrence and overall survival.

Materials and methods

Subjects

A longitudinal, prospective and descriptive study was performed to evaluate the change in nutritional status of Mexican women with LACC. Initially, 99 patients were eligible for the study (see Supporting information, Fig. S1). Eligibility criteria were: women recently diagnosed with LACC (Stages II and III); candidates receiving concomitant treatment with cisplatin-based chemoradiotherapy, followed by brachytherapy; a Karnofsky score of 80–100%; adequate hepatic function; and normal haematological results. Eighty-one patients were included in the study and received an initial nutritional evaluation. During the study, 26 patients were excluded. Reasons for exclusion were: a change in treatment because of additional radiotherapy requirements, patients deciding not to continue with the study, a delay in treatment, and death. In total, 55 subjects were included between 2013 and 2014. Anthropometric, biochemical and dietary assessments were carried out three times for each patient: 2 weeks before beginning of treatment (week −2); during treatment on the third chemotherapy cycle (week +3); and at the end of brachytherapy (week +9). For body composition analysis, we retrieved pre- and post-treatment CT scans from the institutional archiving system. Post-treatment images were acquired when they were available; the mean time was 4.4 months after treatment completion.

Informed written consent was obtained from all patients who agreed to participate in the study. The study was approved by the Ethics and Research Committees of the INCan (018/023/ICI) (CEI1247/18) and carried out according to the Declaration of Helsinki.

Cancer treatment and standardised dietary recommendations

Chemotherapy, based on cisplatin, was applied to ambulatory patients at a dosage of 40 mg m^{-2} body surface area, weekly for 6 weeks. External radiotherapy was administered to patients at four standard pelvic field points, using a total dosage of 50.4 Gy divided by 28 fractions of 1.8 Gy day^{-1} for 5 days a week. After completion of concomitant chemoradiotherapy, low-dose rate

brachytherapy was applied to the intracavitary area, using Fletcher-Suit-Delclos ovoids.

As part of the routine clinical treatment for cervical cancer patients, health professionals provide generalised dietary recommendations of astringent foods to follow during and after treatment. These recommendations exclude dairy, legumes, corn-derived foods, raw fruits and vegetables, thus recommending the consumption of sugar, refined grains and flour, white meat, cooked fruits and vegetables. No other nutritional intervention was performed, except for patients who required nutritional support as a result of severe malnutrition, these were channelled to the nutrition service for an individualised management and were excluded from the final analysis.

Anthropometric measurements

Body weight was measured in kg using a digital scale (SECA model 770; SECA Corp., Hamburg, Germany). Height was measured in m using a wall-mounted stadiometer (SECA model 222; SECA Corp.). Body mass index (BMI) was calculated as: BMI = weight in kg/height in m^2. Ideal body weight (IBW) was determined using the formula suggested by the World Health Organization for women: IBW = (height in $m^2 \times 21.5$) $\pm$ 10%. Percentage IBW was calculated. Percentage weight loss (%WL) was calculated.

Waist and hip circumferences were measured in cm and the waist-to-hip ratio (WHR) was calculated.

Dietary assessment

The 24-h recall questionnaire was applied each visit, the Mexican food equivalent system [18] was used to calculate the energy and macronutrient intake and proportion. Intakes of fibre and lactose were estimated using a food frequency questionnaire [19]. Total energy requirement was determined according to the patient's weight, calculated at 0.12 MJ kg^{-1} day^{-1} (28 kcal kg^{-1} day^{-1}) [20]. Percentage of adequacy of energy intake (%AEI) was calculated.

Biochemical measurements

To assess malnutrition, albumin and haemoglobin levels, as well as total lymphocyte and neutrophil count, were evaluated. Serum albumin levels <3.5 mg dL^{-1}, haemoglobin levels <12 mg dL^{-1}, lymphocyte count <1000 mm^{-3} and neutrophil count <1500 mm^{-3} are associated with malnutrition [21].

Nutritional evaluation

The Subjective Global Assessment (SGA) uses information obtained by clinical history and physical examination to assess a patient's nutritional status [4]. The Patient Generated-SGA (PG-SGA), specifically developed for patients with cancer [20,22,23], classifies the patients into three possible groups: A (well-nourished), B (moderately malnourished or at risk of malnourishment) and C (severely malnourished) [24]. For the present study, the Spanish version of the PG-SGA was used.

To assess the complete nutritional status of cervical cancer patients throughout the course of treatment, we used anthropometric, dietary and biochemical measurements, as described above, with the criteria outlined below [21].

Malnutrition

BMI <20 kg m^{-2} for patients <70 years of age, and <22 kg m^{-2} for patients 70 years and older, linked to weight loss ≥2% in 1 week or ≥5% in 1 month. In addition, we considered %IBW ≤85, AEI <70%, serum albumin levels <3.4 g dL^{-1}, haemoglobin <12 mg dL^{-1}, lymphocyte count <2000 cells mm^{-3} and neutrophil count <2000 cells mm^{-3}.

Well-nourished

BMI = 20–24.9 kg m^{-2}, WHR <0.8, %IBW = 90–110 and AEI = 70–110%.

Overweight

BMI = 25–29.9 kg m^{-2}, WHR ≥0.8 and %IBW = 111–120.

Obese

BMI ≥30 kg m^{-2}, WHR >0.8, %IBW >120 and AEI >110% [25,26].

Body composition analysis

Body composition was determined using CT images obtained pre- and post-treatment. Post-treatment CT-images were acquired with a mean time post-treatment of 4 months (range 3–8 months). A cross-sectional image of the third lumbar (L3) vertebra was analysed to determine the skeletal muscle and adipose tissue areas. The images were analysed by a trained researcher, using the software SliceOmatic 4.3 (Tomovision, Magog, QC, Canada). The skeletal muscle area was calculated using Hounsfield unit (HU) within a range of −29 to +150; subcutaneous adipose tissue was determined within a range of −190 to −30 HU; and visceral adipose tissue was determined between −150 and −50 HU, as described elsewhere [10,11]. Skeletal muscle, visceral adipose tissue and subcutaneous adipose tissue areas were normalised for the patient's squared height (cm^2 m^{-2}) to calculate skeletal muscle index (SMI), subcutaneous adipose tissue index

(SATI) and visceral adipose tissue index (VATI). Muscle mass was calculated using the average value of 6 cm^2 of muscle area per 1 kg of muscle mass; adipose tissue mass was calculated using the average value of 16 cm^2 per 1 kg of adipose tissue mass. Change in body composition was based on the difference between the pretreatment and post-treatment CT images. The duration of treatment was around 3 months, although the time to the post-treatment CT image varied among patients; so, the percentage changes in SMI, SATI, VATI and BMI were calculated as change per 200 days, to allow comparisons among patients.

Statistical analysis

A Kolmogorov–Smirnov test was used for patient characteristics; basal measurements did not present a normal distribution. Quantitative variables (anthropometric, dietary and biochemical measurements) are expressed as median and interquartile range. Wilcoxon's test was used to evaluate the difference of medians among first and second evaluations, and among second and third evaluations. *P*-values are reported. Qualitative variables are expressed as frequencies and percentages. A recurrence curve was measured from date of diagnosis to the date of progression or last follow-up visit. A survival curve was measured from the date of diagnosis to the date of death or last follow-up visit. The Kaplan–Meier method was used to calculate survival fractions and the log-rank test was used to compare between groups. Data were analysed using PRISM, version 7 (GraphPad Software, Inc., San Diego, CA, USA) $P < 0.05$ was considered statistically significant.

Results

Analysis of basal clinical characteristics of study population

Table 1 describes the 55 patients analysed. Mean age was 50.4 years. Histopathologic analysis showed that 85.4% were diagnosed with epidermoid carcinoma, 9.1% with adenocarcinoma and 5.5% with adenosquamous carcinoma. Most patients (92.7%) received five or six chemotherapy cycles. Patients received a median dosage of 340 mg of cisplatin, 50 Gy of radiation and 24 Gy of brachytherapy. The median duration of chemoradiation was 39 days (minimum 28 days; maximum 56 days). Patients had an average performance status of 90.6 according to Karnofsky scale. From the 55 patients analysed, nine (16%) had treatment interruption of one or two chemotherapy cycles. The reason for interruption was treatment-related toxicity, graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.4), including CTCAE grades 2 and 3 haematological toxicity (neutropenia, anaemia, thrombocytopenia, lymphopenia, leucopenia), and CTCAE grades 2 and 3 gastrointestinal toxicity (diarrhoea, vomiting).

Table 1 Basic demographic and clinical characteristics of study population ($n = 55$)

Characteristic	Description	Number (%)
Age (years)*		50.45 (11.4)
Clinical stage	II	44 (80)
	III	11 (20)
Histopathology	Epidermoid carcinoma	47 (85.4)
	Adenocarcinoma	5 (9.1)
	Adenosquamous carcinoma	3 (5.5)
Chemotherapy (cycles)	5 or 6	51 (92.7)
	4	4 (7.3)
Radiotherapy (Gy)*		50 (5)
Karnofsky*		90

*Data presented as the mean (SD); Kolmogorov–Smirnov.

Analysis of anthropometric parameters

Table 2 shows that patients lost weight by the week 3 of treatment (week +3) and continued to lose weight until the end of treatment (week +9), with a total weight loss of 7.5%. Weight loss was classified as severe (>5%), moderate (2–5%) and mild (<2%). The number of patients with severe weight loss almost doubled from week 3 to week 9 (28–43 patients). Only two patients did not lose weight during treatment. Median BMI was reduced from 27.6 to 25.8 during treatment, and to 24.9 by the end of treatment. Waist-to-hip ratio remained elevated (0.8) and unchanged throughout treatment. When the number of patients with cardiovascular risk was analysed, unexpectedly, 90% patients had cardiovascular risk, which was not significantly reduced by the end of treatment.

Analysis of dietary parameters

Total energy intake for patients was significantly reduced throughout treatment (Table 3); by the end of treatment, patients were consuming only a median of 3.40 MJ day^{-1} (813 kcal day^{-1}), which represented 54.2% of their energy requirement. When the nutrient proportion was analysed, more than 60% of energy came from carbohydrates, protein remained constant and energy from fat was reduced during treatment. Total fibre intake was decreased significantly throughout treatment; and lactose was almost eliminated from the patients' diet. We analysed the total macronutrient consumption to determine whether dietary

Table 2 Anthropometric analysis of cervical cancer patients during treatment

Measurement	Week −2	Week +3	$P^{\dagger}$	Week +9	$P^{\ddagger}$
Weight (kg)*	62.7 (42.9–103.7)	57.8 (41.3–98.9)	**0.001**	55.3 (37–96.7)	**0.001**
%IBW*	119.9 (85.1–157.9)	112.3 (80.1–150.6)		108 (74.4–147.2)	
%WL*		5.3 (−5.5 to 13.6)		7.5 (−1.8 to 22.6)	**0.001**
>5 %WL *n* (%)		28 (50.9)		43 (78.2)	
2–5 %WL *n* (%)		17 (30.9)		8 (14.5)	
<2 %WL *n* (%)		5 (9.1)		2 (3.6)	
Body mass index (kg m^{-2})*	27.6 (19.6–36.3)	25.8 (18.4–34.6)	**0.001**	24.9 (17.1–33.9)	**0.001**
Waist-to-hip ratio*	0.8 (0.76–1.02)	0.8 (0.7–0.9)	0.117	0.8 (0.6–0.9)	0.406
Cardiovascular risk *n* (%)	50 (90.9)	47 (85.5)		46 (83.6)	

*Data presented as median (range).

†Statistical difference among first (week −2) and second (week +3) evaluations.

‡Statistical difference among second (week +3) and third (week +9) evaluations. Wilcoxon test.

IBW, ideal body weight; WL, weight loss.

intake is adequate even though the proportion of macronutrients is maintained (Fig. 1). Compared to the first dietary evaluation, energy intake is significantly reduced during and after treatment (Fig. 1a). The same intake reduction is demonstrated for carbohydrates (Fig. 1b), protein (Fig. 1c) and fat (Fig. 1d). Accoridingly, even when the proportions of carbohydrates and protein are maintained, the amount consumed of these nutrients is reduced. Fat intake is reduced in both, quantity and proportion. In Fig. 1e, the percentage change of dietary intake is described. The median decrease is −38.4% for energy, −36.2% for carbohydrates, −37.4% for protein and −53.1% for fat, confirming a decrease in dietary intake. Notably, however, a few patients have a positive change in consumption, particularly in fat intake (one patient had an increase of 1489%).

Analysis of biochemical parameters

By week 9, haemoglobin levels were significantly reduced (see Supporting information, Table S1); in addition, 62.8% of patients had low haemoglobin levels by the same time. Median albumin was maintained throughout treatment, and patients with low albumin levels remained constant. Lymphocyte and neutrophil counts were reduced during treatment; indeed, all patients developed lymphopenia (data not shown). Acute haematological toxicity, including anaemia, has been described previously in cervical cancer patients undergoing concomitant treatment with cisplatin-based chemoradiotherapy [27].

Decline of the nutritional status of locally advanced cervical cancer patients throughout treatment

The nutritional status of each patient was thoroughly analysed before, during and after treatment, as described above (Fig. 2). The nutritional risk according to the PG-SGA score is described in Fig. 2a. Patients were classified as well-nourished (PG-SGA A), moderately malnourished (PG-SGA B) and severely malnourished (PG-SGA C). The percentage of patients with PG-SGA A was dramatically reduced during and after treatment. Most patients developed PG-SGA B in the course of treatment, and a smaller percentage developed PG-SGA C. Before treatment began, no patients were malnourished, 50.9% patients were overweight and 20% were obese; it is important to note that 30.9% patients arrived with a normal, well-nourished nutritional status (Fig. 2b). As patients received concomitant treatment, their nutritional status declined in such a way that, during treatment, 54.5% became malnourished and, by the end of treatment, 69.1% patients were malnourished. Only 23.6% patients presented an adequate nutritional status by week 9 and 7.3% were overweight. Body composition analysis based on CT images is shown in Fig. 2c, for three different patients before and after treatment. These images clearly show that patients became highly catabolic. Patient 1 lost tissue from the three compartments (muscle, visceral and subcutaneous adipose tissues); patient 2 is representative of patients who lost muscle and subcutaneous fat but maintained visceral adipose tissue. The third patient represents a classical cachectic patient, almost completely depleted of muscle and adipose tissues. In Fig. 2d, the percentage change in body composition is shown. There is a negative balance in all compartments and BMI. The median loss is −5.5% for SMI, −17.2% for SATI, −17.7% for VATI and −6.5% for BMI. It is important to note the wide range for the adipose tissue compartments (subcutaneous and visceral). Some patients gain up to 44% SATI and up to 241% VATI; for SMI and BMI, patients gain up to 20%.

Table 3 Dietary analysis of cervical cancer patients during treatment

Measurement	Week −2	Week +3	*P**	Week +9	*P*†
Total energy intake (MJ day^{-1}[kcal day^{-1}])	6.24 (3.42–11.36) [1491 (818–2716)]	4.00 (2.01–11.37) [954.8 (480–2718)]	**0.001**	3.40 (1.77–7.31) [813.2 (424–1747)]	**0.001**
% Adequacy of energy intake	87.7 (35.8–175.1)	55.1 (17.6–181.8)	**0.001**	54.2 (20.2–110)	0.38
% Carbohydrate	61.7 (39–90)	64.7 (32–99.3)	0.06	64.9 (41.4–92.8)	0.35
% Protein	15.1 (4–25.3)	13.7 (0.54–32)	0.16	15.1 (5.1–31)	0.41
% Fat	24.5 (4.1–82.1)	16.4 (0–45)	**0.001**	19.3 (0–39.1)	0.28
Fibre (g day^{-1})	24.1 (6.1–67.9)	12.7 (3.3–70)	**0.001**	7.4 (3.7–56.6)	**0.001**
Lactose (g day^{-1})	7.4 (4–34.8)	0.6 (0–28)	**0.001**	0.64 (0–25.9)	0.59

Data presented as the median (range). Macronutrient proportion is presented as % caloric intake from carbohydrate, protein and fat.
*Statistical difference among week −2 and week +3.
†Statistical difference among week +3 and week +9. Wilcoxon test.

To evaluate the impact of dietary intake on body composition, a correlation analysis was made between the change for each dietary parameter and the change for each component of body composition. Because some patients develop severe sarcopenia, whereas other patients remain stable or even gain muscle mass, we divided the patients into two groups. The first group included patients who lost ≥10% SMI (16 patients). The second group included patients who remained stable or gained (lost <10% or gained SMI). We performed the correlation analysis for each group (see Supporting information, Fig. S2). In the group of patients who lost ≥10%, we found no correlations except for a negative correlation between the change in adipose tissue and change in fat intake (VATI, $r = -0.44$; SATI, $r = -0.47$; TATI, $r = -0.44$; $P < 0.05$). In the group of patients who remained stable or gained muscle tissue, a positive correlation was found between the change in energy intake and SATI ($r = 0.3$, $P < 0.05$). Also, positive correlations were found in this group between change in carbohydrates intake and all body composition compartments (BMI, $r = 0.31$; SMI, $r = 0.29$; VATI, $r = 0.35$; SATI, $r = 0.47$; TATI, $r = 0.47$; $P < 0.05$). We found no correlations between change in skeletal muscle and change in any dietary component.

Next, we analysed the behaviour of each patient using a scatter plot analysis. In Fig. 3a, we observe that, before treatment, the median BMI is 27 (20–37), median SMI is 40.8 (30.4–55.3), median SATI is 86.9 (31.4–206.1) and median is VATI 40.2 (4.8–107.6). Dots circled in black represent patients with sarcopenia. According to the cut-off value of SMI <38.5 reported for women by Prado *et al.* [12], 33.3% patients present sarcopenia by the time of diagnosis, and almost half of these are overweight. In Fig. 3b, we can observe that after treatment the patient population moves to the bottom left, the median for all indices are significantly reduced, BMI is 25 (16–34), SMI is 37.9 (18.3–52.6), SATI 72.2 (6.6–167.9) and VATI 32.3 (3.8–69.9). After treatment, 58.3% patients develop sarcopenia; some of these patients who develop sarcopenia are obese according to a BMI ≥30 and also present high visceral and subcutaneous adiposity.

Loss of skeletal muscle index is associated with a higher risk of tumour recurrence

We observed that some patients are highly catabolic energetically, developing severe sarcopenia and losing more than 10% muscle tissue (16 patients); on the other hand, some patients do not lose or may even gain muscle tissue; thus, we aimed to determine whether highly catabolic patients behave differently in terms of tumour recurrence and overall survival compared to patients who are stable

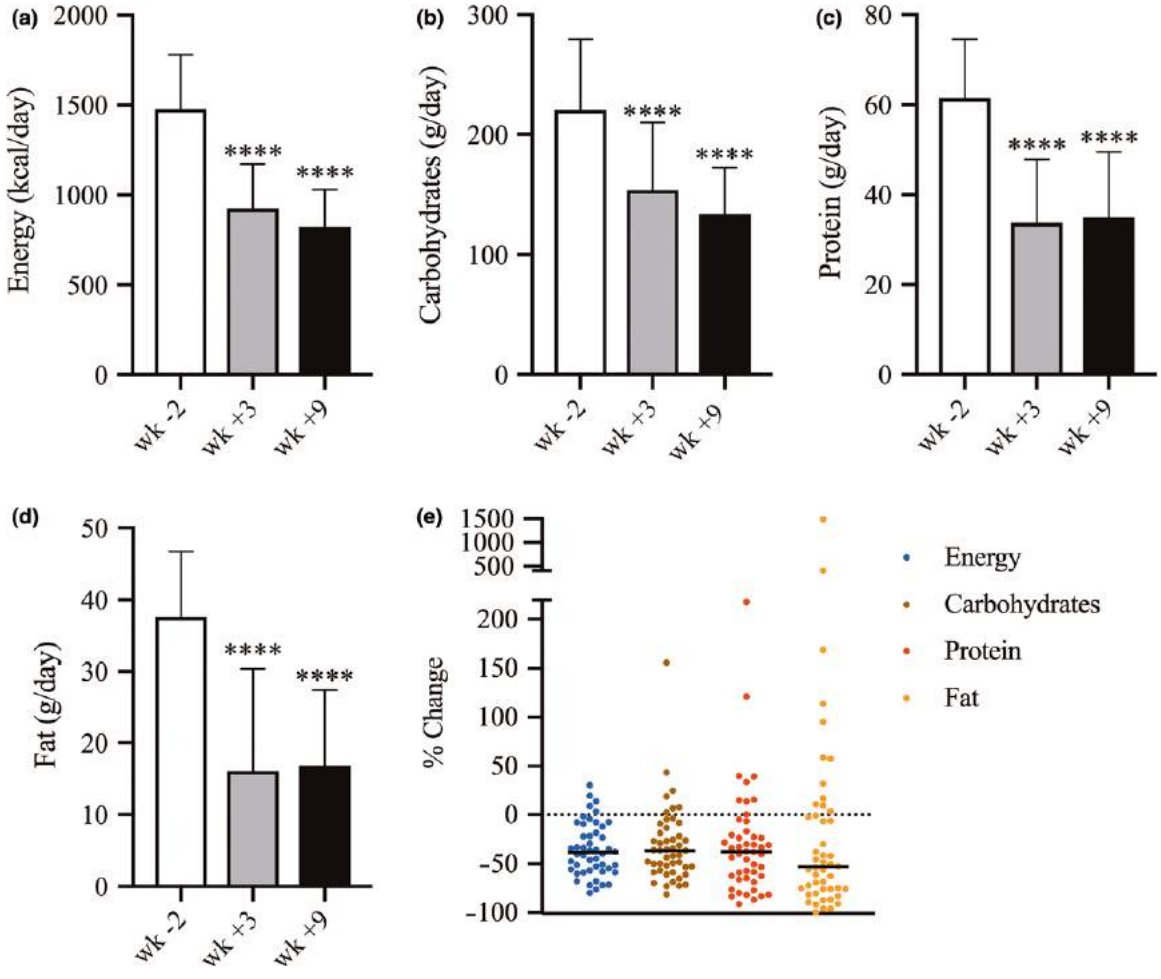

Figure 1 Dietary intake of locally advanced cervical cancer (LACC) patients decreases during treatment. Dietary evaluation of LACC patients was performed before (week −2), during (week +3) and after (week +9) treatment. (a) Total energy intake. (b) Total carbohydrate intake. (c) Total protein intake. (d) Total fat intake. (e) Percentage change between first (week −2) and third (week +9) evaluations for energy (blue dots), carbohydrates (brown dots), protein (red dots) and fat (orange dots) intakes; line at median. Bars represent median (range). ****$P < 0.0001$.

or patients who gain muscle. Figure 4a shows that patients who lose ≥10% muscle have a higher risk of tumour recurrence (hazard ratio = 2.957; $P = 0.006$). Figure 4b shows a tendency towards reduced overall survival for patients who lost ≥10% muscle, although this was not statistically significant (hazard ratio = 2.572; $P = 0.06$). It is important to note that there was no difference in terms of tumour recurrence and overall survival for patients who lost ≥10% subcutaneous adipose tissue (recurrence hazard ratio = 1.64, $P = 0.25$; survival hazard ratio = 3.1, $P = 0.05$) or visceral adipose tissue (recurrence hazard ratio = 0.95, $P = 0.9$; survival hazard ratio = 1.31, $P = 0.56$).

