Publicaciones Científicas y Médicas Relacionadas con Immunocal®

Editado y compilado por Jimmy Gutman MD,
Director de Ciencias, Immunotec

Imagen de anticuerpos

Una colección de artículos de revistas relacionadas con la investigación y desarrollo de un aislado de proteína de suero sin desnaturalizar patentado rico en cisteína: Immunocal

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LIMITACIÓN DE RESPONSABILIDAD

Este libro está destinado a fines educativos y científicos únicamente. No pretende ser una fuente de asesoría médica. El contenido presenta artículos de investigación publicadosque no deben ser considerados como guías de tratamiento o práctica clínica. Se insta al lector a consultar con un profesional de la salud antes de usar cualquier suplemento. Immunocal es un suplemento dietético natural. No tiene como intención tratar, curar o prevenir ninguna enfermedad. Las opiniones expresadas por el Dr. Gutman no necesariamente reflejan las opiniones de Immunotec.

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HISTORIA DE IMMUNOCAL: UN AISLADO DE PROTEÍNA DE SUERO RICO EN CISTEÍNA ESPECIALMENTE PREPARADO

En la década los sesentas, el Dr. Gustavo Bounous, quien originalmente practicaba la cirugía en Italia, inició estudios de investigación en los Estados Unidos para examinar el curso de la recuperación en pacientes posquirúrgicos. El Dr. Bounous observó que los oacientes con síntomas similares podrían tener resultados y una recuperación muy diferente de sus procedimientos. Finalmente, se enfocó en la teoría de que lo que entraba en juego era su ingesta diaria normal de alimentos. Desafortunadamente, se vio obligado a abandonar los Estados Unidos debido a una visa de trabajo vencida. Al reiniciar su investigación en Canadá, se propuso descubrir qué alimentos podrían afectar la curación y la recuperación. Quedó claro que el candidato más probable sería una proteína.

En el curso de investigación del Dr. Bounous, se hizo evidente que ciertas proteínas y aminoácidos tenían un efecto sobre las respuestas inmunológicas en los animales que estaba estudiando. Al no tener antecedentes formales en inmunología, buscó un compañero para ampliar esta tesis. Encontró la pareja perfecta. La Dra. Kongshavn y su doctorado la hacían en ese momento un elemento prometedor en la Universidad McGill, y desempeñó un papel pionero crítico en el nuevo campo de la inmunología clínica. Juntos publicaron su primer artículo en 1978 "El efecto de los aminoácidos en la dieta sobre la reacción inmunológica".

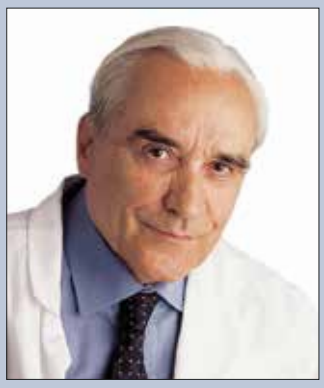
La búsqueda para encontrar una proteína efectiva que mejoraría la función inmune continuó para los Dres. Bounous y Kongshavn. Por fortuna, se envió un extracto de proteína al Dr. Bounous para examinar sus posibles beneficios. La proteína era en ese momento un subproducto casi sin valor de la industria láctea. Como resultado, este extracto de proteína demostró nada menos que efectos espectaculares cuando se probó en animales. Sus efectos en el sistema inmunológico fueron lo suficientemente notables como para permitir empezar los estudios en humanos.

Sus estudios en humanos demostraron ser tan exitosos como los experimentos con animales. Se formó una compañía para enfocarse en promover esta investigación. "Immunotec" fue oficialmente fundada en 1996 (Canadá) y 1997 (Estados Unidos). Y asumió el compromiso de reinvertir una proporción significativa de sus ingresos directamente en la investigación.

John Molson asumió el cargo de vicepresidente ejecutivo de Investigación y Desarrollo y, a pasos agigantados, aseguró socios de investigación de alto nivel en todo el mundo. Bajo su dirección los estudios se acumularon rápidamente y establecieron a este aislado de proteína natural como uno de los suplementos más prometedores con validación de investigación. Immunocal finalmente se incluyó en el American PDR (Physician's Desk Reference –Referencia de Escritorio de Médicos-) y en el Canadian CPS (Compendium of Pharmaceuticals and Specialties -Compendio de Productos Farmacéuticos y Especialidades-)

Este libro analiza el progreso de la amplia historia de investigación de Immunotec presentando el " abstracto " (resumen ejecutivo) de cada estudio publicado relacionado con Immunocal.

SE NECESITARON AÑOS DE ESFUERZO POR PARTE DE PERSONAS TALENTOSAS Y DEDICADAS PARA TRAER IMMUNOCAL AL MUNDO



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AGRADECIMIENTOS

*Al **Dr. Gustavo Bounous**, cuyo genio trajo esta ciencia revolucionaria al mundo.*

*A la **Dra. Patricia Kongshavn**, quien, como verdadera pionera en inmunología, tomó estas ideas y se aseguró de que se convirtieran en realidad.*

*Al **Dr. Wulf Droge**, eminente inmunólogo y experto en medicina antienvejecimiento que se unió al proyecto Immunotec y nos ayudó a darnos renombre.*

*A **John Molson**, quien guió los esfuerzos de Investigación y Desarrollo durante más de 20 años y nos abrió una puerta que de otra manera sería inalcanzable.*

***Annie Karabadjian**, que con sus habilidades increíblemente eficientes manejó la mayoría de los estudios más difíciles de Immunocal como directora de ensayos clínicos.*

MENSAJE DEL DR. JIMMY GUTMAN

Este libro fue producido en un esfuerzo por hacer que la mayoría de los estudios publicados de Immunotec estén fácilmente disponibles para cualquier lector que desee ver el tremendo trabajo realizado para respaldar la validación científica detrás de Immunocal.