Discussion

Studies that have evaluated the nutritional status of gynaecological cancer patients include endometrial, ovarian, cervical and breast cancers [4,22,25,26,28,29]; because these tumours behave in a different manner, the implications on the nutritional status of patients vary. For example, women with endometrial cancer tend to have a higher prevalence of obesity, whereas women with ovarian cancer tend to be severely malnourished. Other studies that have analysed the nutritional status of cervical cancer patients have focused on anthropometric and body composition parameters, before and after treatment [13,16]. Several nutritional parameters such as subjective measures, prognostic nutritional index [5], albumin, transferrin, haemoglobin and anthropometric measurements, including weight and BMI, have been used separately to assess the nutritional status of gynaecological cancer patients [4,28–31]. The present study evaluated the change in nutritional status of patients with LACC throughout oncology treatment, analysing all aspects of nutritional

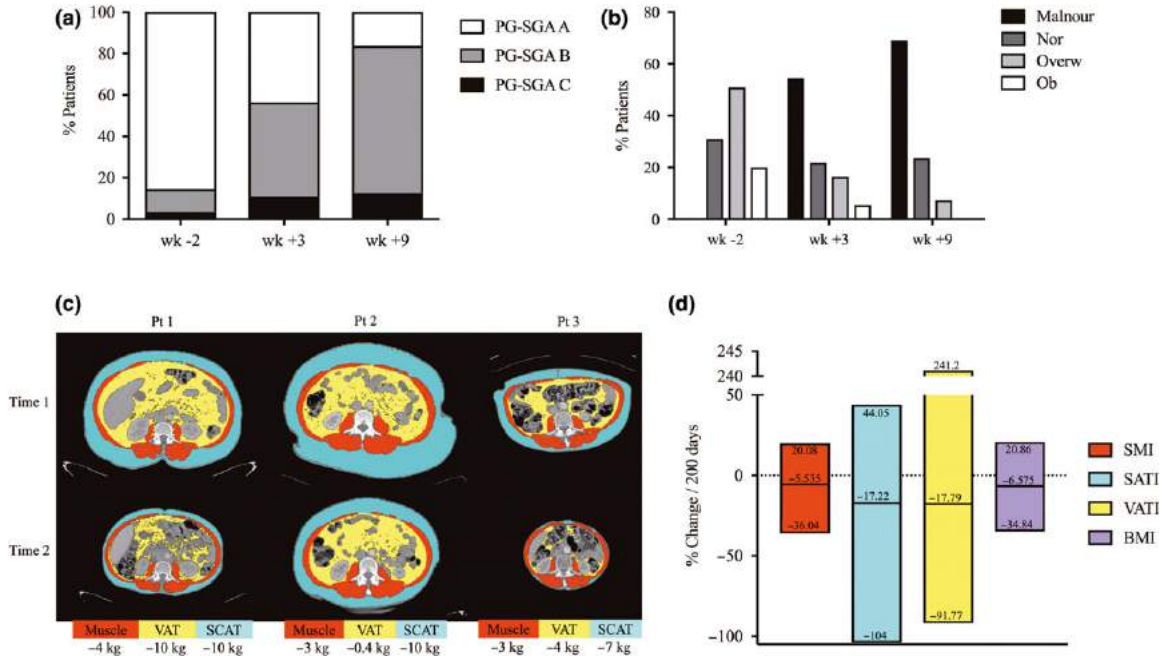

Figure 2 Locally advanced cervical cancer (LACC) patients become malnourished during oncology treatment. Nutritional status of locally advanced cervical cancer patients was evaluated before (week −2), during (week +3) and after (week +9) treatment. (a) Patient Generated-Subjective Global Assessment (PG-SGA). Stacked bars represent the percentage of patients scored as PG-SGA A (no nutritional risk, white bar), PG-SGA B (moderately malnourished, grey bar) or PG-SGA C (severely malnourished, black bar). (b) Percentage of patients for each nutritional diagnosis: malnourished (Malnour, black bars); normal or well-nourished (Nor, dark grey bars); overweight (Overw, light grey bars); or obese (Ob, white bars). (c) Body composition analysis example using computed tomography images from three patients (Pt 1, Pt 2 and Pt 3), before (Time 1, top row) and after (Time 2, bottom row) treatment. Skeletal muscle area is indicated in red, visceral adipose tissue area is indicated in yellow and subcutaneous adipose tissue area is indicated in blue. The bottom of the image indicates the mass loss (kg) for each tissue between Time 1 and Time 2. (d) Percentage change per 200 days of SMI (red bar), subcutaneous adipose tissue index (SATI) (blue bar), visceral adipose tissue index (VATI) (yellow bar) and body mass index (BMI) (purple bar); median (range) are indicated in each bar.

evaluation (anthropometric, dietary, biochemical and change in body composition).

On the first evaluation, no patients were malnourished, and this is consistent with other studies showing that, upon diagnosis, malnutrition is more common among patients with ovarian cancer compared to other types of gynecological cancer [5,28]. Even so, body composition analysis revealed that some of the patients presented sarcopenia, masked by a normal or high BMI; indeed, most patients were overweight, which is consistent with the high prevalence of overweight and obesity in Mexico (75.6% for Mexican women by 2016 [17]).

Involuntary weight loss is a strong predictor of negative outcomes irrespective of magnitude, speed and underlying cause [21]. In this sense, patients with highly catabolic diseases may in 3–6 months lose >10% of their weight and still have BMI values above normal ranges. Moreover, cancer cachexia is defined by either weight loss >5% alone, or weight loss >2% if BMI is reduced (<20 kg/m^2) or skeletal muscle mass is reduced [32]. During and by the end of treatment, 50% and 78% patients, respectively, presented weight loss >5%. Even so, most patients were overweight during treatment. It is common for overweight and obese subjects to be malnourished in the setting of disease [33]. Other studies have reported that a lower lean body mass is associated with treatment-induced haematological toxicity in lung cancer patients, which may be a result of higher doses of chemotherapy per kg of lean body mass [34–36]. This is consistent with our findings of anaemia and lymphopenia in our patients.

The weight loss that we observed at weeks 3 and 9 was consistent with the loss of appetite reflected in the reduced caloric intake of patients. Patients reported early satiety and energy intake diminished significantly during treatment (not before). The %AEI was 87% before treatment and 55% by week 3. Also, intake of carbohydrates, protein and fat by patients diminished significantly during and by the end of treatment. Therefore, we consider anorexia to be a result of treatment, particularly radiation to the abdominal-pelvic area. Indeed, radiotherapy to pelvic tumours carries the risk of pelvic radiation disease, a condition that encompasses a constellation of gastrointestinal symptoms that limit food intake in patients [3,37]. Most patients reported that they intentionally diminished

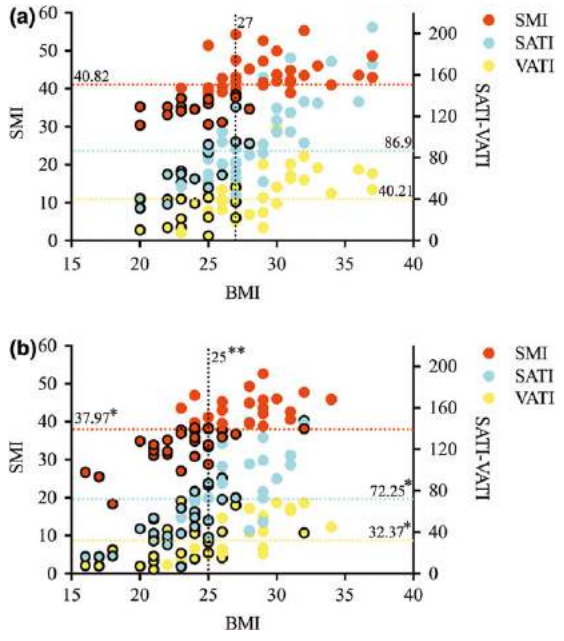

Figure 3 Locally advanced cervical cancer (LACC) patients loose muscle and adipose tissues after treatment. Scatter plot of LACC patients indicating skeletal muscle index (SMI) (red dots), subcutaneous adipose tissue index (SATI) (blue dots) and visceral adipose tissue index (VATI) (yellow dots) for each patient according to body mass index (BMI), before treatment (a) and after treatment (b). Red dotted line indicates median SMI, blue dotted line indicates median SATI, yellow dotted line indicates median VATI and black dotted line indicates median BMI. Dots circled in black represent sarcopenic patients. **Difference of median BMI before versus after treatment, $P < 0.005$. *Difference of median SMI, SATI and VATI before versus after treatment, $P < 0.05$.

food intake to avoid gastrointestinal symptoms. This is counterproductive because patients with malnutrition tend to get more gastrointestinal toxicity during radiotherapy [38].

The dietary recommendations that patients received promote a higher intake of carbohydrates over fat and protein. Even so, we demonstrated a reduced intake of all macronutrients during and after treatment, with an important decrease of 53% of fat intake. Because fat is more energetically dense than carbohydrates, we propose that this reduction in fat intake hinders the opportunity for patients to maintain an adequate energy intake and maintain body weight. Surprisingly, there was no correlation between change in energy intake and change in BMI. It was also interesting that we found no correlation between change in SMI and change in protein intake. In the case of patients who were severely depleted, this finding could be explained by the observation that in refractory cachexia diet alone is not able to reverse muscle loss [32]. Accordingly, it is possible that several factors are contributing to the catabolic state of patients, including tumour metabolism, the cancer treatment itself and inflammation. An interesting observation is that, in the group of patients who lost ≥10% muscle, the correlation graphs show patients in a negative balance for both dietary intake and body composition, whereas, in the group of patients who remained stable or gained muscle, we observed a tendency towards a positive balance in dietary intake and body composition. We also demonstrated that carbohydrates are positively correlated with change in body composition in patients who remained stable and gained muscle tissue. This is an important finding for future studies that aim to prevent a loss in body composition with dietary interventions.

Our findings are opposite to those in rectal cancer patients; even though there is a transient reduction in energy intake during radiotherapy (15%), the percentages of energy derived from fat, protein and carbohydrates did not change for rectal cancer patients [39]. It is interesting to note that, in rectal cancer patients, fibre intake does not change (14.4 g by the end of radiotherapy) and, even though patients presented diarrhoea, mean weight loss was only 1 kg [39]. This suggests that the reduction in fibre and fat intake to reduce diarrhoea may be

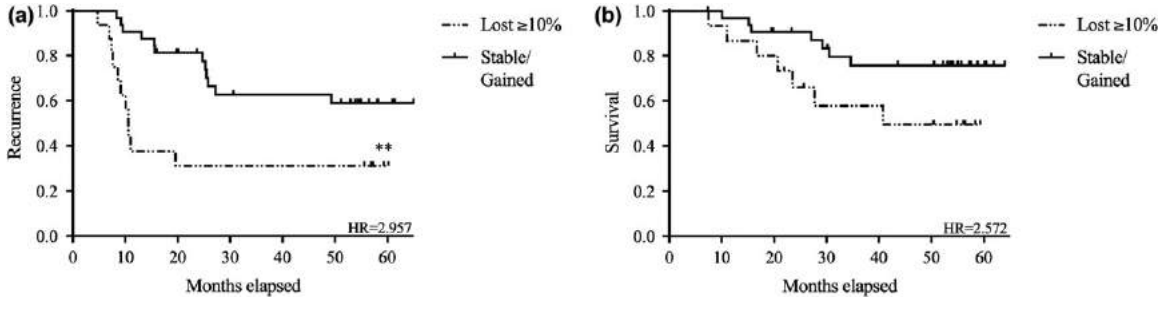

Figure 4 Muscle loss confers a higher risk for tumour recurrence. (a) Tumour recurrence of patients who lost ≥10% skeletal muscle and patients who remained stable or gained ≥10% skeletal muscle. (b) Survival of patients who lost ≥10% skeletal muscle and patients who remained stable or gained ≥10% skeletal muscle. **$P = 0.006$.

unnecessary, and even contribute to the development of malnutrition. We suggest that an effort to maintain an adequate energy intake and nutrient proportion, notwithstanding gastrointestinal symptoms, may protect the nutritional status of patients.

The risk of malnutrition, identified by screening tools, is in itself a condition related to increased morbidity and mortality [33]. The change that we observed in the nutritional status of women with cervical cancer was staggering. By the end of treatment, most patients were malnourished, as can be observed in the nutritional diagnosis analysis of patients (Fig. 2b), which is consistent with the PG-SGA that clearly shows the increase in malnourished patients (Fig. 2a). A study performed in Brazil demonstrated that gynaecological cancer patients having some degree of malnutrition, according to the PG-SGA, had a significantly lower median survival rate. Furthermore, diagnosis of cervical cancer and severe malnourishment increases the likelihood of death [25].

Our data strongly suggest that, although adipose tissue loss is an indicator of a negative energy balance, it is not in itself an adequate indicator of malnutrition in LACC patients. We observed that most patients loose both visceral and subcutaneous adipose tissues, although some patients gain ≥10% adiposity, even in the presence of sarcopenia (Fig. 3). Furthermore, when we analysed the impact of adipose tissue loss on tumour recurrence and overall survival, we observed that there is no association. According to our data, regardless of adipose tissue loss, skeletal muscle loss confers a poor prognosis for LACC patients because it increases the risk of tumour recurrence and tends to diminish overall survival (Fig. 4), which is consistent with other studies [11–13,40–42]. We did not measure physical activity in LACC patients, although our data suggest that change in dietary intake of protein is not related to change in skeletal muscle, and so we propose that physical activity in addition to an adequate protein intake may prove more efficient than diet alone to preserve skeletal muscle mass.

This phenomenon of malnutrition in the presence of excess adiposity reflects the trend toward obesity that the Mexican population is experiencing and may mask skeletal muscle wasting in cancer patients [10,15,43]. The excess adiposity may also contribute to and worsen the inflammatory process, which is associated with the development of cancer cachexia and a poor prognosis [44,45]. The global trend toward overweight and obesity renders the need to perform a complete nutritional evaluation of oncology patients increasingly important. Also, we consider that the increase in carbohydrate intake in the diet of LACC patients may have contributed to the increase in adiposity in some patients. Accordingly, we propose that, besides the thorough nutritional evaluation in these patients, the dietary intervention should focus on protein intake and fat (mainly derived from anti-inflammatory omega-3 fatty acids), in addition to an increase in physical activity, aiming to protect skeletal muscle mass and prevent the increase of visceral adipose tissue and inflammation.

There are some limitations to our work. A useful measurement would have been inflammatory markers in the blood throughout treatment; these would have helped understand the association between nutritional status and inflammatory response. We did not measure gastrointestinal toxicity in these patients, which could help explain the dietary changes that we observed, as well as the association of toxicity with body composition.

In conclusion, the present study demonstrates that women with LACC that undergo concomitant chemoradiotherapy become malnourished; some patients develop severe sarcopenia associated with a poor prognosis. Therefore, it is imperative to establish an adequate nutritional intervention to improve the nutritional status of LACC patients.

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (registered with the Ethics Committee of the Mexican National Cancer Institute) have been explained. The reporting of this work is compliant with STROBE guidelines [46].

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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MS and LC designed the study. MS collected and analysed the data. DC-E analysed the data and wrote the manuscript. JL-M collected the CT-images. RJ-L, JLA-P and DI-O carried out independent peer review of

the data. All authors have approved the final version of the manuscript submitted for publication.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Patient eligibility and recruitment for study.

Figure S2. Correlation analysis between change in dietary components and change in body composition (BC) parameters.

Table S1. Analysis of biochemical parameters of cervical cancer patients during treatment.

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Rev Inves Clin. 2018;70:130-5 BRIEF REVIEW

Nutrient Recommendations for Cancer Patients Treated with Pelvic Radiotherapy, with or without Comorbidities

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ABSTRACT

Radiotherapy is one of the main treatment options used in pelvic cancers. Ionizing radiation induces damage to surrounding tissues, resulting in disruption of normal physiological functions and symptoms such as diarrhea, tenesmus, incontinence, and rectal bleeding, which can all significantly alter the patient's quality of life. These patients are at increased risk of developing protein-calorie malnutrition and micronutrient deficiencies. Therefore, designing a proper nutritional intervention plan, with an optimal proportion of protein, fat, and carbohydrates, is required to reduce or even reverse the patients' poor nutritional status, increase their tolerance and response to oncology treatment, decrease the rate of complications and improve their quality of life. The aim of this review was to establish a nutritional plan that includes recommendations on macronutrient proportions and micronutrient intake in patients receiving pelvic radiotherapy. The following nutritional plan has been recommended in the literature: Energy: 28-31 kcal/kg/day, using the Harris-Benedict formula adjusted for body weight in obese patients; protein: 20-30%; fat: 30-40%; and carbohydrates: 40-50%. The maintenance of adequate levels of Vitamin D, Vitamin E, Vitamin A, calcium, magnesium, thiamin, riboflavin, and niacin must be emphasized. Physical activity must also be increased to maintain muscle mass. Nutrient requirements must be established in an integral manner, considering the patient's age, nutritional status, and the presence of comorbidities. Unnecessary dietary restrictions should be avoided to ensure an adequate nutritional status. (REV INVES CLIN. 2018;70:130-5)

Key words: Pelvic cancer. Radiotherapy. Chemotherapy. Comorbidity. Obesity. Type 2 diabetes. Hypertension. Renal insufficiency. Elderly. Nutrient recommendations.

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INTRODUCTION

As a result of radiotherapy treatment of pelvic tumors, healthy tissues may become compromised by radiation, including the intestinal tract, urinary tract, bone, sexual organs, and skin. A frequent problem is the development of bowel symptoms that may lead to a decrease in food intake, diarrhea and malabsorption, thereby affecting the patients' nutritional status and quality of life. During pelvic radiotherapy treatment, weight loss is an early indicator of a decline in nutritional status. In a period of 6 weeks, approximately 50 Gy of radiation to the pelvic area is associated with a 10% weight loss in 59% of patients[1]. However, when cancer patients receive individualized nutritional advice, their nutritional status is not as compromised as in patients who only receive general recommendations[1,2].

It is important to avoid unnecessary dietary restrictions in patients receiving this treatment modality, to ensure an adequate intake of energy, protein, fat, carbohydrates, vitamins, and minerals, and to avoid weight loss and malnutrition. When establishing nutritional recommendations for this group of patients, the patient's age, nutritional status, disease stage, treatment, and comorbidities such as obesity, diabetes, hypertension, and renal insufficiency should be considered.

MACRO AND MICRONUTRIENT RECOMMENDATIONS FOR PATIENTS WITHOUT COMORBIDITIES

Macronutrients

The impact of the nutritional intervention was assessed in a randomized clinical trial, using nutrition counseling following the American Dietetic Association (ADA) medical nutrition therapy protocol for radiation oncology, specifically for patients treated with pelvic radiotherapy[3]. According to this protocol, the recommended energy intake for these patients is 28-31 kcal/kg/day and 1.1-1.3 g/kg/day of protein. This intervention was proven to be beneficial to the nutritional status of patients, whereby they lost 400 g, compared to the control group who only received a general nutrition talk and booklet, and lost an average of 4.7 kg. In addition, by the 8th week of treatment, 18 patients in the intervention group had an adequate nutritional status, as determined by PG-SGA A, compared with 11 patients in the control group ($p = 0.02$)[3]. Level of evidence A, strength of recommendation 1.