Por más de 20 años he recibido peticiones par hacer un compilado de todos estos estudios en un solo lugar. El lector podrá ver todos los niveles de desarrollo involucrados en los pasos a seguir a través de la concepción, la teoría, los estudios de laboratorio, los experimentos con animales y, en última instancia, lo que cuenta más: los estudios con humanos.

Esto fue realmente un trabajo de pasión: al leer estos artículos adquirí una nueva perspectiva sobre la riqueza de la información y una admiración renovada por todos los autores y científicos que pasaron incontables horas aportando esta valiosa contribución a la ciencia y medicina.

Jimmy Gutman MD
Director de Ciencias, Immunotec

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ESTUDIOS IN VIVO EN ANIMALES

Estos documentos se presentan primero porque contienen los primeros artículos escritos por el Dr. Bounous y la Dra. Konngshavn sobre los orígenes del producto Immunocal. Fueron estos artículos fundamentales los que sentaron las bases para el adelanto en el trabajo a seguir.

Los estudios exitosos en animales dan a los investigadores mucho más ímpetu para continuar con los estudios en humanos. Lejos de ofrecer la garantía de que esta estrategia funcionará en humanos, son sin duda un gran avance en comparación a la investigación en probetas o en cultivo de tejidos. La realidad sorprendente, sin embargo, es que muy pocas intervenciones que prueban que funcionan en animales realmente muestran los mismos éxitos en los seres humanos. Realizar un estudio con animales es mucho más arduo de lo que parece. Para poder acceder a este tipo de investigación, los científicos deben mostrar evidencia teórica y de laboratorio adecuada para revisar en las juntas y comités de ética que poner potencialmente en peligro a los animales tiene suficiente "justificación". Muchos activistas protectores de los animales sienten que rara vez hay alguna razón para experimentar con animales, pero la práctica sigue siendo un paso esencial requerido antes de continuar los estudios en humanos. Afortunadamente, las pautas actuales son mucho más estrictas que en años anteriores para no exponer a estas criaturas a un sufrimiento indebido.

Al observar algunos de los experimentos con animales usados en estudios de investigación con Immunocal en esta sección, observará la mejoría en los animales tratados con Immunocal que fueron esenciales para que estos equipos participaran en ensayos humanos más relevantes.

THE JOURNAL OF INFECTIOUS DISEASES, 144(3): 281, 1981

Influencia del hidrolizado de lactoalbúmina dietética sobre el sistema inmunológico de los ratones y la resistenca a la salmonelosis

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Abstract

In the present study we investigated the effect of four weeks of treatment with a diet containing lactalbumin hydrolysate (LAH: Nestlé, Vevey, Switzerland) on the immune response of C3H/HeN mice. Our data indicate that it was possible to increase the level of this type of protein in the diet above the minimum requirement (12% LAH) and thus produce augmented humoral immune responsiveness and resistance to salmonellosis.

Lactalbumin = Whey Protein Concentrate.

Comentarios del Dr. Gutman

Este es el primero de todos los documentos en esta compilación de la investigación Immunocal. El trabajo de los doctores Bounous y Kongshavn había sentado las bases de la investigación relacionada con el Immunocal, pero el producto en ese momento no era tan refinado como el Immunocal de hoy en día. El Dr. Bounous estaba en la Universidad de Sherbrooke en Quebec y ya había establecido una relación de trabajo con la Dr. Kongshavn, una prometedora pionera de la inmunología clínica en la Universidad McGill de Montreal. El equipo del Dr. Bounous identificó el potencial clínico de ciertos componentes proteínicos del suero y encargó a la empresa lechera suiza Nestlé que produjera pequeños lotes de derivados del suero de acuerdo con sus especificaciones. Esta mezcla única fue el "bisabuelo" de Immunocal. Este estudio muestra que los ratones alimentados con este tipo de suero mejoraron los parámetros del sistema inmunológico y se volvieron más resistentes a la infección bacteriana común "salmonella"

JOURNAL OF NUTRITION, 112:1747-1755, 1982

Influencia de las proteínas alimentarias en el sistema inmunológico de los ratones

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Abstract

The effect of graded amounts of dietary lactalbumin (L) and casein (C) hydrolysates on the immune responsiveness of C3H/HeN and DBA/2 strain mice has been investigated by measuring both the specific humoral immune response to sheep red blood cells (SRBC) and the nonspecific splenic cell responsiveness to phytohemagglutinin, concanavalin A and Escherichia coli lipopolysaccharide after stimulation with Mycobacteriurn bovis, strain BCG. The nutritional efficiency of these diets was similar at both 12 and 28% amino acid levels. The immune responses of mice fed the L diets were found to be significantly greater than those of mice fed the corresponding C diets, especially at the 28% level. Furthermore, in the mice fed L diet, increasing the concentration of amino acid in the diet from 12 to 28% greatly enhanced immune responsiveness by both parameters measured. In the C-fed mice, a comparable enhancement of mitogen responsiveness with increasing amino acid level of diet was seen, but there was no change in the humoral immune response. The enhancement of immune responsiveness observed in mice fed the 28% L diet was moderately reduced by the addition of phenylalanine to the diet, indicating that the lower level of this amino acid in the L protein may be of some significance. These dietary effects on immune responsiveness were remarkably similar in both mouse strains tested.