In the case that a patient develops post-radiotherapy enteritis and in accordance with the ESPEN guidelines, the recommended energy intake is 25-35 kcal/kg/day, considering the catabolic or anabolic conditions of the patient and the disease stage[4]. The previously referred ADA protocol recommends a protein intake of 1.1-1.3 g/kg/day[3]. In case of acute enteritis, protein intake may be increased up to 1.5 g/kg/day[4].

In a controlled trial to evaluate the efficacy of a low or modified fat diet for the prevention of gastrointestinal toxicity, patients with pelvic tumors due to receive radical radiotherapy were randomized to a low-fat (20% total energy from long-chain triglycerides), modified-fat (20% from long-chain triglycerides and 20% from medium-chain triglycerides), or normal-fat diet (40% total energy from long-chain triglycerides)[5]. Gastrointestinal toxicity, assessed with the Inflammatory Bowel Disease Questionnaire-Bowel score, was not significantly different between groups. However, full compliance with the fat content prescription was only 9% in the normal-fat diet group, compared to 93% in the low-fat diet group, and this may have confounded the results. There is no evidence to support a low-fat diet during pelvic radiotherapy; fat recommendation for these patients is 30-40% of the total energy intake, although emphasizing that a higher proportion should be obtained from monounsaturated fatty acids. Level of evidence B, strength of recommendation 2.

Fat restriction (40 g fat per day) may be considered only when fatty acid malabsorption is present[6]. Level of evidence B, strength of recommendation 1. Furthermore, pancreatic enzyme supplements may be used if patients present pancreatic insufficiency or bile binders if the patient presents bile salt malabsorption, to facilitate fat digestion and absorption in patients with steatorrhea[7].

The optimal proportion of carbohydrates and fat in cancer patients has yet to be determined but may be inferred from the following observations. In some

Table 1. Recommended daily intake of vitamins and minerals, and theoretical recommendations for critically ill patients[11]

Micronutrients	Recommended daily intake	Critically ill patients
Vitamin A	700-900 µg	3 mg
Vitamin B1	1.5 mg	100 mg
Vitamin B6	2 mg	100-300 mg
Vitamin B12	2.4 µg	5-10 µg
Biotin	30 µg	30 µg
Vitamin C	75-90 mg + 35 mg in smokers	2000-3000 mg
Vitamin D	5-15 µg	45-100 µg
Vitamin E	15 mg	1000 mg
Copper	900 µg	10 mg
Selenium	55-75 µg	300-500 µg
Zinc	8-11 mg	40 mg

cancer patients, insulin resistance and altered glucose uptake and utilization in muscle have been demonstrated[4]. However, fat oxidation is normal or even increased, suggesting that a higher proportion of fat over carbohydrates is beneficial. Most of the recommendations for patients with cancer anorexia are focused on increasing energy intake, and this is more easily accomplished using fat as the main energy source. Hence, when considering the protein intake that must be ensured in these patients, the recommendation for carbohydrates is 40-50% of the total energy intake[4]. Level of evidence B, strength of recommendation 1.

Micronutrients

Vitamin and mineral deficiencies in cancer patients depend on their nutritional status, and the complications derived from the disease and its treatment. In a prospective study of rectal cancer patients who received radiotherapy, a temporary decrease in vitamin and mineral intake was observed[8]. At the end of radiotherapy, the intakes of calcium, magnesium, retinol equivalents, thiamin, riboflavin, and niacin were reduced; whereas the intakes of vitamins C, D, α-tocopherol, and iron, were unchanged. At treatment completion, fiber, calcium, iron, and Vitamins D and E were below the Dietary Reference Intake (DRI), while magnesium, thiamin, riboflavin, and niacin were in the lower limit but within the DRI. Absorption of fat-soluble vitamins may be decreased if steatorrhea is present, so supplementation of these vitamins is advised if this is the case[8]. Level of evidence B, strength of recommendation 1.

A prospective observational study demonstrated that Vitamin D deficiency is associated with an increase in the severity of radiation-induced acute proctitis (odds ratio = 3.07, p = 0.013)[9]. Even though there is no evidence that proctitis may be prevented with Vitamin D supplementation, established recommendations must be considered to fulfill daily Vitamin D requirements, judging in each individual case whether the patient is exposed to sunlight or not, to activate the Vitamin D precursor in the skin. Level of evidence B, strength of recommendation 1.

A clinical trial demonstrated that supplementation with 400 mg/day of Vitamin E decreased peripheral neurotoxicity caused by cisplatin treatment, with a relative risk = 0.14 (95% confidence interval [CI], 0.2-1; $p < 0.05$)[10]. Therefore, Vitamin E supplementation should be administered to patients receiving cisplatin-based chemotherapy. Level of evidence A, strength of recommendation 1.

To the best of our knowledge, there are no established recommendations of vitamin and mineral intake for cancer patients who receive pelvic radiation therapy. Hence, the recommended daily intake of vitamins and minerals proposed by the National Academy of Sciences is a useful and safe measure in the absence of specific nutrient deficiencies[4]. However, the presence of reduced food intake and hypercatabolism is consistently acknowledged in cancer-associated malnutrition; hence, in severely malnourished patients, daily requirements for micronutrients may be taken from recommendations for critically ill patients (Table 1)[4,11].

NUTRIENT RECOMMENDATIONS FOR PATIENTS WITH COMORBIDITIES

Obesity

Obesity is a risk factor for the development of cancer and mortality. It is estimated that 20% of cancer cases are related to obesity, and obese cancer patients have a worse prognosis[12]. Women with morbid obesity (body mass index ≥ 35) and cervical cancer were proven to have a higher risk of death (hazard ratio = 1.26, 95% CI, 1.1-1.45) when compared to women with cervical cancer and a normal weight[13]. Excess body fat plays a role in cancer recurrence and patient survival. In addition, overweight and obese women need to undergo a greater and more aggressive radiation protocol. Delivery of external radiotherapy is complicated in obese patients since it is associated with an increased risk of preparation errors and requires a larger margin. In the particular case of cervical cancer, the use of high-energy radiation to the middle pelvis without overdosing peripheral healthy tissues represents a technical challenge. For these reasons, it is of utmost importance to implement an adequate nutritional treatment for obese patients with cervical cancer[12,13]. Level of evidence B, strength of recommendation 1. The nutritional approach to obese patients with cancer must be individualized, starting with recommendations focused on lifestyle changes, an increase in physical activity and changes in eating habits. To calculate the energy requirements of obese patients, the Harris-Benedict formula is recommended, using the patient's adjusted body weight to obtain a moderate energy requirement and thus promote gradual weight loss[14]. The adjusted body weight is calculated using the following formula:

Adjusted body weight = Ideal weight + (50% [Current weight – Ideal weight])

Level of evidence B, strength of recommendation 1.

It is important to maintain a balanced macronutrient distribution. To preserve the patient's muscle mass, protein intake must be at least 1 g/kg/day, or the protein proportion must be increased to 20-30% of the total energy intake. The recommended proportion of carbohydrates is 40-50% total energy intake, and the recommended proportion of fat is 30-40%. Fiber intake must be considered according to individual tolerance, but a greater proportion of soluble fiber than insoluble fiber is highly recommended. Concerning physical activity in cancer patients, it is associated with maintenance or significant improvements in aerobic capacity, muscle strength, health-related quality of life, self-esteem, and with reduction in fatigue and anxiety[15]. Clinical trials have provided evidence that physical activity is well-tolerated and safe at different stages of cancer[16]. The American College of Sports Medicine (ACSM) guidelines recommend an increase in physical activity, at least 3 times per week, for a total of 75-150 min of low to moderate intensity exercise per week[17]. Level of evidence B, strength of recommendation 1.

Type 2 diabetes mellitus

To manage the cancer patient with diabetes that receives pelvic radiotherapy, recommendations have not been determined. Albeit, in patients with insulin resistance, glucose metabolism is impaired; however, utilization of fat is normal thus suggesting a benefit for a higher fat proportion[4]. Energy recommendations may be determined with the Harris-Benedict formula using the patient's current weight – if adequate –, or the adjusted weight if the patient is obese. According to the Canadian Diabetes Association, the recommended nutrient proportion is: 40-50% total energy from carbohydrates; 15-20% total energy from protein (or 1-1.5 g/kg/day), taking into account the patient's renal function, and 30-40% total energy from fat, with a greater proportion of monounsaturated fatty acids. Consumption of a variety of unprocessed, nutrient-dense foods is emphasized[18]. Level of evidence A, strength of recommendation 1.

The optimal proportion of carbohydrates, protein, and fat in cancer patients with pre-diabetes has not been determined but may be derived from intervention studies in the general pre-diabetic population. A randomized clinical trial, in pre-diabetic patients, demonstrated that a high protein diet (30% protein, 30% fat, and 40% carbohydrate), compared to a high carbohydrate diet (15% protein, 30% fat, and 55% carbohydrate), leads to remission of pre-diabetes to normal glucose tolerance in 100% of subjects[19]. The high-protein diet group exhibited significant improvement in insulin sensitivity (p = 0.001), cardiovascular risk factors (p = 0.04), inflammatory cytokine levels (p = 0.001), oxidative stress markers (p = 0.001),

and an increased percentage of lean body mass (p = 0.001), and compared to patients on the high-carbohydrate diet at 6 months. These findings suggest that pre-diabetic cancer patients could benefit from a high-protein diet. Level of evidence A, strength of recommendation 1.

Hypertension

In cancer patients with high blood pressure that receives pelvic radiation therapy, there is no evidence on useful dietary interventions. However, energy requirements may be estimated using the Harris-Benedict formula, with adjusted weight if the patient is obese, or the current weight if the patient has a normal body weight. The same macronutrient proportion as described above may be recommended (20-30% protein, 30-40% fat, and 40-50% carbohydrates)[14]. Level of evidence B, strength of recommendation 2.

The dietary approaches to stop hypertension (DASH) diet are a program recommended for patients with hypertension[20]. This diet recommends an increased intake of fruits and vegetables, low-fat dairy, fish, poultry, nuts and seeds, and a decreased intake of red meats; thus favoring an increase in dietary fiber, potassium, magnesium and calcium, and minerals that modulate blood pressure through different mechanisms. With this diet, potassium intake may reach 4700 mg/day, magnesium may reach 500 mg/day, and calcium 1240 mg/day. Level of evidence B, strength of recommendation 1. Although there is no evidence supporting a benefit from this dietary approach in cancer patients with hypertension that receive pelvic radiotherapy, the DASH diet may be considered safe for cancer patients during chemo- and radiation therapy.

Sodium restriction must be enforced depending on blood pressure readings; an intake < 3000 mg/day is recommended. It is important to consider that sodium restriction changes food flavor and palatability, which may be counterproductive in patients with anorexia and taste alterations. The lipid profile in the diet of these patients must also be monitored whereby cholesterol intake must not exceed 200 mg/day and the intake of monounsaturated fatty acids must be increased, which can be easily accomplished with the DASH diet[20]. Level of evidence B, strength of recommendation 1.

Renal insufficiency

No evidence was found concerning dietary interventions in cancer patients with renal insufficiency that receives pelvic radiation. Authors consider that a nutritional approach similar to the one used routinely for patients with renal insufficiency may be utilized for cancer patients as well. In patients with chronic renal failure that is not on replacement therapy and with a glomerular filtration rate (GFR) < 25 ml/min, a protein intake of 0.6 g/kg/day, including 2/3 of high biological value protein, is recommended. In patients with a GFR ranging between 25 and 70 ml/min, the recommended protein intake is 0.6 g/kg/day, including 2/3 of high biological value protein. In patients with a GFR > 70 ml/min, protein intake can oscillate between 0.8 and 1 g/kg/day. In all cases, the recommended energy intake should consider the patient's age: in patients 60 years of age and older, it is 30 kcal/kg/day, and in patients younger than 60, it is 35 kcal/kg/day[21]. Level of evidence B, strength of recommendation 2.

Protein recommendation for clinically stable patients on hemodialysis is 1.2-1.4 g/kg/day. In patients on peritoneal dialysis, the same recommendation applies. In both cases, it is important to monitor that 60% protein is of high biological value. Another significant aspect to consider in patients on peritoneal dialysis is glucose absorption from the dialysis fluid since it alone can provide 25-30% total energy. If the patient is in acute renal failure, basal energy requirements may be estimated with the Harris-Benedict formula, multiplied by a factor of 1.3; the protein requirement is 0.5-1 g/kg/day, and an adequate intake of essential amino acids must be monitored[22]. Level of evidence B, strength of recommendation 2.

Geriatric patients without comorbidities

To the best of our knowledge, there is no evidence of dietary interventions that could benefit elderly cancer patients who receive pelvic radiation therapy. Even so, energy requirements in this population may be determined with the Harris-Benedict formula, multiplied by the activity factor. Protein recommendations for the elderly are 0.9-1.1 g/kg/day, 30-35% fat, and 45-55% carbohydrates[23]. Level of evidence B, strength of recommendation 1.

Table 2. Recommended daily intake of vitamins and minerals in the elderly according to the World Health Organization[23]

Vitamins	Minerals
Vitamin A: 600-700 µg/day	Calcium: 800-1200 mg/day
Vitamin B12: 2.5 µg/day	Chromium: 50 µg/day
Vitamin C: 60-100 mg/day	Folate: 400 µg/day
Vitamin D: 10-15 µg/day	Iron: 10 mg/day
Vitamin E: 100-400 mg/day	Magnesium 225-280 mg/day
Vitamin K: 60-90 µg/day	Selenium: 50-70 µg/day
Riboflavin: 1.1-1.3 mg/day	

Vitamin and mineral requirements for geriatric patients are described in table 2.

CONCLUSIONS

Nutrient requirements for patients undergoing pelvic radiotherapy must be established in an integral manner, considering the age of the patient, the nutritional status and the presence of comorbidities and complications derived from the disease and its treatment. It is of utmost importance to avoid unnecessary dietary restrictions to ensure that the patient sustains an adequate nutritional status.

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

Functional foods modulating inflammation and metabolism in chronic diseases: a systematic review

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ABSTRACT

Chronic diseases are responsible for approximately 71% global deaths. These are characterized by chronic low-grade inflammation and metabolic alterations. "Functional foods" have been attributed with anti-inflammatory properties, demonstrated in cell lines and murine models; however, studies in humans are inconclusive. The purpose of this systematic review is to identify clinical trials that analyzed changes in inflammatory and metabolic mediators, in response to consumption of specific functional foods. A total of 3581 trials were screened and 88 were included for this review. Foods identified to regulate inflammation included cranberries, grapes, pomegranate, strawberries, wheat, whole grain products, low fat dairy products, yogurt, green tea, cardamom, turmeric, soy foods, almonds, chia seeds, flaxseed, pistachios, algae oil, flaxseed oil and grape seed oil. Clinical trials that focus on a dietary pattern rich in functional foods are necessary to explore if the additive effect of these foods lead to more clinically relevant outcomes.

KEYWORDS

Chronic disease; cytokines; functional foods; immune system; inflammation; nutrients

Introduction

Approximately 71% of deaths worldwide are attributed to chronic diseases, such as obesity, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), chronic respiratory disease and cancer (WHO 2018). The common characteristic of these diseases is chronic low-grade inflammation that leads to metabolic alterations (Franceschi and Campisi 2014). Inflammation is a physiologic response to harm that protects the host from invading organisms and provides healing to reestablish homeostasis. As a result of tissue damage or the presence of foreign organisms, the innate and adaptive arms of the immune system are activated and several inflammatory mediators like chemokines, cytokines, vasoactive amines, eicosanoids, and products of proteolytic cascades are synthesized and secreted (Newton and Dixit 2012). In response to the first inflammatory signals, the innate immune cells produce Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-6 and IL-1β, these induce the liver to produce acute phase proteins, including proteins from the complement system, C Reactive Protein (CRP) and fibrinogen. The adaptive arm of the immune system, upon activation, produce Interferon (IFN)-γ, IL-2, IL-8, IL-12, IL-17, among other cytokines, depending on the type of effector response (Franceschi and Campisi 2014). Adhesion molecules and chemokines are also expressed during inflammatory processes, examples are Intercellular Adhesion Molecule (ICAM)-1, Vascular Cell Adhesion Molecule (VCAM)-1, selectins, Regulated on Activation Normal T Cell Expressed and Secreted (RANTES), Matrix Metalloproteinase (MMP)-9, and Monocyte Chemoattractant Protein (MCP)-1. The inflammatory response, if unregulated, may lead to tissue damage and can eventually be harmful. Thus, the immune system has several regulatory mechanisms to stop and prevent harmful inflammation. Among these, cytokines associated with an anti-inflammatory response are IL-10 and Transforming Growth Factor (TGF)-β, produced by several types of cells, mainly regulatory T cells (Treg); also, adiponectin is an adipokine produced by the adipose tissue and has been associated with an anti-inflammatory response, insulin sensitivity and adipose tissue homeostasis (Masternak and Bartke 2012). The measurement of some of these molecules may reflect the presence of inflammation in clinical trials focused on chronic diseases. For example, serum samples from obese individuals with metabolic syndrome show decreased levels of anti-inflammatory mediators IL-10 and TGF-β, and increased levels of proinflammatory mediators CRP, TNF-α, IL-6, IL-1β, IL-8 and IL-33; most of these are also present in CVD, insulin resistance (IR) and cancer (Monteiro and Azevedo 2010; Coussens and Werb 2002).

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Numerous health benefits have been attributed to a group of foods named "functional foods." Among these benefits, their anti-inflammatory capacity may be the most important. According to The European Commission's Concerted Action on Functional Food Science in Europe (FuFoSE), "a food product can only be considered functional if together with the basic nutritional impact it has beneficial effects on one or more functions of the human organism thus either improving the general and physical conditions and/or decreasing the risk of the evolution of diseases. The amount of intake and form of the functional food should be as it is normally expected for dietary purposes. Therefore, it could not be in the form of pill or capsule just as normal food form" (Diplock et al. 1999). Specific nutrients have been identified to regulate inflammatory pathways, thereby conferring them anti-inflammatory properties; well studied examples are omega-3 fatty acids (Calder 2003; Harbige 2003), polyphenols (Gorzynik-Debicka et al. 2018; Alarcon De La Lastra and Villegas 2005), and fiber (Ma et al. 2006; King, Egan, and Geesey 2003). These nutrients have different molecular mechanisms by which they can regulate the immune response toward a more anti-inflammatory profile; some of these mechanisms include blocking signals, downregulation of pro-inflammatory mediators, or activation of anti-inflammatory pathways (Wu et al. 2018). Fiber may regulate inflammation indirectly through the metabolites derived from its fermentation by the intestinal microbiota, in particular short chain fatty acids, which have been shown to exert potent anti-inflammatory results (Vinolo et al. 2011).

Although clinical investigations have studied the effect of specific nutrients on chronic diseases, most of them recommend pharmaceutical supplements at high doses (instead of using their natural source in foods); the results are focused on clinical, anthropometric or metabolic outcomes, not on the measurement of inflammatory mediators; moreover, the studies that report their anti-inflammatory effect are still inconclusive (Mocellin et al. 2016; Lin et al. 2016; Gioxari et al. 2018; Lopez-Huertas 2012; Rangel-Huerta et al. 2012; Sahebkar et al. 2015; Amiot, Riva, and Vinet 2016; Fernandes et al. 2017; Fedorak and Madsen 2004; Wedlake et al. 2014; Khor et al. 2018).

The main purpose of this systematic review is to identify clinical trials that evaluate the impact of the consumption of functional foods on the regulation of pro- and anti-inflammatory mediators in individuals with chronic inflammatory diseases, compared with a control group. We also noted, where available, the effect of the food on metabolic parameters. A secondary outcome reported in this study is the recommended daily intake of these foods and information concerning the length of intervention time before an anti-inflammatory effect was observed.

Methods

A critical and systematic review of relevant and original studies on human populations was performed, using a specific set of mesh terms, in the PUBMED database (only English language). For the web search all possible combinations with the following words were used:

Patients: chronic disease, obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, arthritis, and cancer.

Intervention: functional food and food.

Outcome: inflammation, interleukins, and cytokines.

After the web search was performed, a new search was made using specific foods (using the same search pattern) to identify all relevant studies. The quality of the trials was evaluated according to the GRADE system to decide which articles would be included in this systematic review (Kavanagh 2009). Trial studies were eligible if they included adult patients with any chronic disease, if the intervention was consumption of a particular food with a regular specified frequency, if it was compared to an appropriate control group (without intervention, using a placebo or any other food not known to possess immune-modulating properties), and if the outcome reported included any molecular marker of inflammation. In case any important data was missing, an e-mail was sent to the corresponding author requesting the information; the author had two months to reply or that article was omitted from this review. Neither length of patient follow-up nor year of publication were considered exclusion criteria. All articles identified as duplicates or trials that used nutritional supplements instead of foods as intervention were omitted from this review.

The summary measures were disease, quantity of functional food indicated, time of patient follow up and levels of inflammatory parameters. Additionally, where available, we included levels of metabolic indicators.

Results and discussion

A total of 3581 articles were identified between May and September of 2019 in the MESH search. From these, 3388 were excluded because they did not report the main outcome of this review. Five articles were identified through other sources. As a result, 198 clinical trials were thoroughly screened for eligibility and 73 were excluded because they did not comply with eligibility criteria or were duplicated (Figure 1). A total of 30 articles were excluded because their interventions consisted on the use of an active compound or a supplement, 14 included healthy population, 11 had a wide risk of bias for their analysis or methodology, 9 did not report inflammatory parameters, 7 did not have a control group or it was inadequate for our objective, authors from 3 articles did not reply when we requested additional information and were therefore excluded. Finally, 88 articles were included in this review. The articles were published between the years 1981 and 2018.

The main chronic diseases reported were overweight/obesity, T2DM, metabolic syndrome (MetS), renal disease (RD), and CVD. The results were organized according to food groups. Supplementary Table 1 contains a summary of the articles, including author, year of publication, study type, the details of the interventions and inflammatory and metabolic parameters measured.

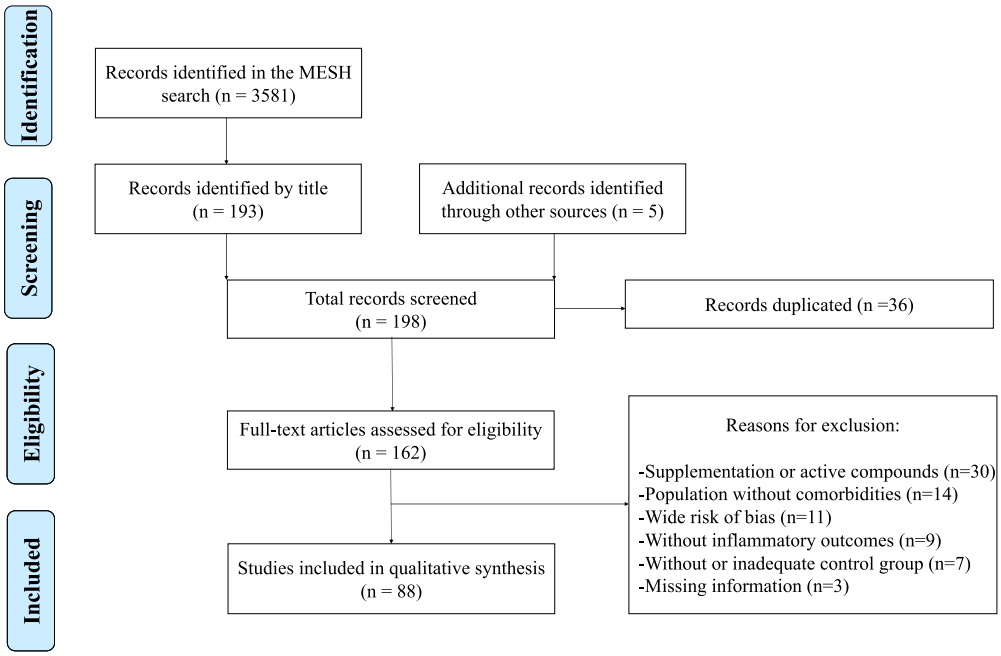

Figure 1. Flowchart of selection and inclusion of clinical trials. For the literature search we used a specific set of mesh terms in the PUBMED data base. A total of 3581 trials were screened and after selection, 88 were included in this review.

Fruits and vegetables

It has been commonly known that a high consumption of fruits and vegetables protect against chronic diseases because of their nutrients and bioactive components (vitamins, minerals, fiber, and phytochemicals), these components could also be involved in the modulation of inflammation (Prasad, Sung, and Aggarwal 2012).

Cranberries

Cranberry is a fruit characterized for its high content of antioxidants, vitamin C, citric, quinic and malic acids, and other phytochemicals. Some benefits have been attributed to cranberries mainly in the urinary tract and cardiovascular system (Cunningham et al. 2004). Polyphenolics and A-type proanthocyanidins are some of the phytochemicals associated with the reduction of urinary tract infections (RR = 0.74, 95% CI: 0.55–0.98), probably because of their interference with the adhesion of bacteria to epithelial cells (Fu et al. 2017). Additionally, the presence of cranberries-derived metabolites correlated with endothelial vasodilation, therefore they could exert a positive effect in cardiovascular function (Rodriguez-Mateos et al. 2016).

In MetS, the consumption of cranberry juice had no effect in inflammatory or metabolic parameters compared to placebo (Simão et al. 2013). However, in the cranberry group, lipid peroxidation markers malondialdehyde and 4-hydroxynonenal (MDA & HNE) were lower at the end of the interventions compared with the placebo group (1.7 ± 0.7 vs $3.2 \pm 0.8\,\mu$M, $p < 0.05$) (Basu, Betts et al. 2011). Schell et al. randomized 25 adults with T2DM and visceral adiposity to consume a breakfast high in fats and dried cranberries or breakfast high in fats and ripe banana (Schell, Betts et al. 2017). Inflammatory and metabolic postprandial parameters were measured. After 2 h glucose decreased in the cranberry group compared to control group (161 ± 8.7 vs 191 ± 7.7 mg/dl, $p < 0.05$). After 4 h, IL-18 (308.2 ± 11.2 vs 341.7 ± 12.7 mg/dl, $p < 0.05$) and glucose (152 ± 8.5 vs 176 ± 5.9 mg/dl, $p < 0.05$) decreased compared to control. Furthermore, the cranberry group had lower levels of MDA & HNE after 4 h compared to the placebo group (1.6 ± 0.8 vs $3.3 \pm 1.1\,\mu$M, $p < 0.05$).

In summary, dried cranberries and not cranberry juice were shown to reduce IL-18 in patients with T2DM. A positive effect in glucose metabolism was observed in patients with MetS. Importantly, reduction of lipid perdoxidation was demonstrated in both, T2DM and MetS patients.

Grapes

Grape is a phenol-rich fruit that contains resveratrol. This potent antioxidant component is in the skin and seeds of red, purple and black grapes, and it has been associated with several health benefits attributed to the Mediterranean diet (Xia et al. 2010).

Bardagjy, et al. analyzed the effect of the consumption of freeze-dried whole grape powder in 20 obese adults and found a significant increase in sVCAM-1 (Bardagjy et al. 2018). In a similar intervention in individuals with MetS without dyslipidemia, the freeze-dried whole grape powder increased levels of IL-10 and adiponectin (Barona et al. 2012). When analyzing individuals with MetS and dyslipidemia no benefits were observed. In similar studies, no effect was reported with the consumption of grape products on inflammatory or metabolic parameters, in patients with chronic kidney disease (CKD) on hemodialysis, and in obese individuals (Janiques et al. 2014; Zunino et al. 2014). A grape extract containing resveratrol (GECR) was compared

Table 1. Summary of the inflammation modulating effect of foods in chronic diseases.

Food Group	Food	Overweight/obesity	T2DM	MetS	GID	KD	OA	Cancer	CVD	NAFLD	References
Fruits and vegetables	Carrot	😐									161
	Cranberry		🙂	😐😐							13, 129, 136
	Grape	☹️😐	😐	🙂		😐					9, 11, 60, 145, 170
	Grapefruit	😐									29
	Pomegranate		🙂🙂	😐		🙂			😐😐		6, 97, 120, 133, 138, 139
	Strawberry	😐😐😐	😐	☹️			🙂🙂				12, 15, 16, 32, 96, 130, 169
Whole grain products	Wheat								🙂		158
	Whole grain products	🙂🙂🙂😐😐		😐							18, 76, 80, 123, 150, 152
	Sorghum	😐									141
Animal source food	Low-fat dairy products			🙂							31
	Yogurt	🙂😐	🙂🙂								59, 105, 149, 166
	Sardines		😐								8
Tea and spices	Black tea								😐		160
	Green tea	😐	😐	😐					🙂		14, 17, 43, 110
	Cardamom	🙂									66
	Nigella Sativa				😐						108
	Red pepper	😐									107
	Turmeric	😐			🙂	🙂😐					67, 74, 107, 127
Legumes	Soy foods			🙂🙂		🙂😐😐😐			☹️	🙂	1, 7, 35, 63, 95, 101, 135, 144
	Spanish beans	😐									54
	Yellow pea	😐									81
Nuts and seeds	Almonds		🙂🙂😐						😐		25, 48, 62, 86
	Chia seeds	😐	🙂						😐		106, 146, 153
	Flaxseed	😐	😐			🙂					57, 68, 121
	Hazelnut	😐									142
	Nut Mixes			🙂😐							21, 82
	Pistachios		😐😐	🙂							49, 116, 128

Oils	Algae	😊													103
	Canola		😐												10
	Fish			😐		😐						😐			26, 44, 99, 117, 133, 135, 147
				😐								😐			
												😊			
	Flaxseed				😊		😐								53, 83, 115
					😊										
	Grape seed					😊									58
	Nigella sativa					😞									90
	Rapeseed					😊									79

T2DM: Type 2 Diabetes Mellitus; **MetS:** Metabolic Syndrome; **GID:** Gastrointestinal Disease; **KD:** Kidney Disease; **OA:** Osteoarthristis; **NAFLD:** Nonalcoholic Fatty Liver Disease. The number of emoji faces represent the number of articles that provided the evidence of the effect: 😊 Anti-inflammatory effect; 😐 no demonstrated effect; 😞 proinflammatory effect.

with a grape extract lacking resveratrol (GELR) and placebo in individuals with T2DM, hypertension (HT) and coronary artery disease (CAD) (Tomé-Carneiro et al. 2013). Although at the end of interventions no differences were observed in inflammatory parameters, before starting treatment the GECR group had the highest levels of IL-6, which were significantly reduced overtime.

In summary, grape consumption seems to increase the anti-inflammatory mediators IL-10 and adiponectin in MetS, this could promote tolerogenic mechanisms.

Pomegranate

Pomegranate contains several antioxidants, phenolic compounds (flavonoids, anthocyanins, ellagitannins, flavones, flavonol-3-ols, anthocyanidins, anthocyanins), hydroxycinnamic acids, hydroxybenzoic acids, conjugated and non-conjugated fatty acids, phytosterols, vitamins and minerals, all of which could be involved in the modulation of inflammation (Akhtar, Ismail, and Layla 2019). Their mechanism has been associated with cyclooxygenase-2 (COX-2) inhibition and the consequent reduction in inducible Nitric Oxide (iNO), prostaglandin E-2 (PGE-2), inflammatory cytokines, and reactive oxygen species (ROS) (Akhtar, Ismail, and Layla 2019).

The effect of pomegranate was investigated in HT volunteers randomized to drink pomegranate juice or water (Asgary et al. 2014). Two weeks after intervention, volunteers that consumed pomegranate juice presented a significant reduction in high sensitivity C Reactive Protein (hs-CRP), ICAM-1 and VCAM-1. When compared to placebo, the pomegranate juice group had higher levels of E-Selectin and lower levels of ICAM. Additionally, a decrease was observed in systolic and diastolic blood pressure. In MetS, the consumption of pomegranate juice had no effect on hs-CRP, but surprisingly, higher levels of very low density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) were observed (Moazzen and Alizadeh 2017). Sohrab, et al. analyzed the effect of drinking pomegranate juice for 12 weeks in subjects with T2DM (Sohrab et al. 2014). After the intervention, hs-CRP and IL-6 were lower in the intervention group compared to the control group. A subsequent analysis reported that those who drank pomegranate juice had lower levels of soluble E-selectin (sE-selectin) (Sohrab et al. 2018). In a study by Razani et al., hospitalized patients with ischemic heart disease (IHD) were randomized to drink pomegranate juice or water for 5 days (Razani, Dastani, and Kazerani 2017). No differences were found in inflammatory or metabolic parameters, but a positive effect was observed in levels of MDA and troponin in patients that consumed pomegranate juice compared to control, these results suggest less damage to the heart. In another clinical trial, patients with chronic hemodialysis were randomized to drink pomegranate juice or placebo for 1 year (Shema-Didi et al. 2012). At the end of the intervention, TNF-α and IL-6 were lower in the intervention compared to the control group. Moreover, lower levels of oxidative stress indicators, fewer hospitalizations due to infections, and fewer cases of worsening carotid artery thickness were observed in the

intervention group compared to control; however, after three months of discontinuation, the benefits were lost.

Overall, consumption of pomegranate juice seems to reduce inflammation in individuals with T2DM and RD; moreover, some benefits in metabolic and clinical outcomes were observed in HT and IHD. However, adverse metabolic results were reported in individuals with MetS, possibly caused by the sugar and fructose content in juice.

Strawberry

Strawberry is a fruit rich in flavonoids (anthocyanins and catechins), flavonols (quercetin and kaempferol), phenolic and ellagic acids, glutathione, and ascorbic acid. Due to its high content of antioxidants, it could regulate inflammation in chronic diseases (Hannum 2004).

In a study that included 27 subjects with MetS, individuals were randomized to consume a strawberry beverage and water or just water (Basu et al. 2010). After 8 weeks of intervention, there was a reduction of VCAM-1, total cholesterol (TC) and LDL cholesterol (LDL-C) in the intervention compared with control group. In a subsequent study (Basu et al. 2014), 60 volunteers with abdominal adiposity and elevated serum lipids were randomly assigned to drink a low dose freeze-dried strawberry beverage (equivalent to 250 g/day of fresh strawberries), high dose freeze-dried strawberry beverage (equivalent to 500 g/day of fresh strawberries), placebo low dose beverage or placebo high dose beverage. After 12 weeks, inflammatory parameters were not affected with either intervention, but a benefit was described in the reduction of TC, LDL-C and MDA levels in the group that consumed the high dose strawberry beverage compared to the other groups. The same freeze-dried strawberry beverage (equivalent to 500 g/day of fresh strawberries), or placebo, was randomly indicated to 17 obese adults with knee osteoarthritis for 12 weeks (Basu et al. 2018). Authors reported that high sensitivity TNF-α (hsTNF-α) and soluble TNF-Receptor2 (sTNF-R2) decreased in the strawberry group compared to control group. The effect of strawberry beverages were also studied in overweight/obese adults (Ellis et al. 2011) and women with T2DM (Moazen et al. 2013). After 6 weeks, no significant differences were found in inflammatory and metabolic parameters between groups, in either study. Another study randomized 17 obese adults with knee osteoarthritis to drink a strawberry beverage or placebo (Schell, Scofield et al. 2017). After 12 weeks of intervention, a significant reduction of IL-6, IL-1β and MMP-3 was observed in individuals that consumed the strawberry beverage compared with control. Interestingly, in the intervention group, a reduction of constant pain, intermittent pain and total pain was described, measured by the intermittent and constant osteoarthritis pain questionnaire (ICOAP). A different study included 20 obese adults randomized to consume a frozen strawberry powder spread over several foods and drinks or placebo (Zunino et al. 2012). Diet was individualized and controlled for all participants. Even so, after 3 weeks of intervention, no differences were observed in inflammatory parameters, but TC was lower in the group that consumed strawberry powder compared with placebo.

In summary, a positive benefit in reducing inflammation was observed with the consumption of strawberry beverages specifically in MetS and obese adults with osteoarthritis. Additionally, strawberries contributed to reduction of TC, LDL-C and displayed antioxidant effects in overweight/obese individuals. Clinically, consumption of strawberries helped reduce pain in patients with osteoarthritis.

Other fruits and vegetables

Several plant foods have been found to contain high amounts of diverse antioxidant compounds, vitamins and minerals (Prasad, Sung, and Aggarwal 2012); however, few have been investigated for their possible anti-inflammatory effects on humans. The effects of purple carrot and grapefruit are described.

A study included 16 overweight/obese men, randomized to consume dried purple carrot or dried orange carrot (Wright, Netzel, and Sakzewski 2013). It is important to note that purple carrots have 4.6 times more phenolic compounds and 2 times more α-carotene than orange carrots (Alasalvar et al. 2001); even so, no differences were observed in CRP or metabolic parameters.

Another study analyzed overweight/obese adults that consumed fresh Rio red grapefruit compared to control (Dow et al. 2013). Both groups were advised to consume a standard diet restricted in vegetables and fruits with high content of polyphenols and carotenoids. Inflammatory parameters were not affected by the intake of grapefruit. However, it is important to note that 10 individuals that had baseline hs-CRP $\geq$3.0 mg/L showed decreased levels of this molecule after intervention (4.1 ± 0.7 to 3.3 ± 1.2 mg/L, $p = 0.08$). This suggests that individuals with high baseline levels of hs-CRP could benefit from regular grapefruit consumption.

More high-quality studies are necessary to evaluate the effects of fruits and vegetables on inflammation and metabolism.

Whole grain products

In comparison with fruits and vegetables, whole grains have more insoluble fiber, bound phenolic compounds, vitamin E, and phytosterols (Neacsu et al. 2013; Zhang and Hamaker 2010; Fardet 2010). Fiber from whole grain products has been attributed with multiple health benefits, including better digestion and establishment of a well-balanced microbiota that promotes a healthy gut barrier, prevents establishment of pathogens and provides immune-modulating nutrients (Zeng, Lazarova, and Bordonaro 2014).

Most of the trials analyzed the effect of the consumption of whole wheat products, compared to refined wheat products as a control, on serum cytokines and some metabolic parameters, on overweight and obese adults (Brownlee et al. 2010; Kopf et al. 2018; Lambert-Porcheron et al. 2017; Roager et al. 2019; Vitaglione et al. 2015). Even though, no differences were observed in inflammatory or metabolic parameters between groups, some studies reported lower levels of lipopolysaccharide binding protein (LBP) (Kopf et al. 2018) and TNF-α (Vitaglione et al. 2015) in the groups

that consumed whole wheat products. The consumption of a biscuit high in slowly digestible starch, compared to a rusk biscuit low in slowly digestible starch, resulted in lower fasting blood glucose (FBG) levels (Lambert-Porcheron et al. 2017). Interestingly, when whole grain products were consumed *ad libitum*, compared to refined products consumed *ad libitum*, levels of CRP, IL-6 and IL-1β were reduced (Roager et al. 2019); additionally, a positive outcome was observed in reduced body weight and sagittal abdominal diameter, and increased fat free-mass in the group that consumed whole grains *ad libitum*. Another study compared a group that consumed sorghum products with a group that consumed wheat products; both groups followed a hypocaloric diet (Stefoska-Needham et al. 2017). At the end of the interventions no differences were observed.

Whittaker et al. included 22 adults with acute coronary syndrome (ACS) to consume organic khorasan wheat products or organic semi whole wheat products as a control group for 8 weeks (Whittaker et al. 2015). A washout period of 8 weeks was implemented between interventions. Several differences were observed, levels of TNF-α, fasting blood glucose (FBG), total cholesterol (TC), LDL-C and insulin decreased in the group consuming organic khorasan wheat products compared with control; additionally, oxidative markers (L-derived ROS, M-derived ROS, L-lipoperox and M-lipoperox) were also reduced significantly in the intervention group. In overweight/obese individuals with MetS, a diet based on whole grain cereal products did not result in differences in inflammatory or metabolic parameters, when compared to a diet based on refined cereal products (Vetrani et al. 2016). On the other hand, an increase in serum propionate production was observed in the individuals that consumed the whole grain diet, which probably resulted from fiber fermentation by the microbiota in the colon. The increase in propionate could lead to a reduction in postprandial insulin concentrations.

In summary, the consumption of whole grains can regulate inflammation and some metabolic parameters in overweight/obesity and ACS; moreover, it promotes propionate production, particularly when whole grain products are consumed *ad libitum*, as part of a whole grain rich diet.

Animal source food

Yogurt

Yogurt is a fermented dairy product that constitutes a natural source of probiotics that can survive their passage through the stomach and intestine. Yogurt is also an adequate source of protein and calcium, among other nutrients. Jaffari et al. evaluated the effect of low fat yogurt enriched with vitamin D versus low fat yogurt, in postmenopausal women with T2DM (Jafari et al. 2016). After 12 weeks of intervention, hs-CRP, FBG, insulin and HOMA-IR (homeostatic model assessment of insulin resistance) were reduced in the individuals that consumed vitamin D enriched yogurt, whereas omentin levels were increased. The increase in omentin has an important clinical significance because it is an anti-inflammatory adipokine associated with insulin sensitivity, glucose metabolism and cardiovascular protection (Watanabe et al. 2011). There were other important differences like lower BMI, waist circumference and percentage of fat mass in women that consumed vitamin D enriched yogurt.