Comentarios del Dr. Gutman

Continuando sus estudios en ratones, los doctores Bounous y Kongshavn buscaron más datos para comprender mejor los efectos del derivado de la proteína del suero especialmente preparado, que más tarde se convertiría en Immunocal. Evaluando una variedad de mediciones de la respuesta inmunológica, reunieron datos que les permitirían refinar el producto, aumentando su eficacia en la respuesta inmunológica.

JOURNAL OF NUTRITION, 113: 1415-1421, 1983

Influencia del tipo de proteína dietética en el sistema inmunológico de los ratones

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Abstract

The effect of graded amounts of dietary lactalbumin (L), casein (C), soy (S), wheat (W) protein and Purina rodent chow (stock diet) on the immune responsiveness of C3H/HeN mice has been investigated by measuring the specific humoral immune response to sheep red blood cells (SRBC), and horse red blood cells (HRBC) as well as the nonspecific splenic cell responsiveness to phyto-hemagglutinin (PHA) and concanavalin A (Con A) after stimulation with Myco-bacterium bovis, strain BCG. The nutritional efficiency of these diets was normal and similar. The immune response of mice fed the L diets, was found to be almost five times higher than that of mice fed the corresponding C diets. The humoral immune response of mice fed C, S, and W diets was substantially lower than that of mice fed stock diet, whereas that of mice fed L diet was higher. The above-described immune effect of all tested proteins was obtained at 20 g/100 g concentration with no further increments with 30- and 40 g/100 g protein in the diet. Mitogen responsiveness to PHA and Con A in L diet-fed mice was only slightly higher than that of C diet-fed mice. Little difference in immune responses was noted among mice fed C, S or W protein diets. The principal factor responsible for the observed immune effect does not appear to be the availability or concentration of single essential amino acids but rather the composite effect of the specific amino acid distribution in the protein.

Comentarios del Dr. Gutman

Los doctores Bounous y Kongshavn habían demostrado sin lugar a dudas que su derivado de la proteína del suero mejoraba la respuesta inmunológica, pero aún no podían explicar por qué. Sus colegas científicos cuestionaron si era sólo el resultado de una mejor nutrición. De no ser así, sería necesario identificar algún tipo de "actividad biológica específica" en el suero. Usando proteínas similares en su composición de aminoácidos, este estudio y otros que siguieron demostraron que la capacidad de la proteína para elevar los parámetros inmunológicos no tenía nada que ver con sus efectos nutricionales. Una sustancia desconocida estaba estimulando la respuesta inmunológica. Pasarían años antes de que descubrieran que era el glutatión.

JOURNAL OF NUTRITION, 115: 1403-1408, 1985

Efecto diferencial del tipo de proteína dietética en las respuestas inmunológicas de las células B y T en ratones

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Abstract

The effect of 20 g/100 g diet of lactalbumin (L), casein (C), soy (S) and wheat (W) protein on the immune responsiveness of C3H/HeN mice has been investigated by measuring the humoral immune response to the T cell-independent antigen, TNP-Ficoll. The humoral immune response of mice fed the L diet was found to be higher than that of mice fed the C, S and W diets. On the other hand, delayed-type hypersensitivity, and splenic cell mitogen responses to phytohemagglutinin and concanavalin A did not differ among mice fed the various diets. Similarly, the type of diet did not appear to influence host resistance to Salmonella typhymurium. It is postulated that the type of protein in the diet influences directly the intrinsic capacity of the B lymphocytes to respond to an immunogenic stimulus.

Comentarios del Dr. Gutman

Mientras continuaban evaluando el derivado de la proteína del suero que habían desarrollado, los doctores Bounous y Kongshavn los compararon con otras fuentes de proteína dietética. En este estudio, se evaluó una versión temprana de Immunocal junto con proteínas de caseína, soya y trigo. Sólo la proteína derivada del suero provocó una mayor respuesta inmunológica, reconfirmando los anteriores experimentos en animales y en laboratorio.

JOURNAL OF NUTRITION, 115: 1409-1417, 1985

Mecanismo de respuesta alterada de las células B inducida por cambios en el tipo de proteína alimentaria en ratones