Meijil et al. randomized 35 overweight and obese adults to consume low-fat dairy products or fruit-derived products rich in carbohydrates during 8 weeks (van Meijl and Mensink 2010). At the end of the interventions, sTNFR-2 was higher in the group that consumed low-fat dairy products compared with the group that consumed fruit-derived products. One of the biological mechanisms that can restrict the potentially harmful effects of TNF-α is the inducible proteolytic cleavage of cell surface TNF receptors. This results in the downregulation of the membrane receptors and the formation of soluble forms of the receptor which, by competing for TNF, can block its function (Sedger and McDermott 2014). Studies have indicated that cleavage of the TNF receptors occurs constantly and is enhanced in inflammatory conditions. Thus, production of TNF in chronic diseases is therefore likely to result in increased serum concentrations of sTNFR that have an antagonist function. It has been correlated with BMI ($r = 0.50$), fat-free mass ($r = 0.61$), and waist-to-hip ratio ($r = 0.39$) (Fernández-Real et al. 1998).

In another clinical trial conducted by Neyestani, et al., 90 adults with T2DM were randomized to drink a Persian yogurt drink fortified with different concentrations of calcium and vitamin D (CDD: 500 mg calcium and 1000 IU vitamin D3; DD: 300 mg calcium and 1000 IU vitamin D3; PD: 300 mg calcium and no detectable vitamin D3) (Neyestani et al. 2012). This study reported that 73.3% of patients had vitamin D deficiency at baseline, so it is not unexpected that supplementation with vitamin D resulted in lower fibrinogen levels compared with the group that did not receive vitamin D. In epidemiological studies vitamin D deficiency has been associated with elevated levels of fibrinogen (Mellenthin et al. 2014) and cardiovascular complications (Kannel et al. 1987), since fibrinogen is an important component of the main mechanisms of cardiovascular disease (inflammation, thrombogenesis and atherogenesis) (Libby 2006). Moreover, in the last years, vitamin D supplementation has been associated with increased insulin sensitivity, mostly in individuals with vitamin D deficiency, but results are still controversial (Krul-Poel et al. 2017). In this study, HOMA-IR was lower in the groups that consumed vitamin D fortified yogurt than in those without vitamin D. It is important to mention that even though patients were consuming the yogurt fortified with vitamin D, they did not reach normal serum concentrations (Neyestani et al. 2012).

A study by Zarrati, et al. included 75 overweight/obese adults. Participants were randomized to drink a yogurt supplemented with probiotics in addition to a low calorie diet (PLCD), a yogurt supplemented with probiotics without a low calorie diet (PWLCD) or a standard yogurt and low calorie diet (SLCD) (Zarrati et al. 2014). The probiotic yogurt was prepared with the starter cultures *Streptococcus thermophilus* and *Lactobacillus bulgaricus,* and was enriched with

probiotic cultures based on lactobacilli and bifidobacteria (*Lactobacillus acidophilus* LA5, *Lactobacillus casei* DN001, *Bifidobacterium lactis* BB12). The concentration of each probiotic strain was 1×10^7 colony-forming units/mL. Standard yogurt was prepared with the same starter cultures *S. thermophilus* and *L. bulgaricus*. According to basal and final measurements, the three groups showed significant reductions in hs-CRP, IL-17 and TNF-α. Comparison between groups showed changes in these molecules were different; however, the addition of a low-calorie diet to the probiotic yogurt seems to enhance the benefits. The importance of probiotics in chronic inflammatory conditions is related to the establishment of a healthy gut microbiota, which contributes to the integrity of the intestinal mucosal barrier function. Gut microbiota also favors the production of metabolites, such as short chain fatty acids, through prebiotic fermentation. These metabolites possess epigenetic mediated metabolic- and immune-modulating mechanisms. For example, probiotics have been shown to restore and prevent relapse in inflammatory bowel disease (Derwa et al. 2017; Kim, Keogh, and Clifton 2018).

Overall, the most evident benefits for the regulation of inflammatory parameters in overweight, obesity and T2DM, were demonstrated in yogurt fortified with vitamin D and yogurt enriched with diverse strains of probiotics. In individuals with overweight and obesity the consumption of yogurt in addition to a low-calorie diet is effective in modulating inflammation.

Other animal source food

Sardines are affordable fish rich in omega-3 fatty acids, eicosapentaenoic, docosahexaenoic and alpha-linolenic acids (EPA, DHA and ALA). These provide a beneficial effect preventing heart diseases by lowering lipoprotein levels, they are also associated with other positive health outcomes related to their anti-inflammatory properties. Moreover, fish is an excellent source of protein and contains no carbohydrates, these characteristics contribute to glucose control in patients with T2DM (Evert et al. 2014).

In a pilot trial that included 35 adults with T2DM, patients were randomized to a standard diet enriched with sardines or a standard diet (Balfegó et al. 2016). No differences were found among groups; however, after 6 months of intervention, the sardine group had a significant reduction in HOMA-IR and an increase in total adiponectin. These results suggest that frequent consumption of sardines may contribute to insulin sensitivity and, because of the increased levels of adiponectin, to reduced inflammation. The control group had a significant reduction of HOMA-IR that could be associated with the dietary intervention, but showed an increase in TNF-α, which suggests an exacerbation of inflammation.

In another study, 24 women with MetS were randomized to consume low-fat dairy products (milk, yogurt and cheese) or carbohydrate rich products (granola bars and juice) (Dugan et al. 2016). After 6 weeks of intervention, the dairy products group had lower levels of TNF-α and MCP-1 compared with control group.

To summarize, dairy products could help regulate inflammation in individuals with MetS. More studies are necessary to evaluate the effect of other animal source foods rich in omega-3 fatty acids, probiotics, or other anti-inflammatory components.

Tea and spices

Through history, cultures around the world have added spices and herbs to food preparations, not only to add flavor and color, but also for medicinal purposes (Low 2006). Some molecular components in tea and spices are antioxidants and have been identified to possess anti-inflammatory properties through different mechanisms (Howitz and Sinclair 2008). The following section describes teas, spices, and condiments studied for their anti-inflammatory properties.

Green tea

For years green tea has been consumed for its health benefits, which have been recently related to its antimicrobial and antioxidant properties. These benefits are linked to its high content of catechins, which include epicatechin, epicatechin-3-gallate, epigallocatechin, and, the most abundant, epigallocatechin-3-gallate (EGCG) (Nikoo, Regenstein, and Gavlighi 2018). EGCG is the most biologically active component of green tea, in animal models it has been shown to be effective in modulating multiple aspects of innate and adaptive immunity; particularly, the anti-inflammatory and T cell-suppressing effects of green tea appear to have a potential clinical application (Wu et al. 2018).

In a study by Basu, et al., 35 adults with MetS were randomized to consume, for 8 weeks, 4 cups of green tea, 2 capsules of green tea extract, or water (Basu, Du et al. 2011). No differences were found between groups. Nevertheless, groups that consumed green tea showed reduced levels of plasma serum amyloid alpha (SAA) compared with control. SAA is a group of proteins related to the acute phase response and functions as a cytokine-like protein, so it has become recognized in inflammatory pathways (Sack 2018). Because of its lipophilicity, SAA is related to lipid transport and metabolism, as well as atherosclerosis, and could be involved in reduced levels of adiponectin; moreover, it is correlated with BMI ($r = 0.8$) (Yang et al. 2006).

Bogdanski et al. randomized 56 obese adults with HT to consume green tea extract or placebo (Bogdanski et al. 2012). After 3 months of intervention, a higher reduction in CRP, TNF-α, TC, LDL-C, TG, HOMA-IR and insulin, and an increase in high density lipoprotein-cholesterol (HDL-C) were observed in the green tea group compared with the placebo group. Additionally, a positive change in systolic and diastolic blood pressure was observed in the green tea group compared to control. No differences were observed in hs-CRP or metabolic parameters, in adults with prediabetes or T2DM that consumed less than 1 bag of green tea a day for 2 months, compared to control (Fukino et al. 2005).

Obese women with pre-hypertension that consumed green tea extract showed no differences in inflammatory or metabolic parameters, but a positive change in systolic blood pressure was observed, when compared to control (Nogueira et al. 2017).

Overall, consumption of green tea for at least 3 months reduces inflammation and improves metabolism in obesity and HT. Additionally, it could help regulate blood pressure.

Turmeric

A spice commonly used in Indian cuisine is turmeric, which has been widely studied in the recent decade. Its active ingredient, curcumin, constitutes approximately 2–5% of turmeric powder (Chainani-Wu 2003). This compound regulates some pathways involved in the inflammatory response (AhR, IL-1β, PKD and COX), energy metabolism (mTOR), and cellular stress response (AKT) (Howitz and Sinclair 2008). Curcumin has been studied in multiple clinical trials, but few studies have used turmeric root. For this review, 16 articles were excluded because they used the active compound curcumin instead of turmeric.

The bactericidal effect of turmeric was analyzed in 36 adults infected with H. pylori, individuals were randomized to take turmeric tablets or drug treatment for 4 weeks (Koosirirat et al. 2010). A gastric biopsy was obtained from individuals and mRNA expression of *Il1b*, *Tnfa* and *Il18* was measured. No differences were found among groups. The percentage of individuals that cleared the infection was lower in the group that received turmeric than in the group that received drug treatment (5.9 vs 78.9, $p < 0.0001$).

Adults with diabetic nephropathy (DN) were randomized to consume turmeric or placebo for 2 months (Khajehdehi et al. 2011). At the end of intervention, the turmeric group had lower levels of urinary IL-8, serum TGF-β, and proteinuria, compared with the placebo group. The decrease in proteinuria is an important finding that may prove the clinical relevance of turmeric in patients that suffer from DN. In a similar study, 71 adults with chronic hemodialysis were randomized to take turmeric or placebo for 12 weeks (Samadian et al. 2017). Although no differences were observed between groups, the turmeric group had a significant reduction in IL-6. It is important to note that before the intervention, albumin levels were lower in the turmeric group and at the end of the intervention there were not differences between groups, so the recovery in albumin levels was statistically and clinically significant.

In summary, turmeric is a spice with multiple benefits and a powerful antioxidant, and should be recommended to reduce inflammation; importantly, in individuals with nephropathy or in hemodialysis, turmeric may help reduce proteinuria.

Other spices and condiments

Among other spices, cardamom is common in Indian and middle-eastern cuisine, it has been attributed with properties such as antioxidant, diuretic, anti-cancer and anti-inflammatory (Majdalawieh and Carr 2010; Gilani et al. 2008). In a clinical trial, 80 overweight/obese women with IR were randomized to take cardamom or placebo capsules (Kazemi et al. 2017). Hs-CRP decreased in the cardamom group after intervention, compared with control.

Red pepper is rich in vitamin C, vitamin E, carotenoids and, importantly, capsaicin (Palevitch and Craker 1996). Studies on capsaicin have shown positive effects decreasing TC and TG levels, it has anti-lithogenic properties, protects the integrity of red blood cells, and has antioxidant and anti-inflammatory effects (Srinivasan 2016). The effect of red pepper was compared with turmeric or placebo, added to food preparations, in women with overweight or obesity (Nieman et al. 2012). After 4 weeks of intervention, no differences were found in inflammation or metabolism.

Nigella sativa (also known as black seed) contains an array of nutrients, including unsaturated fatty acids, cardiac glycosides, saponins, flavonoids, vitamin C, calcium, iron and phosphorus (Kooti et al. 2016). In a clinical trial, 48 adults with mild or moderate ulcerative colitis (UC) were randomized to consume *Nigella sativa* powder or placebo for 6 weeks (Nikkhah-Bodaghi et al. 2019). Surprisingly, the individuals from the intervention group had increased levels of hs-CRP and TNF-α, compared with the placebo group. This report could suggest that *Nigella sativa* has immune stimulating and pro-inflammatory effects, which could be helpful as an adjuvant in the treatment of infectious diseases but should be indicated with caution.

Black tea is a staple and one of the most frequently consumed beverages worldwide; drinking tea has been considered a health promoting habit since ancient times. *Camellia sinensis*, from which tea is produced, is a plant rich in polyphenols, amino acids, volatile compounds, and alkaloids, that have been demonstrated in vitro to block signaling pathways that lead to the activation of transcription factors that promote the expression of pro-inflammatory genes. Theaflavins, which are the main polyphenolic compounds of black tea are responsible for most of the physiological effects of black tea in prevention of cardiovascular diseases, particularly atherosclerosis and coronary heart disease (Singh et al. 2017; Khan and Mukhtar 2013). A study included 66 adults with CAD, individuals were randomized to a group that consumed black tea or to a control group (Widlansky et al. 2005). After 4 weeks of intervention, no differences were found in CRP or metabolic markers between groups.

All in all, tea and multiple spices are commonly used as part of culinary traditions and for their medicinal properties; however, existing studies describing their impact on inflammation are controversial. More clinical trials, considering different doses or presentations of the wide variety of tea and spices, are necessary to provide scientific evidence of their anti-inflammatory effect. Nevertheless, their continued use as part of food preparation and tradition is recommended.

Legumes

Since ancient times, legumes have been the main source of protein in many cultures of the world and continue to be so

mainly because of their accessibility. Its health benefits have been attributed to the high amounts of fiber and minerals they provide (Tharanathan and Mahadevamma 2003).

Soy

Soy is a legume that contains an important source of aminoacids and polyphenols (Friedman and Brandon 2001). The most abundant polyphenols in soy are isoflavones. These have been attributed benefits for women undergoing menopause and for cardiovascular system health (Han et al. 2002).

Acharjee, et al. analyzed the effect of the addition of half a cup of soy nuts to the standard diet of 11 postmenopausal women with MetS, and compared them with a control group that consumed a standard diet (Acharjee et al. 2015). After 8 weeks of intervention CRP, sICAM-1, and TG, decreased in the intervention group compared with control. Additionally, diastolic blood pressure decreased in women that consumed soy nuts. In the same study, a subanalysis indicated that in women without MetS, neither systolic and diastolic pressure, nor CRP decreased with the consumption of soy. In a crossover trial that included 42 postmenopausal women with MetS, participants were randomized to eat roasted soy nut (instead of red meat), soy nut protein (instead of red meat) or no soy nut (one serving of red meat/day), during 8 weeks (Azadbakht et al. 2007). The three groups were instructed to follow a diet based on the "Dietary Approaches to Stop Hypertension" (DASH) recommendations. After the interventions, differences among groups included CRP, TNF-α and E-selectin; the group that consumed roasted soy nut had the highest improvements in inflammatory parameters, which suggests an added benefit for consuming the whole food. Authors analyzed the patients' food diary and reported that the control group that consumed red meat also consumed more total fat and less polyunsaturated fatty acids and fiber.

No effect was observed in adults with end-stage renal disease (ESRD) on chronic hemodialysis that consumed soy products, compared to control (Fanti et al. 2006). Fortyfive adults with nonalcoholic fatty liver disease (NAFLD) were included in a study by Kani et al.; individuals were randomized to a low-calorie and low-carbohydrate diet containing soy, a low-calorie and low-carbohydrate diet, or a low-calorie diet (Kani et al. 2017). After 8 weeks, the first group had lower levels of hs-CRP than the other groups. Another study analyzed the effect of soymilk in 25 adults with DN (Miraghajani et al. 2012). Patients were randomized to drink 240 mL/day of soymilk or cow milk, but no differences were detected among groups. In a crossover trial, Nasca et al. evaluated the effect of soy consumption in 12 postmenopausal women with HT (Nasca, Zhou, and Welty 2008). Women were randomized to consume soybeans (replacing 25 g of non-soy protein) and were indicated to follow the "Therapeutic Lifestyle Change" recommendations (TLC), or to follow the TLC recommendations (control group). The soy group consumed more energy, less total fat and saturated fat compared with control. In a previous study in the same cohort of patients, no differences were found in physical activity (Welty et al. 2007). At the end of the interventions, sVCAM-1, LDL-C and Apo B decreased in the soy diet group compared with the control group. The effect of the consumption of kinako (soy product) was evaluated in 30 women with MetS, but no differences were observed when compared with the control group (Simão et al. 2012). In a clinical trial with 38 adults in hemodialysis, individuals were randomized to consume whey soy protein, soy protein, or placebo (Tomayko et al. 2015). After 6 months of intervention, IL-6 was lower in both soy groups, compared with placebo group.

In summary, postmenopausal women with MetS and subjects with NAFLD may benefit from soy consumption to regulate some inflammatory parameters. Moreover, soy consumption could help reduce TC and TG levels, and may be beneficial in HT control.

Other legumes

A randomized controlled trial included 30 overweight/obese adults (Hermsdorff et al. 2011). The intervention group consumed a diet based on legumes (lentils, chickpeas, peas, or beans, but no soybean legumes), and the control group consumed a diet restricted in legumes. Both groups had a 30% restriction of total energy requirement and the interventions lasted 8 weeks. At the end of interventions, no differences were observed between groups.

Lambert et al. included 44 overweight or obese adults and randomized them to consume yellow pea fiber distributed in three biscuits or placebo (three biscuits without yellow pea fiber) for 12 weeks (Lambert et al. 2017). To avoid gastrointestinal symptoms, fiber was gradually increased, 5 g at a time. Leptin was lower in the pea fiber group after intervention. Additionally, FBG, insulin, gastric inhibitory peptide, glucagon-like peptide 1, ghrelin, amylin and peptide YY, were measured during the oral glucose tolerance test and, compared with placebo, the results suggest that intake of yellow pea fiber could regulate postprandial glucose metabolism.

Overall, the beneficial effects demonstrated from the consumption of legumes could be explained by their high fiber content and the fact that, in these clinical trials, animal protein was replaced by legume protein. Saturated fatty acid consumption was consequently reduced in the diet of the participants. Also, fiber contributed to better glucose metabolism and may have aided in better digestion. Soy consumption could regulate inflammation in postmenopausal women with MetS, HT, in individuals with NAFLD and in maintenance hemodialysis.

Nuts and seeds

Several epidemiological studies have focused on nuts and seeds because of their association with prevention of CVD and T2DM. Their protective effect is related to their content of unsaturated fatty acids, fiber, and antioxidants such as vitamin E, all of which have anti-inflammatory properties. They are also a good source of protein (Jiang et al. 2006).

Almonds

Almonds are a type of nut rich in fatty acids (35 to 67 g/100 g of almonds), protein (14 to 61 g/100 g of almonds) and fiber (2.5 to 14 g/100 g of almonds); its nutrient content depends on the region it was cultivated. It is important to note that the fatty acids contained in almonds are mainly mono and polyunsaturated; moreover, almonds are rich in vitamins E, biotin, folate, niacin, pantothenic acid, pyridoxin, riboflavin and thiamin (Yada, Lapsley, and Huang 2011).

In a randomized crossover trial, 45 adults with CAD were studied (Chen et al. 2015). The intervention consisted in consuming almonds and following the National Cholesterol Education Program (NCEP) Step I recommendations, for 22 weeks; the control group followed the NCEP Step I recommendations. No differences were found among groups.

In another clinical trial, 20 adults with T2DM were randomized to consume 20% of total energy intake from almonds, or to a control group (Gulati, Misra, and Pandey 2017). After 24 weeks of intervention, the reduction in hs-CRP was higher in intervention than in control group. Also, FBG, TC and LDL-C were significantly reduced in the group that consumed almonds compared with control. Importantly, levels of adiponectin increased in the intervention group. In a similar article, 20 adults with T2DM were randomized to consume 20% of total energy intake from almonds and follow the NCEP Step II recommendations, or to follow the NCEP Step II recommendations (Liu et al. 2013). Both interventions lasted 4 weeks. After the intervention, the almond group showed a decrease in CRP and IL-6, compared with control. In a study that included 84 adults with T2DM, individuals were randomized to consume almonds or isocaloric cookies (Jung et al. 2018). After 4 weeks, no differences were found in inflammatory parameters among groups. Differences between groups were observed in TC and LDL-C.

To summarize, almonds can help lower inflammation as was demonstrated by the reduction in CRP and IL-6 in individuals with T2DM. Moreover, consumption of almonds mainly produces a metabolic effect, lowering levels of glucose, TC, and LDL-C, while increasing levels of the anti-inflammatory adipokine, adiponectin.

Chia

Chia is a seed originated in South America which has been used for its medicinal properties since the 16th century. It is high in fat (21.5 to 32.72 g/100 g of chia), protein (18.5-22.3 g/100 g of chia), and fiber (20 to 40 g/100 g of chia). Furthermore, it has a high content of antioxidant phenolic compounds (8.19 g/100 g of chia) (Cahill 2003). Chia seeds have been attributed several health-promoting and anti-inflammatory properties, mainly because of its high content of omega-3 fatty acid ALA (75% of its weight) (Valdivia-López and Tecante 2015).

To prove its effect in chronic low-grade inflammation, Nieman et al. randomized 76 obese adults to consume chia seeds or placebo during 12 weeks (Nieman et al. 2009). No differences between groups were observed, except for ALA levels, which dramatically increased in the group that consumed chia compared with placebo (24.4% *vs* −2.8%, $p = 0.012$). Another study reported no differences in CRP or metabolic parameters, in 26 adults with HT randomized to consume chia flour or placebo, after 12 weeks of intervention (Toscano et al. 2014).

Vuksan et al. randomized 77 adults with T2DM and a BMI between 25 and 40 kg/m^2 to consume chia or bran and oats as placebo (Vuksan et al. 2017). After 6 weeks of intervention, the chia group had lower levels of CRP and higher levels of adiponectin, compared to the placebo group. Additionally, total body weight and waist circumference were reduced significantly in the intervention group compared with placebo.

Overall, chia consumption by overweight and obese individuals with T2DM, for more than 6 weeks, may regulate inflammation, improve metabolism and reduce body weight.

Flaxseed

Flaxseed is also rich in ALA (approximately 52% of total fatty acids), protein, fiber, and vitamin E. Several benefits have been attributed to this seed, such as cancer prevention, serum lipid regulation, anti-inflammatory and antioxidant (Oomah 2001).

In a randomized crossover trial, Hutchins et al. included 25 pre-diabetic adults (Hutchins et al. 2013). They were supplemented with 26 g/day of flaxseed, 13 g/day of flaxseed or not supplemented (control), for 12 weeks. No significant differences were found in inflammatory parameters post-intervention; however, FBG was significantly reduced in the group that consumed 13 g of flaxseed compared with control. Insulin was significantly lower in the group that consumed 13 g compared to both, the group that consumed 26 g (mean change -2 ± 4.7 *vs* 1 ± 4.3, $p = 0.021$) and the control group (mean change -2 ± 4.7 *vs* 2 ± 6.8, $p = 0.013$). Similarly, the HOMA-IR was significantly lower in the group that consumed 13 g compared to both, the group that received 26 g (mean change -2 ± 4.7 *vs* 4 ± 1.2, $p = 0.012$) and the control group (mean change -2 ± 4.7 *vs* 0.7 ± 1.8, $p = 0.08$). Authors analyzed the nutrient composition from the participants' diet and reported that the consumption of vitamin E and soluble fiber was higher in the group that consumed 26 g of flaxseed, which is explained by the higher consumption of flaxseed. The reduction observed in insulin resistance could be related to the high fiber content of flaxseed. It is well known that a high amount of fiber in the intestine may delay nutrient absorption, promote production of short chain fatty acids and bring balance to the microbiota (Weickert and Pfeiffer 2008).

In a study that included 30 patients in hemodialysis with lipid abnormalities, individuals were randomized to consume 40 g a day of flaxseed or to a control group (Khalatbari Soltani et al. 2013). After 8 weeks of intervention, the group that consumed flaxseed had reduced levels of CRP, TC, LDL-C and TG, and increased levels of HDL-C, compared with control group. In a randomized crossover trial, 9 obese insulin resistant adults were advised to

consume flaxseed or wheat bran for 12 weeks (Rhee and Brunt 2011). No differences in inflammatory parameters were found among flaxseed and wheat bran groups; however, a significant reduction in FBG was observed in the flaxseed group compared with the wheat bran group.

Flaxseed was proven to have a positive effect reducing CRP in adults in hemodialysis with lipid abnormalities. Moreover, the metabolic benefits of flaxseed were consistent in the regulation of insulin resistance and dyslipidemia.

Pistachios

Pistachios have been part of the eastern diet since ancient times. They are attributed with several cardiovascular and metabolic benefits due to their high content of polyunsaturated fatty acids (approximately 30% of total fat), and their high content of fiber, antioxidants, potassium, magnesium, and vitamins K and E (Dreher 2012).

Gulati et al. included 60 adults with MetS, individuals were randomized to consume 20% of total energy from pistachios for 24 weeks, or to a control group (Gulati et al. 2014). The group that consumed pistachios had reduced levels of hs-CRP, TNF-α, FBG, TC and LDL-C, and increased levels of adiponectin, compared with control. In a very similar study, 30 patients with T2DM were randomized to consume 20% of their total energy from pistachios or to a control group (Sauder et al. 2015). After 4 weeks of intervention, no differences were observed between groups in inflammatory parameters, but the pistachios group had lower TC and TG than the control group.

Another study by Parham et al. randomized 48 adults with T2DM to consume 50 g of pistachios or placebo for 12 weeks (Parham et al. 2014). No differences were observed in CRP, but lower levels of FBG and glycated hemoglobin (HbA1c) were reported in the intervention group, compared with placebo.

In summary, the high content of fat, fiber, antioxidants, vitamins, and minerals in pistachios may contribute to the modulation of inflammation and lipid metabolism in individuals with MetS and T2DM.

Nut mixes and other nuts

Casas-Agustench et al. analyzed the effect of consuming a mixture of nuts (walnuts, almonds and hazelnuts) and standard dietary recommendations for 12 weeks, compared with standard dietary recommendations (control group) (Casas-Agustench et al. 2011). The study included 50 adults with MetS. At the end of the intervention, differences among groups were observed in lower levels of IL-6, insulin and HOMA-IR, in the intervention group. A similar study analyzed the effect of consumption of mixed nuts (walnuts, peanuts, and pine nuts), compared to a control group, in 60 adults with MetS (Lee et al. 2014). However, after 6 weeks, no differences were observed.

Another study included 107 overweight/obese adults, randomly assigned to consume 60 g/day of hazelnuts, 30 g/day of hazelnuts or no hazelnuts (control) for 12 weeks (Tey et al. 2013). At the end of intervention, no differences were observed in either inflammatory or metabolic parameters among groups.

These studies show that nut mixes could be effective in reducing IL-6 and modulating insulin metabolism, preferably those that include walnuts, almonds and hazelnuts.

Oils

Oils contain saturated, monounsaturated, and polyunsaturated fatty acids, each in different proportions. Some examples of vegetable oils containing less amounts of saturated fatty acids are rapeseed, flaxseed, safflower, sunflower, almond, peanut and grape oils (Orsavova et al. 2015; Khattab and Zeitoun 2013). Other oils with higher proportions of mono and polyunsaturated fatty acids are those obtained from cold-water fish and algae (Kris-Etherton, Grieger, and Etherton 2009).

Fish oil

Even though several vegetable oils contain high quantities of polyunsaturated fatty acids, omega-3 fatty acids, EPA and DHA, are more abundant in cold-water fish oil because fish feed on algae rich in DHA and EPA (Kris-Etherton, Grieger, and Etherton 2009). Both fatty acids have been demonstrated to have positive effects on cardiovascular health, such as reduction of TG and increase of HDL-C (Eslick et al. 2009).

In a clinical trial that randomized 37 women with breast cancer to consume fish oil or placebo for 30 days no differences were observed in hs-CRP, lymphocyte populations or metabolic parameters (da Silva Paixão et al. 2017).

In a study that included 50 overweight/obese adults, individuals were randomized to consume fish oil or placebo for 6 weeks (Gammelmark et al. 2012). By the end of intervention, no differences were observed in inflammatory parameters. However, higher levels of adiponectin and FBG were observed in the fish oil group compared with placebo. It is important to note that baseline levels of FBG were significantly higher in the fish oil group than the placebo group. No differences were observed in another study that included 11 obese men, randomly assigned to consume fish oil or placebo for 6 weeks (Plat et al. 2007).

Two similar studies investigated the effect of fish oil on inflammatory cytokines in colorectal cancer patients (Mocellin et al. 2013; Silva et al. 2012). Both studies randomized patients to consume 2 g of fish oil or placebo, for 9 weeks. Mocellin et al. included 11 patients undergoing chemotherapy treatment and found that the fish oil group had significantly lower CRP levels compared with placebo. Silva et al. included 18 patients receiving chemotherapy election treatment, and by the end of intervention found no differences among groups.

In a study that included 34 women with MetS, patients were randomized to consume fish oil or to a control group (Simão et al. 2012). After 90 days of intervention, no differences were observed between groups. The study by Toupchian et al. found no differences in *Tnfa* and *Il6* gene

expression in peripheral blood mononuclear cells (PBMCs) from adults with T2DM that consumed fish oil, compared to control, after 8 weeks of intervention (Toupchian et al. 2018).

Overall, according to the clinical studies analyzed in this review, fish oil consumption has little or no effect regulating systemic inflammation. Still, tissue specific inflammation may be impacted with fish oil supplementation. Also, the increase in adiponectin levels could benefit overweight/obese individuals consuming fish oil.

Flaxseed oil

While fish oil is the main source of DHA and EPA, flaxseed oil is one of the main sources of the fatty acid ALA. Although the human organism is not very efficient converting ALA into DHA and EPA, the total content of polyunsaturated fatty acids (about 52%) in flaxseed oil seems to show promise in reducing inflammation (Riediger et al. 2008).

In a clinical trial by Hashemzadeh et al., 60 adults with T2DM and coronary heart disease (CHD) were randomized to consume flaxseed oil or placebo for 12 weeks (Hashemzadeh et al. 2017). A reduced gene expression of *Tnfa* and *Il1* was observed in the group supplemented with flaxseed oil compared to placebo. Furthermore, up-regulation of *Pparg* and down-regulation of lipoprotein (a) gene expression were reported in the flaxseed oil group, compared with the placebo group. In a different study, a reduction of CRP levels was demonstrated in adults in chronic hemodialysis that consumed flaxseed oil for 120 days, compared with placebo (Lemos et al. 2012).

Pan et al. included 68 participants with T2DM. They were randomized to consume 360 mg/day of flaxseed oil or placebo (rice flour devoid of soluble fiber) (Pan et al. 2007). After 12 weeks of intervention, hs-CRP and HbA1c levels were lower in intervention group than in placebo. Results on hs-CRP and IL-6 were obtained from a subsequent publication (Pan et al. 2008).

In summary, flaxseed oil proved to be efficient in lowering inflammation in individuals with T2DM and in individuals undergoing chronic hemodialysis. Also, patients with T2DM could benefit from the consumption of this oil to reduce HbA1c levels.

Other oils

In a trial by Baril-Gravel et al., 45 adults with abdominal obesity were randomized to one of five groups: canola oil enriched with oleic acid and DHA, canola oil enriched with oleic acid, canola oil, mix of flax and safflower oils or mix of corn and safflower oils (Baril-Gravel et al. 2015). After 4 weeks of intervention, when comparing all groups, individuals in the canola oil group had a reduction in hs-CRP. The highest increase of hs-CRP, in addition to a reduction in adiponectin, was observed in individuals that consumed the mix of flax and safflower oils; the group that consumed canola oil enriched with oleic acid and DHA had the highest increase in adiponectin. Irandoost et al. compared grape seed oil with sunflower seed oil in a study that included 39 overweight/obese women with IR (Irandoost, Ebrahimi-Mameghani, and Pirouzpanah 2013). In both interventions, the oil provided 15% of total energy intake; also, participants consumed a calorie restricted diet (500 kcal subtracted from total energy requirement). After 8 weeks, hs-CRP was significantly lower in the grape seed oil group compared with the sunflower oil group.

A study included 18 obese men randomized to consume rapeseed oil or olive oil for 4 weeks (Kruse et al. 2015). Authors chose rapeseed oil because it contains the same amount of monounsaturated fatty acids than olive oil but contains more polyunsaturated fatty acids. However, to assign the observed effects exclusively to the fatty acid contents in the oils, nutrient depleted cold-pressed extra virgin olive oil and nutrient depleted refined rapeseed oil were used. When comparing both groups, no differences were found in serum CRP and IL-6. Furthermore, *Il1b* and *Il6* mRNA were measured from a periumbilical adipose tissue biopsy, taken 4 hours after an overnight fasting and again after breakfast. *Il6* mRNA was lower in the rapeseed oil group in the fasted state and increased 4 h after the test meal. These transcriptional changes may suggest an inflammatory response in adipose tissue after feeding. This is consistent with other studies that demonstrate that during the fasting state metabolic changes occur that cause a switch toward oxidative phosphorylation, and this switch activates anti-inflammatory pathways (Mattson 2008). This adaptation process is part of the protection mechanisms activated in response to stress. Moreover, this process is reversed upon feeding, where the cells' metabolism switches back to glycolysis and may activate inflammatory pathways, demonstrated in this study by the increased expression of *Il6* mRNA. Even so, these changes were not reflected in the cytokine proteins measured in peripheral blood.

In a study that included 84 obese women, participants were randomized to consume Nigella sativa oil capsules or sunflower oil capsules as placebo (Mahdavi et al. 2016). For all participants, a calorie restricted diet was indicated (500 kcal subtracted from total energy requirement). After 8 weeks of intervention, the Nigella sativa oil group had lower levels of TNF-α and hs-CRP, compared with the placebo group. Neff, et al. included 36 overweight/obese adults, volunteers were randomized to consume algal DHA oil or a mixture of corn and soybean oils as placebo (Neff et al. 2011). After 4 months of intervention, the group that consumed algal oil had lower levels of TNF-α and higher levels of TC, compared with the placebo group. The cytokine results were provided by the authors.

The oils that were investigated in this review had positive results regulating inflammatory responses in individuals with obesity, T2DM, and colorectal cancer.

Summary of evidence

Table 1 gives an overview of all the foods analyzed. Foods able to modify inflammatory molecules in chronic diseases are indicated, these include cranberries, grape, pomegranate, strawberry, wheat, whole grain products, dairy products,

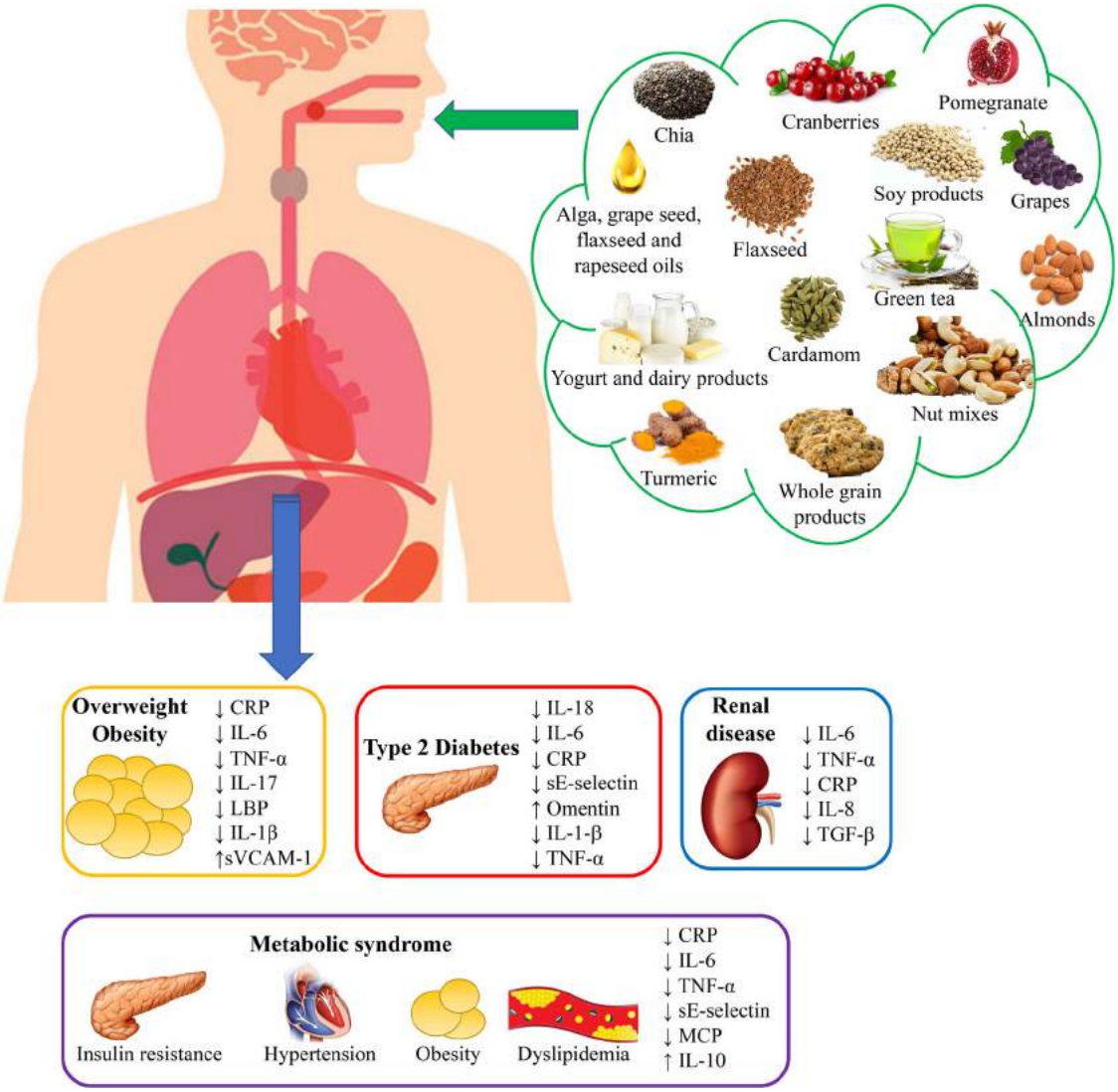

Figure 2. Graphical abstract of functional foods that modulate inflammation in chronic diseases. In this review several foods were described for their ability to modulate cytokines and other inflammation-related molecules in individuals with overweight/obesity, type 2 diabetes, renal disease and metabolic syndrome.

yogurt, green tea, cardamom, turmeric, soy foods, almonds, chia seeds, flaxseed, pistachios, algae oil, flaxseed oil and grapeseed oil. Chronic diseases that have been thoroughly studied and demonstrated to be more sensitive to food-mediated immune modulation are overweight/obesity, T2DM, MetS, and RD. Figure 2 illustrates foods demonstrated to have a positive effect downregulating inflammation for each disease. Only the conditions with more available information were included. It is important to note that for the purpose of this review authors identified foods with anti-inflammatory effects that were studied in clinical trials, however, other foods available may also have immune modulating properties.

Discussion

The importance of an adequate diet to maintain good health and homeostasis has been universally acknowledged. The Western dietary pattern—characterized by foods high in saturated fatty acids, hydrogenated oils, red meat and sodium, very low in high fiber foods like fruits, vegetables and whole grains, and low in fish and legumes— is associated with the development of low-grade inflammation, metabolic disturbances, dysbiosis in the gut microbiota and leaky gut, which sustains a proinflammatory vicious cycle (Franceschi and Campisi 2014; Monteiro and Azevedo 2010; Prasad, Sung, and Aggarwal 2012). On the other hand, the Mediterranean dietary pattern—characterized by foods high in unsaturated fatty acids, high fiber foods including fruits, vegetables, legumes and whole grains, high in fish and omega-3 fatty acids, and low in foods rich in saturated fatty acids, hydrogenated oils and sodium—has been associated with anti-inflammation, metabolic homeostasis, eubiosis in the gut microbiota and a healthy intestinal barrier. These factors lead to overall health and homeostasis. Because the Mediterranean dietary pattern has been associated with these health benefits, evidence on the foods, from all food groups, that have been proven to possess anti-inflammatory properties in a clinical setting were analyzed in this systematic review.

We analyzed several fruits and vegetables, dried cranberries, grapes, pomegranate and strawberries had effects at

reducing molecules associated with inflammation and metabolic alterations; even so, in some of the reports no effect was observed when compared to placebo. It is important to highlight the effect of grapes in increasing levels of IL-10 and adiponectin in individuals with metabolic syndrome. IL-10 is a potent anti-inflammatory cytokine, secreted by a number of immune cells, mainly regulatory T lymphocytes, its effect in tissues, including the adipose tissue, is to regulate inflammation and promote repair mechanisms. Adiponectin is an adipokine mainly secreted in the adipose tissue by adipocytes and other cell populations, it has an anti-inflammatory and regulatory effect on immune cells, and it is strongly involved in adipose tissue homeostasis (Monteiro and Azevedo 2010; Coussens and Werb 2002). The increase of both of these molecules may confer health benefits to individuals with MetS; however, no effect was observed in obese individuals. Strawberries demonstrated to have an anti-inflammatory effect, not only observed in the reduction of inflammatory cytokines, but importantly the effect was clinically observed in the reduction of pain in patients with osteoarthritis. This finding may be applied in the treatment of this population, since the addition of strawberries to the diet of patients with osteoarthritis may help manage pain and this alone can make a difference in their quality of life.

Whole grain products had the most positive impact in reducing inflammation in overweight and obese individuals. This is probably related to the high fiber content in these foods. Fiber, both soluble and insoluble, has been demonstrated to modulate the gut microbiota, this in turn shapes the immune response, both locally and systemically, toward a tolerogenic anti-inflammatory environment (Neacsu et al. 2013; Zeng, Lazarova, and Bordonaro 2014; Zhang and Hamaker 2010; Fardet 2010). Yogurt also had demonstrated anti-inflammatory effects in the same population and in T2DM, the effect was enhanced in yogurt fortified with vitamin D and enriched with probiotics. These may be responsible for the observed effects that, like fiber, may modulate the gut microbiota (Derwa et al. 2017; Kim, Keogh, and Clifton 2018). By reducing inflammation through the consumption of whole grain foods and yogurt in individuals with overweight and obesity, the development of associated diseases may be prevented. We stress the importance of recommending the addition of these foods to patients in the clinic.

It was surprising to discover that black and green tea had little effect in inflammation. Tea has constantly been associated with antioxidant and anti-inflammatory properties (Singh et al. 2017; Khan and Mukhtar 2013), and only one study demonstrated an anti-inflammatory effect in patients with CVD. Several factors may have influenced the results, including the type of dietary pattern the subjects consumed and the exposure to oxidizing agents, such as pollutants, which may have neutralized the antioxidant compounds in green tea. This is an important concern in the clinical trials analyzed, few controlled the diet of the study participants and this is an important confounding variable that should be controlled to have a more reliable observation of the specific effect of the food analyzed, although we understand the challenge of controlling the diet of the study population. On the other hand, turmeric had a positive effect in reducing inflammation in gastrointestinal disease. Few spices had a demonstrated effect on inflammation in clinical trials, probably because spices are usually added in small amounts to food preparations, we think that a sensible recommendation is to use a great variety of spices in small amounts to promote an added effect, as we have discussed, but also to protect the tissues from possible adverse effects that may be observed with higher doses (Low 2006; Chainani-Wu 2003).