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Abstract

The effect of 20 g/100 g dietary lactalbumin (L) or casein (C) diets or a nonpurified (NP) diet on the immune responsiveness of C57B1/6J, C3H/HeJ and BALB/cJ mice has been investigated by measuring the response to the T cell-independent antigen, TNP-Ficoll. To investigate the possible influence of dietary protein type on the supply of B lymphocytes, bone marrow lymphocyte production has been examined by a radioautographic assay of small lymphocyte renewal and an immunofluorescent stathmokinetic assay of pre-B cells and their proliferation. The humoral response of all mice fed the L diet was found to be higher than that of mice fed the C diet or non purified diet. A similar pattern of dietary protein effect in (CBA/N x DBA/2J) F1 mice carrying the xid defect was observed following challenge with sheep red blood cells (SRBC). An even greater enhancing effect of dietary L was noted in normal (DBA/2J x CBA/N) F1 mice after immunization with SRBC, but in contrast, the normal large-scale production of B lymphocytes in mouse bone marrow was independent of the type of dietary protein. Dietary protein type did not affect blood level of minerals and trace metals. The free plasma amino acid profile essentially conformed to the amino acid composition of the ingested protein, suggesting that the changes in plasma amino acid profile might be a crucial factor in diet-dependent enhancement or depression of the B-cell response. The findings indicate that the observed effects of altered dietary protein type on humoral immune responsiveness are not exerted centrally on the rate of primary B-lymphocyte production in the bone marrow, but may reflect changes either in the functional responsiveness of the B lymphocytes themselves or in the processes leading to their activation and differentiation in the peripheral lymphoid tissues.

Comentarios del Dr. Gutman

Habiendo confirmado su acción única en el sistema inmunológico, el Dr. Bounous y la Dra. Kongshavn reclutaron a otros científicos para una mayor investigación sobre la "lactoalbúmina dietética" (su primera versión de Immunocal). Ya se había demostrado que mejoraba la actividad de las células T (glóbulos blancos que atacan directamente a los microbios), y este estudio confirmó además un efecto similar en las células B (glóbulos blancos que atacan a los microbios con anticuerpos). Lo que es significativo es que la activación tanto de las células B como de las células.

IMMUNOLOGY, 172:151-156, (1986)

El glutatión aumenta la activación de los linfocitos T citotóxicos 'in vivo'

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Abstract

The activation of cytotoxic T lymphocytes (CTL) in vivo was found to be augmented by glutathione if injected i.p. in the late phase but not in the early phase of the response. The effect of glutathione possibly resembles the augmenting effect of 2-mercaptoethanol in lymphocyte cultures.

Comentarios del Dr. Gutman

Aunque no se trata específicamente de un estudio de Immunocal, incluí este trabajo porque fue el primero en explorar el impacto directo del glutatión en el sistema inmunológico de una criatura viva (in vivo). El Dr. Wulf Droge, el autor principal, era un eminente inmunólogo europeo con un interés especial en el glutatión. En el momento de escribir este artículo, el Dr. Droge aún no se había unido a Immunotec. Este documento histórico dio más tarde pistas sobre cómo el equipo de Immunotec en Canadá estaba utilizando con éxito su derivado específico de la proteína del suero. El Dr. Droge años más tarde sería fundamental en la formulación del Immunocal " Platinum", y lo que es más importante, liderando la investigación en Immunotec después del fallecimiento del Dr. Bounous.

CLINICAL AND INVESTIGATIVE MEDICINE, 11: 213-217, 1988

La proteína del suero de leche en la dieta inhibe el desarrollo de la neoplasia inducida por la dimetilhidrazina

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Abstract

This study investigates the influence of two formula diets containing 20 g/100 g diet of either whey protein concentrate or casein or Purina mouse chow, on the humoral immune responsiveness and dimethylhydrazine induced colon carcinogenesis in A/J mice. After 20 weeks of dimethylhydrazine treatment, the number of plaque forming cells per spleen, following intravenous inoculation with 5 x 106 sheep red blood cells, was nearly three times greater in the whey protein-fed group than in the casein-fed mice although both values were substantially below normal. After 24 weeks of dimethylhydrazine treatment the incidence of tumors in the whey protein-fed mice was substantially lower than that in mice fed either the casein or Purina diet. Similarly, the tumor area was less in the whey protein group in comparison to either the casein or Purina groups, with some difference between casein and Purina groups. Body weight curves were similar in all dietary groups.

In conclusion, a whey protein diet appears to significantly inhibit the incidence and growth of chemically induced colon tumors in mice

Comentarios del Dr. Gutman

Este es un fascinante trabajo teórico en el que el Dr. Bounous examina la variedad de proteínas de la leche en los mamíferos. Señala que 1) La leche humana tiene la menor concentración de proteínas (lo que posiblemente explica por qué los humanos tardan tanto en llegar a la edad adulta), y 2) La leche humana tiene la mayor concentración de suero en comparación con la caseína. El punto del Dr. Bounous es que la preponderancia del suero en la leche humana puede ayudar a explicar el lento desarrollo de los bebés humanos y la longevidad de la especie humana.

CLINICAL AND INVESTIGATIVE MEDICINE, VOL. 11,.NO. 4,.PP 271-278,. 1988

La propiedad inmunoestimulante del concentrado de proteína de suero dietético

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Abstract

The plaque-forming cell response to sheep red blood cells was found to be enhanced in mice fed a formula diet containing 20 g lactalbumin /100 g diet in comparison to mice fed equivalent formula diets of similar nutritional efficiency containing 20 g / 100 g diet of either casein, soy, wheat or corn protein, egg albumin, beef or fish protein, Spirulina maxima, or Scenedesmus protein, or Purina mouse chow. This effect was manifest after 2 weeks and persisted for at least 8 weeks of dietary treatment. Mixing lactalbumin with either casein or soy protein in a 20 g protein / 100 g diet formula significantly enhanced the immune response in comparison to that of mice fed diets containing 20% soy protein or casein.