In the Legumes group, only soy foods were anti-inflammatory in individuals with MetS, KD and NAFLD; importantly, soy proved effective at reducing blood cholesterol and triglyceride levels. Other legumes did not have a significant effect in inflammation but did show other health benefits in glucose and lipid metabolism. These effects may be related not only to their bioactive components and fiber, but also to the increase of plant-based protein to the expense of animal protein, some authors have associated this exchange to a lower risk of developing chronic diseases (Tharanathan and Mahadevamma 2003). Most of the Nuts and seeds group had an anti-inflammatory effect, these included almonds, chia seeds, flaxseed, nut mixes and pistachios in T2DM, MetS and KD. As in the case of legumes, these nuts and seeds had an important metabolic effect. Almonds also showed an increase in adiponectin, which, as mentioned above, is essential for adipose tissue homeostasis. An important finding is that chia seeds helped reduce body weight and waist circumference in overweight and obese individuals. This may also be related to the effect soluble fiber in chia may have in the modulation of the gut microbiota, an important player in the development of obesity, and the intestinal barrier, which also plays a key role in endotoxemia and systemic inflammation (Valdivia-López and Tecante 2015). Among the Oils group, flaxseed oil had the most consistent effect in T2DM and KD, probably because of its high content of ALA fatty acids. Surprisingly, in spite of its high content of omega-3 fatty acids, fish oil had little effect in reducing inflammatory molecules; however, fish oil, like sardines increased levels of adiponectin, so even if inflammatory cytokines were not reduced, the increase in adiponectin suggests that these may regulate the immune response and, as in other foods analyzed, promote adipose tissue healing. The immune-modulating mechanisms of these foods were more thoroughly discussed in the previous section.

It is interesting that no one food had a dramatic effect in reducing inflammation. But this is to be expected because foods have small amounts of bioactive compounds, not to be compared to pharmacological products. Still, it is amazing to observe that one food may have a detectable effect. If all of these foods were consumed together as a dietary pattern, we would expect to see the sum of the individual foods' effects and lead to results that may be tangible not only at the molecular level but measured also in clinical parameters. Of course, this must be demonstrated in a clinical trial where a dietary pattern is administered to a human population and compared with a control group.

Conclusion

There is a tendency toward a beneficial effect by consuming the foods analyzed in this review, even though some of the studies show no statistically significant differences in inflammatory and metabolic parameters. It is important to emphasize that the diet of an individual—the total amount of food consumed in a day— has an integral effect in the health of each subject. Therefore, it is biologically challenging to demonstrate the effect of any given food or nutrient without controlling the rest of the subject's diet and other habits that may interfere with the results, such as physical activity, stress levels and smoking, among others. These factors could explain many of the confusing or contradictory results observed in clinical trials. Overall, we conclude that consumption of the foods reviewed here will help modulate inflammation and metabolism of individuals with chronic inflammatory diseases. We recommend the consumption of these food groups—fruits and vegetables, fish, yogurt, whole grain products, spices, tea, nuts and seeds, omega-3 rich and polyunsaturated oils—together and frequently as part of the habitual diet, for individuals with overweight/obesity, type 2 diabetes, hypertension, cancer and other chronic diseases.

One limitation of this research is that the inflammatory response could vary among the different conditions, so an anti-inflammatory food portion for a given condition could be insufficient for a different one. Moreover, the individual characteristics of each patient should be considered, as well as the individuals' access to food, before recommending a functional food. For example, consumption of nuts and seeds have been associated with higher incomes, so in some regions these may not be affordable (Jiang et al. 2006).

More clinical trials are necessary to confirm that these functional foods, given together as a dietary pattern, have immune regulatory properties. Low doses of nutrients and substances contained in functional foods are beneficial for health; however, higher doses could be harmful. For this reason, supplements should be recommended with caution.

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Conflict of interest statement

All authors declare they have no conflict of interest.

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Rev Invest Clin. 2020;72(4):219-30 IN-DEPTH REVIEW

Immunonutrition in Cervical Cancer: Immune Response Modulation by Diet

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ABSTRACT

In the development of cervical cancer (CC), the immune response plays an essential role, from the elimination of human papillomavirus (HPV) infection to the response against the tumor. For optimal function of the immune response, various factors are required, one of the most important being an adequate nutrition. The complex interaction between nutrients and microbiota maintains the immune system in homeostasis and in case of infection, it provides the ability to fight against pathogen invasion, as occurs in HPV infection. The purpose of this article is to describe the role of diet, food, and specific nutrients in the immune response from the onset of infection to progression to precancerous lesions and CC, as well as the role of diet and nutrition during oncological treatment. The immunomodulatory role of microbiota is also discussed. A detailed analysis of the evidence leads us to recommend a nutritional pattern very similar to the Mediterranean diet or the prudent diet for an optimal immune response. Moreover, pre- and probiotics favorably modulate the microbiota and induce preventive and therapeutic effects against cancer. (REV INVEST CLIN. 2020;72(4):219-30)

Key words: Immunonutrition. Diet. Human papillomavirus. Cervical cancer. Microbiota.

INTRODUCTION

The optimal function of the immune system is crucial for health in general, for the prevention and elimination of infections, and in immune surveillance against tumor cells. Nutrition is one of the most important factors that modulate different aspects of immune function[1]. The ability of the immune system to identify and respond against cancer is determined by several factors, including the host's genetic makeup, the somatic profile of cancer cells and the environment. Nutrition is a fundamental environmental factor that

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acts through systemic or local effects within the tumor microenvironment, by modulating cell metabolism pathways through specific nutrients, such as antioxidants, by immune system modulation, and intestinal microbiota regulation[2].

The impact of nutrition on the immune system is an area that remains under investigation. However, studies conducted to date, provide compelling evidence that nutritional status and the immune system are strongly linked, and that integrity of the immune system can be rapidly altered by changes in the nutritional status[3].

Immunonutrition is a discipline that studies the relationships between nutrition, immunity, infection, inflammation, injury, and healing. Its development has underscored the fact that with nutrition, it is possible to prevent disease in healthy individuals and to treat disease in compromised individuals; it has also allowed to analyze the effects of nutrition on the modulation of the innate and adaptive immune responses.

Nutrition is a determining factor in immune system responses, with malnutrition being the most common cause of immunodeficiency worldwide. Protein deficiency malnutrition has been associated with a significant decrease in cell-mediated immunity, phagocytic function, the complement system, secretion of immunoglobulin A antibodies, and cytokine production. In addition, the lack of some specific nutrients also results in disruption of the immune response, including micronutrients such as zinc, selenium, iron, copper, Vitamins A, C, E, and B-6, and folic acid[4].

The diet can affect the microbial community of the gut, a complex and dynamic system, crucial for the development and maturation of both systemic and gut mucosal immune responses, and also plays an important role in metabolism, nutrition, and physiological characteristics. Therefore, the complex interaction between available nutrients, the bacterial community, and the immune system is the main regulator maintaining homeostasis; it establishes an effector response against pathogen invaders[5] and maintains immune surveillance for the elimination of malignant cells.

In this review the interaction of nutrition and immune response against human papillomavirus (HPV)-infected and cervical cancer (CC) cells will be explained, along with the role that the microbiota have been thus far identified to play in this interaction. We will also discuss how therapeutic approaches have been directed against the tumor, but with adverse consequences on the nutritional status of individuals suffering from this disease. At present, novel targeted treatments, in particular, immunotherapies, are also being rapidly developed, although their effect on nutrition is yet to be assessed. For this review, the NCBI-PubMed database was used to search for original articles that investigated the effects and associations between specific nutrients, foods, and dietary patterns on infection with HPV, development of cervical intraepithelial neoplasia (CIN), CC, and cancer treatment. We also searched for articles that investigated the interaction of nutrition with the microbiota and its association with chronic HPV infection, the development of the disease and treatment-related toxicities. All authors participated in the search, reviewing (according to the GRADE system), and discussion of the articles included in this review, and elaborated recommendations accordingly.

DIETARY PATTERNS, FOODS, AND NUTRIENTS ASSOCIATED WITH AN EFFICIENT IMMUNE RESPONSE AGAINST HPV

Although HPV infection is a necessary condition for the development of CC, the presence of other factors is required for the infection to progress to cervical lesion and subsequently to cancer. Nutritional status can be an important factor, since a poor nutritional status can lead to failure of the immune response to eliminate the infection, thus favoring the persistence of infection, and the progression to CIN.

Other factors, such as malnutrition, obesity, visceral adiposity, and their metabolic and pro-inflammatory effects, have also been linked to the development of tumors[6]. In the case of CC, obesity (Body mass index > 30 kg/m^2) is a factor that increases the risk of developing this neoplasm by 10% (hazard ratio [HR] = 1.10; 95% confidence interval [CI]: 1.03, 1.17)[7]. Excessive visceral adipose tissue induces a low-grade chronic inflammatory response, since it increases the secretion of inflammatory molecules,

such as tumor necrosis factor-alpha, interferon-gamma, interleukin IL-6, and IL-1beta, in addition to modifying endogenous hormone metabolism[8]. This chronic inflammation has been associated with 25% of all tumors and implicated in the oncogenic process[9].

An adequate diet that covers energy-protein and micronutrient requirements is essential to maintain the immune system in optimal function[10]. Therefore, including in the diet foods that are rich in some nutrients has led to a decrease in the risk of persistent HPV infection[11]. Further, the intake of Vitamins A, C, E, and D, and folate has been reported to help inhibit cell proliferation, prevent DNA damage, and enhance immune functions[12].

The European Prospective Investigation into Cancer (EPIC) study analyzed the relationship between nutrition and the incidence of cancer. The study followed 142,605 men and 335,875 women from ten different countries over a period of 8.7 years. Overall, 9669 cases of cancer were identified in men and 21,062 cases in women. Adherence to the Mediterranean diet was associated with a decreased cancer risk, with a HR of 0.96 (95% CI: 0.95-0.98) for all types of cancer ($p < 0.0001$). When considering the risk by food groups, an apparent protective effect of fruits and nuts, vegetables, grains, and a high unsaturated/saturated fatty acid ratio was observed. High meat consumption was associated with an increased risk of cancer, as well as moderate alcohol intake. Analyses of the different components of the diet on all types of cancer seem to indicate that the beneficial effect of the Mediterranean diet is not due to any specific component, but to the combined effect of a range of nutrients and other components offered by a diet rich in antioxidants, fiber and polyphenols, with a fatty acid profile that favors the consumption of omega-3 fatty acids[13].

Barchitta et al.[14] conducted a cross-sectional study in which three dietary patterns and their possible association with the development of high-risk HPV infection were analyzed. The patterns compared were the western diet, the Mediterranean diet, and the prudent diet. The Mediterranean diet is characterized by the consumption of vegetables, fruits, olive oil, fish, legumes, and whole grains. The western diet pattern is characterized by a higher intake of sugars, refined flours, dressings, vegetable oil, snacks, and chips, among others. The prudent diet includes raw and cooked vegetables, fruits, olive oil, potatoes, and legumes, among others. The regression model performed to establish associations between dietary patterns – derived by principal component analysis of the dietary pattern – and the risk of high-risk HPV infection, showed that the Mediterranean diet was associated with a lower risk of high-risk HPV infection (odds ratio [OR] = 0.79; 95% CI = 0.66-0.96; $p = 0.018$), whereas the western diet was associated with an increased risk of HPV infection (OR = 1.44; 95% CI = 1.03-2.03, $p = 0.036$). No significant differences were found with the prudent diet.

If we compare the western against the Mediterranean diet, we can see that the western diet lacks an adequate supply of fiber, polyunsaturated fatty acids, vitamins, minerals, antioxidants, and other nutrients; conversely, it provides more saturated fatty acids and empty calories that contribute to the development of metabolic disease. At the time of HPV infection, an increase in the production of reactive oxygen and nitrogen species by innate immune cells generates an increase in oxidative stress and if there are insufficient antioxidant compounds (as is the case when an individual follows a western dietary pattern), this oxidative stress will condition a pro-oncogenic environment, and the infection will progress more efficiently to neoplastic transformation. Although specific nutrients have beneficial effects on health, it is highly likely that a diet with a wide diversity of nutrients would have a greater impact as a protective factor against infection than one single nutrient. However, as described below, some authors found associations between specific nutrients and persistent HPV infection.

In the study by Lopes et al.[12], several dietary components were analyzed as potential risk factors for the persistence of oncogenic, non-oncogenic, and unclassified HPV infection. Individuals with persistent oncogenic HPV infection were observed to have a higher energy consumption ($p = 0.0051$), lower vitamin A ($p = 0002$), and lower folate intakes ($p = 0.0001$). Individuals with persistent non-oncogenic HPV infection had a lower intake of Vitamin B12 ($p = 0.0436$). Those with persistent unclassified HPV infection had a decreased intake of alpha-carotene ($p = 0.0241$), beta-carotene ($p = 0.0241$), and lutein + zeaxanthin ($p = 0.0403$).

Giuliano et al.[15] conducted a cohort study with a follow-up period of 1 year. During follow-up, nutrient consumption was assessed: beta-cryptoxanthin (OR = 0.47; 95% CI = 0.26-0.85), lutein + zeaxanthin (OR = 0.49; 95% CI = 0.27-0.87), and vitamin C (OR = 0.5; 95% CI = 0.27-0.92) were found to be dietary components that could be acting as protective factors, contributing to the elimination of HPV infection. Other nutrients associated with a lower risk of HPV infection were folate, retinol, lycopene, and Vitamin A[16]. In addition, carrots and papaya (> 200 g/day) were associated with a lower risk of HPV persistent infection[17]. Resveratrol, a compound that is naturally found in some fruits and seeds, has been observed to be able to stimulate the immune response with an increase in natural killer cell-mediated elimination of virus-infected and cancer cells. Grapes and red wine are foods with the highest amount of resveratrol, followed by blackberries, currants, cranberries, nuts, and cocoa. Incorporation of resveratrol into the diet through these foods can have immunomodulatory effects[18].

According to the results obtained, we can conclude that the factors which could limit the immune response during HPV infection are low fruit and vegetable intake (mainly those that contribute with components such as Vitamins A and C, carotenes, cryptoxanthin, folate, lutein, zeaxanthin, and resveratrol), and excessive energy consumption, with the latter probably being related to overweight and obesity. This leads us to recommend an eating pattern very similar to the Mediterranean diet or the prudent diet.

ROLE OF FOODS AND NUTRIENTS IN THE CONTROL AND ELIMINATION OF CIN

The study by Barchitta et al.[14] also analyzed whether the prudent diet pattern was associated with the development of CIN2+. The results showed that the prudent diet might be a protective factor against the development of CIN2+ (OR = 0.50; 95% CI = 0.26-0.98; p = 0.039). No significant differences were found with the western diet or with the Mediterranean diet.

Tomita et al.[19] conducted a case–control study to determine if there was an association between dietary intake and newly diagnosed CIN1, CIN2, and CIN3. In this study, the consumption of carrots (between 203 g and 1321 g/day) was found to likely be a protective factor against the development of CIN3 (OR = 0.50; 95% CI = 0.27-0.95). In addition, a blood sample was obtained to measure serum tocopherols and carotenes and analyzed their possible association with the development of CIN or invasive CC. The results showed that low serum levels of alpha-tocopherol, gamma-tocopherol, total carotenes, and lycopene increase the risk for developing CIN Grades 2 and 3, and invasive CC.

Tomita et al.[20] conducted another study in which the relationship between the presence of CIN3 and a limited consumption of five different food groups was analyzed. When analyzing all individuals, an association was observed between CIN3 and the consumption of ≤ 39 g/day of dark green and deep yellow fruits and vegetables (OR = 1.71; 95% CI = 1.15-2.52), as well as with an intake of ≤ 79 g/day of fruit and fruit juice (OR = 1.51; 95% CI = 1.05-2.17), consumption of ≤ 79 g/day of citrus fruits and citrus juices (OR = 1.44; 95% CI = 1.02-2.03), and a total consumption of ≤ 319 g/day of fruits and vegetables (OR = 1.52; 1.06-2.17). When individuals were classified as smokers and non-smokers, only the first group (≤ 39 g/day of dark green and intense yellow fruits and vegetables) was found to remain as a risk factor in smokers (OR = 1.96; 95% CI = 1.15-3.33).

Previously, low levels of serum folate were reported to increase the risk of CIN progression[21]. Two hundred and forty-seven cases of cervical low-grade squamous intraepithelial lesions (LSIL), 125 cases of cervical high-grade squamous intraepithelial lesions (SIL) and 877 controls were analyzed. The increase in CIN was associated with higher rates of hrHPV infection and lower levels of serum folate. On the other hand, a study[22] was conducted to determine the effects of long-term folate supplementation on regression and metabolic status of patients with CIN1. A higher percentage of women in the folate group developed lesion regression compared to the placebo group (83.3 vs. 52%, p=0.019).

Although the evidence might seem to be inconsistent, a cohort study investigated the association between the consumption of fruits and vegetables within the EPIC study[23]. A total of 343,518 women from 23 different centers in Europe with a follow-up

period of 9 years were included in the study. A statistically significant inverse association was found when fruit consumption was increased to 100 g/day (HR: 0.83; 95% CI: 0.72-0.98) in women with invasive squamous cell CC; however, no significant association was found with the increase in vegetable consumption (100 g/day; HR: 0.85; 95% CI: 0.65-1.10).

In a study conducted in 390 women, the only dietary factors that were associated with the development of CIN Grades 2 and 3 were boiled coffee and dairy products[24]. Total fat, saturated, monounsaturated and polyunsaturated fatty acids, total fiber, fiber from grains, fiber from fruits and berries, fiber from vegetables, Vitamin C, and folate were also analyzed. Other foods associated with a lower risk of CIN progression were fruits in general, papaya, vegetables in general, onion, legumes, nuts, and a general intake of fruits and vegetables > 140 g/day. Consumption of ≤ 70 g/day of fruit and ≤ 39 g/day of dark-green fruits and vegetables was associated with a higher risk of CIN progression. Among the antioxidant compounds, polyphenols such as turmeric[25-28], ferulic acid[29], epigallocatechin gallate[29,30], and resveratrol[30] have been found to possess antiviral, cytotoxic, anti-inflammatory, and chemopreventive effects.

Other studies have also found an inverse relationship between blood antioxidant levels and the grade of cervical dysplasia. One study reported blood alpha-tocopherol levels of (21.57 µg), compared to women with CIN1 (21.18 µg), CIN2 (18.10 µg), and CIN3 (17.27 µg) (p = 0.012)[15]. In addition, higher consumption of papaya or orange is inversely related to the risk of developing cervical SIL (p = 0.01 and p = 0.02, respectively), with the strongest association being with papaya consumption > 1 times/week (OR = 0.19; 95% CI: 0.08-0.49) or orange consumption > 1 times/week (OR = 0.32; 95% CI: 0.12-0.87)[31].

A study by Feng et al.[32] assessed the consumption of certain food groups and their protective role in the development of CIN+. Consumption of ≥ 15.95 servings of onion per week was associated with a lower risk (OR = 0.654; 95% CI = 0.437-0.978; p = 0.036), as well as consumption of ≥ 2.69 servings of legumes per week (OR = 0.655; 95% CI = 0.439-0.978; p = 0.038), consumption of ≥ 0.61 servings of nuts per week (OR = 0.590; 95% CI = 0.394-0.882; p = 0.008), and consumption of ≥ 0.94 servings of meat per week (OR = 0.651; 95% CI = 0.429-0.987; p = 0.047).

Hwang et al.[33] analyzed a cohort with a 3-year follow-up, to determine the relationship between the intake of fruits and vegetables and the development of cervical dysplasia (CIN1, CIN2, and CIN3) in HPV+ and HPV- subjects. Fruit consumption of < 109 g/day (OR = 2.93; 95% CI = 1.25-6.87; p = 0.01) and vegetable consumption of < 302 g/day (OR = 2.84; 95% CI = 1.26-6.42; p = 0.06) were found to be associated with CIN2 and CIN3 in HPV+ subjects.

We conclude that, for the control and elimination of CIN, it is advisable to include in the diet a frequent intake of onions, legumes, nuts, and fruits and vegetables in general. Although meat would appear to be a protective factor (probably due to its Vitamin B12 content), increasing its consumption is not recommended due to its association with colon cancer. For the purposes of this review, a portion not exceeding 80 g of red meat per week is suggested.