Comentarios del Dr. Gutman

Los doctores Bounous, Kongshavn y Gold (Jefe de Medicina de la Universidad McGill) consideraron necesario seguir probando el derivado de la proteína del suero desarrollado por el equipo, en particular para confirmar que era clínicamente mejor para fortalecer el sistema inmunológico que otras proteínas. Aquí se comparó el progenitor del Immunocal con la proteína extraída de la caseína, la soya, el trigo, el maíz, el huevo, la albúmina, la carne de res, el pescado y las algas. El grupo alimentado por Immunocal fue el único que se vio beneficiado.

CLINICAL AND INVESTIGATIVE MEDICINE, 12: 154-61, 1989

Propiedad inmunoestimulante de la proteína del suero de leche dietética en ratones: función del glutatión

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Abstract

The spleen cells immune response to sheep red blood cells of C3H/HeJ mice fed a 20 g whey protein/100 g diet is substantially higher than that of mice fed an equivalent casein diet of similar nutritional efficiency. The present study indicates that the observed immunoenhancing effect of the whey protein mixture is dependent on the overall amino acid pattern resulting from the contribution of all its protein components. Whey protein contains substantially more cysteine than casein. Dietary cysteine is considered to be a rate limiting substrate for the synthesis of glutathione which is necessary for lymphocyte proliferation. Our studies show that enhancement of host humoral immune response is associated with greater and more sustained production of splenic glutathione during the antigen driven clonal expansion of the lymphocyte in whey protein fed mice in comparison to mice fed the equivalent casein or the cysteine-enriched casein diet. Hence the efficiency of dietary cysteine in inducing supernormal glutathione levels is greater when it is delivered in the whey protein than as free cysteine. Administration of S-(n-butyl) homocysteine sulfoximine, which reduces splenic glutathione level by half, produces a 4-5 fold drop in the humoral immune response of whey protein diet-fed mice. This is further evidence of the important role of glutathione in the immunoenhancing effect of dietary whey protein.

Comentarios del Dr. Gutman

La labor anterior del Dr. Bounous atrajo la atención de otros prominentes investigadores de la Universidad McGill, que posteriormente contribuyeron a la comprensión científica de su precursor de glutatión derivado del suero. Entre esos científicos figuraban Gerry Batist, destacado oncólogo e investigador canadiense, y el Dr. Phil Gold, que fue Jefe de Medicina del Hospital General de Montreal. En este estudio con ratones, demostraron que los animales alimentados con una versión temprana de Immunocal se beneficiaron de los niveles elevados de glutatión y, lo que es más importante, aumentaron la producción de glóbulos blancos (la defensa de primera línea del sistema inmunológico.

CLINICAL AND INVESTIGATIVE MEDICINE, 12: 343-349, 1989

La influencia de la proteína del suero en el glutatión de los tejidos y las enfermedades del envejecimiento

Gustavo Bounous[1,2], Francine Gervais[1,3], Victor Amer[1,3], Gerald Batist[3], and Phil Gold[1,3]

The Montreal General Hospital Research Institute[1] and McGill University, Departments of Surgery[2], and Medicine[3]

Abstract

This study compared the effects of a whey-rich diet (20 g / 100 g diet), with that of Purina mouse chow or casein-rich diet (20 g / 100 g diet), on the liver and heart glutathione content and on the survival of old male C57BL / 6 NIA mice. The study was performed during a limited observation period of 6.3 months. In mice fed the whey protein-rich diet between 17 months and 20 months of age, the heart tissue and liver tissue glutathione content were enhanced above the corresponding values of the casein diet-fed and Purina-fed mice. Mice fed the whey protein diet at the onset of senescence, exhibited increased longevity as compared to mice fed Purina mouse chow over the 6.3 month observation period extending from the age of 21 months (corresponding to a human age of 55 years) to 26-27 months of age (corresponding to a human age of 80 years), during which time 55% mortality was observed. The corresponding mean survival time of mice fed the defined casein diet is almost identical to that of Purina-fed controls. Body weight curves were similar in all three dietary groups. Hence, a whey protein diet appears to enhance the liver and heart glutathione concentration in aging mice and to increase longevity over a 6.3 month observation period.

Comentarios del Dr. Gutman

Este experimento con ratones fue un estudio de "gran avance". El resultado fue sorprendente, atrajo gran atención y tuvo profundas implicaciones. Se establecieron tres grupos: 1) recibieron la alimentación estándar de los ratones, 2) recibieron una dieta rica en caseína (la caseína es una importante proteína de la leche), y 3) recibieron una versión temprana de Immunocal. Como era de esperar, el grupo alimentado con Immunocal mostró niveles tisulares más altos de glutatión. Además, ¡su vida útil aumentó en más de 6 meses! En términos humanos esto es como extender un promedio de vida de 55 a 80 años. Los humanos no son ratones y no podemos esperar ninguna correlación directa, pero los resultados elevaron significativamente el optimismo del equipo de investigación e impactaron enormemente a otros científicos e investigadores para seguir esta estrategia.

MINERVA GASTROENTEROLOGICA E DIETOLOGICA, 35(4): 241-5, 1989

Cambios en las inmunoglobulinas biliares secretoras en las proteínas de suero de leche de los ratones

Costantino AM, Balzola F, Bounous G

Abstract

Background: A whey protein diet has been shown to enhance splenic immune response to sheep red blood cells (SBRC) in mice. This study was designed to investigate the influence of the type of dietary protein on the biliary secretory IgA. A/J mice were fed defined formula diets containing either 20% whey protein, or 20% casein. Another group was fed Purina mouse chow. After 3 weeks of dietary treatment the body weight of each mouse was recorded and the gall-bladder was removed and its whole content analyzed by ELISA to determine S-IgA secretion. Body weight curves were similar in all dietary groups; higher biliary levels of S-IgA appeared in the whey protein fed mice than in the casein (p less than 0.025) or purine (p less than 0.025) fed mice. Dietary protein type may have a direct influence on the immune response in the gastrointestinal tract, without affecting body weight.

Comentarios del Dr. Gutman

Basándose en pruebas anteriores de que el Immunocal mejora la respuesta inmunológica en los animales, este estudio se centró en una medida particular de la respuesta inmunológica. El equipo demostró que los animales alimentados con una formulación temprana de Immunocal tenían mejores niveles de anticuerpos y respuesta inmunológica que los animales con una dieta estándar o una dieta de caseína (la principal proteína de la leche). Al combinar estos hallazgos con las pruebas existentes, los investigadores presentaron y obtuvieron una patente por los beneficios de mejora inmunológica de Immunocal.

TUMOR BIOLOGY 11: 129-136, 1990

Las proteínas lácteas de la dieta inhiben el desarrollo de la neoplasia inducida por la dimetilhidrazina

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Abstract

This study investigated the influence of two formula diets containing 20 g/100 g diet of either whey protein concentrate or casein, or Purina mouse chow on 1,2dimethylhydrazine (DMH)-induced colon carcinoma in A/J mice. Four weeks after the 24th DMH treatment the incidence of tumour and tumour area in the whey protein-fed mice was substantially less in comparison to either the casein or Purina groups. The Purina group exhibited the greatest tumour burden. At the end of the experiment all animals continuously fed the whey protein diet were found to be alive, whereas 33% of those on the casein or Purina diet had died. Animals fed Purina diet for 20 weeks and then switched to either milk protein diet for a further 8 weeks exhibited a decrease in tumour burden as compared to those animals fed the Purina diet continuously. Body weights were similar in all dietary groups. In conclusion, a whey protein diet appears to significantly influence the development of chemically induced colon tumours and the short-term survival of mice.

Comentarios del Dr. Gutman

Los ratones con tumores malignos fueron alimentados con tres fórmulas nutricionales diferentes: 1) comida estándar para ratones, 2) caseína (la principal proteína de la leche), y 3) una temprana formulación de Immunocal. Después de cuatro semanas, la masa total del tumor en los animales alimentados con Immunocal fue sustancialmente menor que en los otros dos grupos. Esto estableció una vez más que las proteínas extraídas ofrecían claras ventajas sobre otras fuentes de proteínas en la lucha contra el cáncer. Estos fueron resultados muy alentadores para estos primeros días, e inspiraron futuras investigaciones.

CLINICAL AND INVESTIGATIVE MEDICINE, 14: 296-309, 1991

La actividad biológica de las proteínas de suero de leche dietéticas no desnaturalizadas: función del glutatión

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Abstract

This study compared the effects of different sources of whey protein concentrate (20 g/100 g diet) and of casein on the spleen, liver, and heart glutathione content of C3H/HeJ mice, and on the immune response of their spleen cells to sheep red blood cells. Body weight curves were similar in all dietary groups. Our data indicate that the humoral immune response is highest in mice fed a dietary whey protein concentrate exhibiting the highest solubility (undenatured conformation) and a greater relative concentration of the thermolabile cystine rich proteins. In addition, the mice fed this type of whey protein concentrate exhibit higher levels of tissue glutathione. The presence in the serum albumin fraction of glutamylcysteine groups (rare in food protein) and the specific intramolecular bond as related to the undenatured conformation of the molecule are considered to be key factors in the glutathione-promoting activity of the protein mixture.

Comentarios del Dr. Gutman

En este momento el Dr. Bounous y su equipo sabían que ciertos grupos de proteínas en el suero podían elevar los niveles de glutatión, pero aún no sabían cuáles. Este estudio determinó cuáles estaban activos, cómo extraerlos sin perder su disponibilidad biológica y qué formulación mejoraba la respuesta inmunológica. El estudio confirmó que los grupos de proteínas más eficaces son: a) ricos en cistina y cisteína y, b) no desnaturalizados (descompuestos) por exposición al calor. Una vez establecidos estos dos hechos críticos, los científicos perfeccionaron las técnicas de producción para obtener la forma más adecuada de aislado de proteína de suero para aumentar el glutatión.

CANADIAN JOURNAL OF CARDIOLOGY VOL 19, NO 10, 1163-1168, SEPTEMBER 2003

La proteína del suero de leche disminuye la producción de radicales libres de oxígeno en un modelo murino de miocardiopatía crónica por exceso de hierro

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Abstract

Chronic iron overload is a major cause of organ failure worldwide, but its pathogenesis remains to be elucidated.

To examine in an experimental murine model of iron-overload cardiomyopathy the relation between milk whey protein and, first, the production of reactive oxygen free radical species and, second, antioxidant reserve status.