ROLE OF FOODS AND NUTRIENTS IN CERVICAL CANCER CARCINOGENESIS

Inflammation is the central component of the innate immunity response. In general, inflammation is a local response to tissue injury characterized by an increase in blood flow, capillary dilation, leukocyte infiltration, and localized production of molecular mediators responsible for eliminating pathogens and repairing tissue injury. This inflammatory process is resolved with the effects of acute phase proteins, anti-inflammatory cytokines, and other anti-inflammatory components. However, a low-grade chronic inflammatory state is associated with a wide variety of chronic conditions, including the metabolic syndrome, steatohepatitis, type 2 diabetes mellitus, cardiovascular disease, and cancer[34].

The correlation between chronic inflammation and cancer has been supported by epidemiological and experimental studies in humans and animals. Chronic inflammation plays a role in all cancer stages, increasing the rate of genetic mutations, and epigenetic mechanisms that lead to the onset of cancer, promoting tumor progression, and promoting a metastatic spread[35].

Inflammation has been considered a predisposing factor to the development of tumors, with at least 20% of all types of cancer resulting from of a chronic inflammatory process[36]. Dietary intake plays a role in the physiological response to inflammation. Consequently, nutrition can influence both, the development and progression of inflammatory conditions and their prevention and treatment. Studies conducted to assess the relationship between dietary intake and low-grade inflammation have shown evidence that Mediterranean dietary patterns can be particularly beneficial in decreasing inflammation. In particular, the consumption of fruits, vegetables, and whole grains is associated with a decrease in the concentrations of C-reactive protein and fibrinogen, both inflammatory biomarkers.

Studies focusing on specific nutrients have shown that dietary antioxidants such as beta-carotene, zinc, selenium, Vitamin C, and Vitamin E are associated with lower levels of inflammation markers. The effect of diet on HPV-16-induced carcinogenesis was tested in a study with nude mice fed a folate-rich diet or a folate-deficient diet. The mice who consumed the folate-rich diet had a lower expression of oncogenic proteins E6 and E7 when compared to the mice that were fed a folate-deficient diet[21]. Other non-nutritive components such as flavonoids, which can be found in fruits, vegetables, teas, coffee, red wine, and cocoa, also have high antioxidant power and anti-inflammatory activity[2]. Foods rich in omega-3 fatty acids also help curb inflammation, since they are associated with a reduction in the production of pro-inflammatory cytokines and eicosanoids. In one study, after 2 weeks on a diet rich in omega-3 fatty acids, study subjects showed a decrease in inflammatory mediators, which was maintained for 2 weeks after the dietary intervention[37]. In a population-based study, the consumption of foods rich in omega-3 fatty acids has considerably decreased in the last 20 years[38]. Vitamin E acts by reducing lipid peroxidation in cell membranes. If membrane lipid peroxidation is not controlled, it can generate free radicals that act as carcinogens. Besides exerting an antioxidant effect, Vitamin E also decreases the neurotoxic effects of chemotherapy[39].

In addition, studies in mice have shown that the use of prebiotics has anti-cancer and anti-inflammatory properties, since they modulate cyclooxygenase-2, nuclear transcription factor-kappa B (NF-kappa B), inducible nitric oxide synthase, and gastrointestinal glutathione peroxidase expression[40,41].

Ghosh et al.[42] conducted a case–control study, reporting that consumption of certain nutrients might be protective against the development of CC. These nutrients are: Polyunsaturated fatty acids > 12 g/day (OR = 0.57; 95% CI = 0.34-0.97; p = 0.04), fiber > 29 g/day (OR = 0.59; 95% CI = 0.37-0.94; p = 0.03), Vitamin C > 224 g/day (OR = 0.53; 95% CI = 0.33-0.8; p < 0.01), Vitamin E > 8.9 mg/day (OR = 0.44; 95% CI = 0.27-0.72; p < 0.01), Vitamin A > 12.7 IU/day (OR = 0.47; 95% CI = 0.3-0.73; p < 0.01), alpha-carotenes > 1.393 µg/day (OR = 0.41; 95% CI = 0.27-0.63; p < 0.01), beta-carotenes > 7.512 µg/day (OR = 0.44; 95% CI = 0.29-0.68; p < 0.01), lutein (OR = 0.51; 95% CI = 0.33-0.79; p < 0.01), lycopene > 5.837 µg/day (OR = 0.65; 95% CI = 0.44-0.98; p = 0.04), and folate > 433.2 µg/day (OR = 0.55; 95% CI = 0.34-0.88; p = 0.01).

In a multicenter study by González et al.[23], they searched for an association between the consumption of fruits and vegetables and the development of invasive squamous cell CC. Leafy vegetables (HR = 0.52; 95% CI = 0.29-0.95; p = 0.034), Vitamin C (HR = 0.59; 95% CI = 0.39-0.89; p = 0.047), and Vitamin D (HR = 0.47; 95% CI = 0.3-0.76; p = 0.004) were found to be protective factors. A case–control study by Hosono et al.[43] was designed to determine if there is any association between calcium and Vitamin D intake and the development of invasive cervical carcinoma. A calcium consumption of ≥ 502.6 mg/day was observed to confer protection (OR 0.5; 95% CI= 0.35-0.73; p = 0.004). When the population was stratified by smoking status, the protective factor was observed to persist in non-smokers (p = 0.006), as well as in patients with a squamous type histology (p = 0.005); however, in the group of smokers (p = 0.796) and in patients with adenocarcinoma-type histology (p = 0.493), this protection is lost. Something very similar occurs with Vitamin D, where consumption of ≥ 162 IU/day confers protection (p = 0.014), especially in non-smokers (p = 0.002) and in patients with squamous-type histology (p = 0.017); however, in smokers (p = 0.731) and in patients with

adenocarcinoma-type histology (p = 0.423) this protection is lost.

The process of carcinogenesis takes years, which is why we insist in this review on the importance of nutritional education at all levels. The lack of compelling evidence generated in studies suggests that supplementation with a nutrient or multivitamins, or controlling dietary habits for a short period of time is not sufficient, since nutrient elements, including vitamins, minerals, antioxidants, and other components in food interact with each other, and this interaction might have an additive effect that could confer a state of protection. Studies that have investigated the Mediterranean diet agree that it decreases the risk of a variety of cancers by modulating multiple interconnected processes involved in carcinogenesis and in the inflammatory response, such as production of free radicals, NF-kappa B activation, and the expression of inflammatory mediators. In particular, the capability of this diet to induce an anti-inflammatory response has been described, as well as its usefulness in maintaining intestinal microbiota homeostasis and epigenetic oncogenesis modulation through specific microRNAs[35]. Finally, it is necessary to complement the diet with physical activity and to lead a healthy lifestyle. In addition, it should be noted that the protective effect provided by diet and lifestyle changes is blunted by smoking.

ROLE OF NUTRITIONAL STATUS AND ITS IMPACT ON TREATMENT RESPONSE

Several studies have reported that, at the time of CC diagnosis, patients are usually not undernourished[44]. Depending on the instrument used, undernourishment is estimated to range between 0% and 42.8% at diagnosis, and to increase up to 69% by the end of treatment with concomitant chemoradiation therapy and followed by brachytherapy. Overweight and obesity are more common, since they occur in 61.8-75.8% of patients and, simultaneously, sarcopenia is present in 10.5%-33.3%[45,46]. Furthermore, around 40.8% of women with CC have some comorbidity[45], which represents a huge challenge for diagnosis and nutritional approach, since a combination of the previous diagnoses can be found in a single individual[45].

EFFECT OF NUTRITIONAL INTERVENTIONS ON TOXICITY AND INFLAMMATION IN CERVICAL CANCER

An adequate diet is also indispensable as adjuvant therapy in cancer patients. Tumor cells have metabolic abnormalities that lead to high levels of reactive oxygen species, glucose metabolism changes, and micronutrient deficiencies. The ketogenic diet, which is restricted in carbohydrates and high in fat, limits glucose availability and promotes metabolic adaptations that favour oxidative phosphorilation; thus, with this type of diet enery is preferentially obtained from fatty acids. There is evidence, both clinical and in animal models, that a ketogenic diet increases oxidative stress in cancer cells, since they develop a glycolysis-dependent metabolism and are unable to obtain energy from fatty acids. Some preliminary reports of studies that are assessing the ketogenic diet as adjuvant therapy in cancer, indicate that patients who have been able to maintain the ketogenic diet for more than 3 months show improvement, tumor reduction, slowed growth, and stabilization of their physical condition. Available data indicate that cancer patients who undergo standard radiation and chemotherapy can also benefit from ketogenic diets[47].

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) is thought to benefit patients with CC under treatment with pelvic external-beam radiotherapy. However, when investigating whether the low-FODMAP diet can decrease the severity of intestinal toxicity and improve aspects related to quality of life and decrease deterioration of performance status, no statistically significant differences were found[48]. Nevertheless, symptomatic and quality of life improvement has been observed in patients with chronic toxicity induced by radiotherapy[49]. Even so, the effects of dietary FODMAP restriction on the immune response, the production of short-chain fatty acids (SCFA), and the composition of intestinal microbiota in patients with CC, remain to be determined.

Another diet that might be beneficial for patients with CC that develop pelvic radiation disease (PRD), is the anti-inflammatory diet which has been tested in patients with inflammatory bowel disease (IBD), and whose symptoms are very similar to those occurring in PRD. This anti-inflammatory diet consists of five

basic components: (1) limiting the intake of simple carbohydrates such as sugars and refined flour or processed foods; (2) eating foods with pre- and probiotics in the form of soluble fiber, such as prickly pear, banana, papaya, oatmeal, leeks, onions, and fermented foods, to restore gastrointestinal microbiota balance; (3) reducing the intake of saturated and total fats, eliminating hydrogenated oils and increasing the consumption of foods rich in omega-3 fatty acids; (4) examining eating patterns to identify possible intolerances and detect missing nutrients; and (5) modifying the texture of food to facilitate its absorption, by cooking or grinding. Despite the difficulties following an anti-inflammatory diet, patients with IBD and good adherence have obtained improvement in symptoms[37], so this could be a recommendable diet for patients with CC who are candidates for concomitant chemoradiotherapy and who are at risk of developing PRD.

Although these types of diets are promising due to their metabolic and anti-inflammatory effects, it is important to demonstrate the effect of these diets through clinical trials in CC patients, to prove their effectiveness. In conclusion, we recommend that patients with CC who are candidates for treatment based on chemoradiotherapy followed by brachytherapy, should follow a diet that meets their energy-protein requirements to avoid malnutrition, and in particular sarcopenia. Furthermore, a diet limited in simple carbohydrates and sugars, and that includes foods rich in antioxidant and anti-inflammatory nutrients, might help control intestinal inflammation and thus prevent the development of PRD and gastrointestinal toxicity.

In addition to diet, fasting has been used by many cultures throughout the history of humanity for religious and health-related reasons. A great deal of research has investigated the effects of several types of fasting and calorie restriction regimens on different tissues and the metabolism. Clinical studies have shown beneficial effects on obesity, diabetes, cardiovascular disease, autoimmune and inflammatory conditions, and cancer. In animal models, fasting reduces the development of tumors, protects the animals from treatment-related toxicity, while sensitizing the tumor to chemotherapeutics' toxicity. The mechanism involves a metabolic switch that occurs during fasting in healthy cells, which makes them resistant to stress. Cancer cells are incapable of this metabolic adaptation; thus, they become sensible to stress and unable to obtain sufficient energy. Clinical trials are underway to understand the effects of fasting and calorie restriction on several types of cancer, as reviewed elsewhere[50]. It will be interesting to investigate if fasting protects against chronic HPV infection and the development of CC; however, the evidence reviewed suggests that food-related factors, in particular, dietary patterns, contribute to regulate inflammation.

MICROBIOTA IN CERVICAL CANCER

The microbiota, both intestinal and vaginal, are closely linked to the immune system, and are a relevant factor associated with the development of precancerous cervical lesions in addition to HPV infection. Ninety percent of intestinal microbiota in healthy individuals is made up of *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria,* and *Fusobacteria.* In contrast, vaginal microbiota is made up of *Firmicutes, particularly Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners,* and *Lactobacillus jensenii*[51].

Imbalance in the microbiota composition or metabolic activity has a significant impact on an individual's health. Mechanical factors, such as vaginal douching or sexual intercourse, as well as biological factors, such as infections or the cytokine profile and the use of antibiotics, alter the vaginal microenvironment, which favors the persistence of HPV infection[52]. As a result, the diversity and composition of cervical microbiota differ at each stage in the natural history of CC, with an increase in microbiota diversity in CC in comparison with individuals without lesions. Lactobacillus spp. is highly abundant in the cervix of women without Pap smear abnormalities, while *L. crispatus* and *L. iners* are the most abundant species in HPV- and HPV+ women without lesions, respectively. In the presence of HPV+ SIL, *Sneathia* spp. is the most abundant species. In late CC stages, *Fusobacterium* spp. is significantly more abundant than in early stages (regardless of HPV infection), and *Fusobacterium necrophorum* is only observed in patients with CC[53]. In addition, *Atopobium vaginae* has been associated with high-risk CIN and L. *iners* with CIN2[54].

There is a highly important association between dietary patterns and microbiota composition. In

patients with CIN, a semi-western diet (low intake of rice, vegetables, fiber, carotenes and Vitamin C, and high intake of bread, pasta, eggs, dairy products, soft drinks, and red meat) increases the risk of CIN by favoring the establishment of A. vaginae as the dominant species in the cervix (OR: 20.8; 95% CI: 2.21-195.6; p = 0.01)[55]; this suggests an association between diet and microbiota, and the susceptibility to developing CC. Finally, nutritional deficiencies have been observed to contribute to an increased risk of infection, since abnormal bacterial metabolite levels have been linked to the development of some tumors[56,57].

The differences in gastrointestinal microbiota of patients with CC compared with controls have also been identified. There is an increase in *Proteobacteria* in patients with CC, specifically the *Escherichia Shigella, Roseburia, Pseudomonas, Lachnoclostridium, Lachnospiraceae* _UCG -004, *Dorea,* and *Succinivibrio genera*[58]. Diet regulates the composition and function of intestinal microbiota. A high-fat diet is associated with the presence of *Bacteroidetes,* and a high-carbohydrate intake is associated with *Prevotella*. Pre- and probiotics favorably modulate the microbiota and induce preventive and therapeutic effects against cancer. The anticancer mechanisms that have been associated with the intake of pre- and probiotics include quantitative and qualitative alterations in the microbiota as well as in its metabolic capacity, inactivation of mutagenic or carcinogenic compounds, host antitumor immunity, production of anticancer, and epigenetic compounds which are involved in histone acetylation, DNA methylation, and metabolites that directly reduce intestinal inflammation[59].

One of the main metabolites that have been described is butyrate, which participates in the suppression of intestinal inflammation by favoring the differentiation of regulatory T cells (Treg)[60,61]. In murine models, a fiber-rich diet leads to a higher number of Tregs and to an increase in the production of SCFA compared to a low-fiber diet[62]. Butyrate restricts the synthesis of pro-inflammatory cytokines in macrophages[63], suggesting a mechanism involving the innate immune response to induce tolerance to commensal microbiota and food antigens. Taken together, these data show the importance of bacterial metabolites in immune regulation, and their probable participation in the effector response against HPV infection.

In addition to modulating the immune response, there is also evidence of the contribution of microbiota to radiation therapy toxicity. Radiation-related intestinal mucosal lesions are modified by intestinal microbiota[64-67]. Development of toxicity is associated with changes in microbiota composition, signals derived from bacterial components, alarmins or danger-associated signals, and cytokine-mediated signals[68]. Patients undergoing pelvic radiotherapy show changes in microbial diversity, with a higher abundance of *Proteobacteria* and *Gamma-proteobacteria* and lower abundance of *Bacteroides*. The presence of *Megamonas, Novosphingobium,* and *Prevotella,* and a decrease in Bacteroides, *Bacteroidaceae* and Plebeius, is associated with radiotherapy. *Coprococcus* and *Desulfovibrio* are enriched before radiotherapy. There are also differential changes in microbiota abundance according to the degree of radiation enteritis (RE). In RE1 there is an abundance of *Virgibacillus* (p = 0.008), *Alcanivorax* (p = 0.010), and *Phenylobacterium* (p = 0.038); and in RE2, abundance of *Coprococcus* (p = 0.044), Collinsella (p = 0.022), and rc4_4 (p = 0.020)[69]. Patients undergoing pelvic radiotherapy showed a higher *Actinobacteria* abundance and significantly less abundant *Fusobacteria* before treatment[70], but it changed during treatment. In gynecological and colorectal cancers, there is much evidence of microbiota involvement in tumor establishment and progression[53,71,72]. These observations underscore the need and possibility of finding biomarkers for early detection of the risk of developing RE and, on the other hand, finding species associated with the development of tolerance that could be used as prophylactic probiotics.

However, nutritional, dietary, and physical activity factors, which could have an impact on microbiota modulation and its effect as a risk or protective factor in the development of CC, have been poorly studied[73] and, in some cases, studies have not been conclusive; therefore, further investigations are required to prove their possible interaction with the microbiota and indirectly with HPV infection and carcinogenesis.

Probiotics are a mechanism to attempt to restore homeostasis in the microbiota. A pilot study examined the effect of probiotics in women with HPV and LSIL[74]. Fifty-four women were randomized to consume probiotics (commercial fermented dairy beverage with *Lactobacillus casei* Shirota) or to follow

standard care for 6 months (without treatment and with the indication not to consume probiotics); 50% of the women in the intervention group had a negative result for intraepithelial lesion compared to 29.6% of women in the control group.

A series of randomized, double-blind, and placebo-controlled trials have assessed in detail the effect of probiotics. In locally advanced CC, a probiotic containing *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* (Infloran) decreased the incidence of diarrhea when patients underwent radiotherapy concomitantly with cisplatin (45% in the placebo group and 9% in the intervention group). During follow-up, the use of antidiarrheal drugs significantly decreased in the intervention group (68% in placebo vs. 91% in study group, p = 0.03), while patients in the study group had a significant improvement in stool consistency (35% in placebo vs. 81% in study group, p = 0.001)[75]. In patients undergoing radiation of pelvic tumors with or without chemotherapy, supplementation with Bifilact double strain probiotics (*L. acidophilus* LAC-361 and *Bulgaricus longum* BB-536), resulted in a decrease in diarrhea severity in 35% of patients in the group that received the probiotic, in comparison with only 17% of patients in the placebo group (p = 0.04)[64]. In sigmoid, rectal or CC, patients who received the VSL # 3 probiotic (*L. casei, Lactobacillus plantarum, L. acidophilus, Lactobacillus delbrueckii* spp. *Bulgaricus, B. longum, Bulgaricus breve, Bulgaricus infantis,* and *Streptococcus salivarius* sub sp. *thermophilus*), on the 1st day of radiotherapy, had significantly less diarrhea than those who received placebo (31.6% in the probiotic group vs. 51.8% in the placebo, p = 0.001), and the severity of diarrhea in patients receiving the probiotic was significantly lower (55.4% in the placebo group vs. 1.4 in the probiotic group, p = 0.001). In addition, the number of daily bowel movements in the placebo group was 14.7 ± 6 in comparison with 5.1 ± 3 in the probiotic group (p = 0.05)[76]. In cervical carcinoma or endometrial adenocarcinoma, a probiotic beverage with *L. casei* DN-114 001, did not significantly decrease the incidence of radiation-induced diarrhea or the use of antidiarrheal medication (p = 0.568), but patients did report significantly better stool consistency (p = 0.04)[77]. In gynecological cancer patients, a prebiotic (50% inulin + 50% fructo-oligosaccharides) protected from gastrointestinal radiotherapy-induced toxicity[65]. Taken together, the results of these studies indicate that probiotics can mitigate radiation-induced toxicity in patients with gynecological cancer who receive radiation therapy to the pelvic area.

Several recent studies have shown that microbiota plays a role in the response to immunotherapy. Microbiota and its metabolites alter IL-12 and toll-like receptor (TLR2)/TLR4 signaling pathways, which results in CTLA-4[78,79] and PD-L1 blockade[80,81]. Therefore, the intestinal microbiome is an important clinical marker and a therapeutic target for immunotherapy in CC.

CONCLUSIONS

The relationship between diet, nutritional status, and microbiota shows that prevention and treatment in CC should be comprehensive, to provide better strategies for the prevention, diagnosis, and prediction of the risk of recurrence. Treatment with diet, pre- and probiotics should be routinely administered to modulate the immune system that contributes to a decreased risk of HPV infection and CC development and, in patients with CC, prevents treatment-associated inflammation and toxicity, thus improving the patients' quality of life.

RECOMMENDATIONS

1. The consumption of a prudent dietary pattern, rich in vegetables, fruits, whole grains, omega-3 fatty acids, and limited in red meats, saturated fatty acids, and scarce in sugar and refined processed products is recommended, since it is associated with an optimal immune function, tolerogenic to the commensal microbiota and food antigens, and responsive to potential infectious pathogens. This dietary pattern is also associated with a high antioxidant status capable of neutralizing the redox state and preventing carcinogenesis. Quality of evidence: (GRADE) **Moderate.** Strength of recommendation: **Strong in favor of its use.**

2. The consumption of probiotic supplements during treatment with pelvic radiotherapy is recommended because it is associated to a decrease in gastrointestinal symptom severity and frequency. Quality of evidence: (GRADE) **Low.** Strength of recommendation: **Weak in favor of its use.**

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