B6D2F1 mice were randomly assigned to four treatment groups (n=8 per treatment group): placebo control; iron only; whey only; and iron with whey. Reactive oxygen free radical species in the heart were quantified by the cytotoxic aldehydes malondialdehyde (MDA), 4-hydroxy-nonenal (HNE) and hexanal, while antioxidant reserve status was quantified by glutathione (GSH) and glutathione peroxidase (GPx) activity in the heart tissue.

Significantly decreased concentrations (pmol/100 mg wet weight tissue) of MDA (2468 ± 261), HNE (912 ± 38) and hexanal (5385 ± 927) were observed in the heart tissue of the group receiving iron with whey, in comparison with the iron-only treatment group (MDA 9307 ± 387, HNE 1416 ± 157, hexanal 14,874 ± 2955; P<0.001). Significantly increased GPx (141 ± 38 IU/L) and GSH (521 ± 136 IU/L) activity were observed in mice receiving iron with whey, in comparison with mice receiving iron only (GPx 100 ± 10 IU/L, GSH 446 ± 33 IU/L; P<0.001).

Mice receiving iron treatments with whey supplementation had significantly lower concentrations of cytotoxic aldehydes and significantly higher cardiac levels of GPx and GSH activity than did iron-only treated mice. Additional basic research is warranted to examine the exact mechanisms by which milk whey protein protects the heart.

Comentarios del Dr. Gutman

El hierro es una espada de dos filos (juego de palabras). Es una necesidad crítica en los humanos, pero sólo en niveles bajos, de lo contrario, es tóxico. El exceso de hierro provoca el fallo de varios órganos, incluyendo el corazón. El término médico es "miocardiopatía por exceso de hierro". Este grupo de investigadores quería saber si la dieta de Immunocal podría mejorar la condición de los animales que sufren de una enfermedad similar. Los ratones se beneficiaron de los elevados niveles de glutatión y hubo menos evidencia de daño al tejido cardíaco.

Lait 86 (2006) 213–226

Proteínas dietéticas, función inmunológica y carcinogénesis de colon en el ratón

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Abstract

Immune stimulation and colon cancer development were studied in A/J mice injected with azoxymethane (AOM) which were maintained on undenatured whey protein concentrate (WPC), Immunocal (IM), soy protein isolate (SPI) and a commercial casein (CC) as the only source of dietary protein for 32 weeks. No difference in growth rate and body weight was found for the different treatments. Immune stimulation, after challenge by subcutaneous injection of 5 × 106 sheep red blood cells, was evaluated by PFC (Plaque-Forming Cells) in the spleen. Response was equal and significantly higher for WPC- and IM-fed mice, the lowest response was found for the SPI group and an intermediate response for CC. A parallel increase was observed between PFC in the spleen and glutathione concentration in the liver. Aberrant crypt foci (ACF) were confirmed as reliable markers for colon carcinogenesis and were detected by fixation in formaldehyde solution and staining with methylene blue. A high linear correlation was found between ACF and actual number of colon tumors. The most important result of this work was the significant effect of the cysteine-rich proteins in the immunological response to SRBC antigen and tumor formation. These findings confirm and extend the works reported by other investigators.

Comentarios del Dr. Gutman

Este equipo de científicos brasileños se centró en la bioquímica de los alimentos y en las posibles aplicaciones clínicas de los derivados de la leche. Al conocer el trabajo del doctor Bounous y de la doctora Kongshavn sobre Immunocal y el cáncer de colon, quisieron repetir y validar los resultados positivos. Utilizando un modelo de ratón expuesto a un potente carcinógeno (sustancia química cancerígena), confirmaron la naturaleza protectora de Immunocal en esta enfermedad.

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 58:12729-12734 (2010)

Efectos del Concentrado de Proteína de Suero (WPC por sus siglas en inglés) en la distribución de subpoblaciones de linfocitos en ratas con excesiva ingesta de alcohol

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Abstract

To investigate the effects of whey protein concentrate (WPC) on antioxidant statuses and the lymphocyte subpopulations in the rats with alcohol intake, the antioxidant statuses in the peripheral blood (PB) and the lymphocyte subpopulations in the PB, spleen, and bone marrow (BM) of the rats fed with WPC (0.334 g/kg) and alcohol (6 g/kg) for 3 months were analyzed. Results showed that the effects of WPC on the glutathione peroxidase and glutathione in the PB, the T and B cells in the spleen, and the B cells in the BM were more apparent in the rats with alcohol intake; however, they are not apparent in the controls. Taken together, our results indicated that the immunity of rats might be enhanced by the increased antioxidant ability after WPC supplementation and the effects of WPC on the lymphocyte subpopulations were mainly in the spleen and BM and not in the PB.

Comentarios del Dr. Gutman

Dando Immunocal a los animales sometidos a la toxicidad del alcohol, este equipo taiwanés encontró grandes beneficios para el sistema inmunológico. Aunque este estudio se llevó a cabo sólo en animales, hay razones para creer que podría beneficiar también a los humanos. Se justifican más estudios.

BRITISH JOURNAL OF NUTRITION (2011), 105, 1465–1470

A whey-based glutathione-enhancing diet decreases allergen-induced airway contraction in a guinea-pig model of asthma

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Abstract

Since an allergen-induced early asthmatic reaction is likely to be accompanied by oxidative stress and since levels of the endogenous anti- oxidant glutathione can be enhanced by a whey-based diet (undenatured whey protein concentrate, UWPC), it was investigated whether UWPC could alleviate allergen-induced lung contractions. Guinea pigs were fed water or UWPC twice a day starting at day 23 up to day 20. The animals were sensitised to ovalbumin or received saline on day 0. Serum samples were taken at several days after sensitisation to measure allergen-specific IgG. On day 20, lungs were isolated and perfused with buffer containing the allergen ovalbumin. Airway contractions were assessed, and mediators and indicators for oxidative stress were measured in the lung effluent. Moreover, glutathione levels were determined in the liver. The indicator of oxidative stress and airway contractile mediator, 8-iso-PGF2a, was increased upon ovalbumin challenge in ovalbumin-sensitised groups. Furthermore, thiobarbituric acid-reactive substances (TBARS) were increased as well. Sensitisation with ovalbumin increased IgG levels from day 12 up to day 20, which were not influenced by the UWPC diet. In contrast, the UWPC diet significantly enhanced glutathione levels in the liver. Moreover, the UWPC diet significantly reduced the ovalbumin-induced anaphylactic response by 45 % and decreased PGE2 levels by 55 % in the effluent fluid. We show for the first time that during anaphylaxis, there is acute oxidative stress in the respiratory tract. The UWPC diet did not influence the sensitisation response to the allergen but did increase endogenous glutathione levels. The UWPC diet profoundly reduces allergen-induced airway constrictions, which opens new avenues for dietary management of allergic diseases.

Comentarios del Dr. Gutman

Este equipo de investigación internacional estaba interesado en ver si el asma, y sobre todo la anafilaxia (reacción alérgica que pone en peligro la vida), puede ser menos grave si se trata previamente a los animales con una proteína potenciadora del glutatión. La proteína UWPC, Undenatured Whey Protein Concentrate, (concentrado de proteína de suero no desnaturalizado) que se utilizó en este ensayo fue la "HMS 90", una versión anterior de Immunocal que desarrollaron los doctores Bounous y Kongshavn. HMS 90 fue el nombre que se utilizó en Canadá durante los primeros años en que Immunocal estuvo disponible comercialmente en ese país. Los resultados fueron claros. Los animales expuestos a un alérgeno (sustancia que provoca alergia) mejoraron significativamente. Los niveles de glutatión aumentaron, pero, lo más importante, la mejora clínica de los animales tanto del asma como de la anafilaxia fue "extremadamente" superior.

ANTIOXIDANTS (BASEL) 2014 DEC 12;3(4) :843-65

Un suplemento de suero rico en cisteína (Immunocal®) retrasa el inicio de la enfermedad y evita el agotamiento del glutatión de la médula espinal en el modelo de ratón Hsod1 (G93a) de la esclerosis lateral amiotróficas

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Abstract

Background: Depletion of the endogenous antioxidant, glutathione (GSH), underlies progression of the devastating neurodegenerative disease, amyotrophic lateral sclerosis (ALS). Thus, strategies aimed at elevating GSH may yield new therapeutics for ALS. Here, we investigated the effects of a unique non-denatured whey protein supplement, Immunocal®, in the transgenic Gly position 93 to Ala (G93A) mutant hSOD1 (hSOD1(G93A)) mouse model of ALS. Immunocal® is rich in the GSH precursor, cystine, and is therefore capable of bolstering GSH content. Transgenic hSOD1 (G93A) mice receiving Immunocal® displayed a significant delay in disease onset compared to untreated hSOD1(G93A) controls. Additionally, Immunocal® treatment significantly decreased the rate of decline in grip strength and prevented disease-association reduction in whole blood and spinal cord tissue GSH levels in end-stage hSOD1(G93A) mice. However, Immunocal® did not extend survival, likely due to its inability to preserve the mitochondrial GSH pool in spinal cord. Combination treatment with Immunocal and the anti-glutamatergic compound, riluzole, delayed disease onset and extended survival in hSOD1(G93A) mice. These findings demonstrate that sustaining tissue GSH with Immunocal® only modestly delays disease onset and slows the loss of skeletal muscle strength in hSOD1(G93A) mice. Moreover, the inability to Immunocal® to rescue mitochondrial GSH in spinal cord provides a possible mechanism for its lack of effect on survival and is a limiting factor in the potential utility of this supplement as a therapeutic for ALS.

Comentarios del Dr. Gutman

La ELA (Esclerosis Lateral Amiotrófica) también se conoce como "Enfermedad de Lou Gehrig", un devastador proceso neurodegenerativo que degrada la función muscular y conduce a una eventual parálisis. Los ratones que sufren una enfermedad similar se utilizan en el laboratorio para explorar posibles tratamientos para los humanos. Alimentando con Immunocal a estos ratones, el equipo de Linseman en Denver encontró aumentos significativos en los niveles de glutatión y - lo que es más importante - una mejora clínica en la fuerza muscular. Immunocal también retrasó la aparición de la enfermedad. Los ratones sobrevivieron aún mejor cuando su dieta combinó Immunocal con el fármaco Riluzole.

FREE RADICAL BIOLOGY AND MEDICINE, 2017 SEP;110:162-175

El aislado de proteína de suero rico en cisteína (Immunocal®) mejora los déficits del modelo de ratón GFAP.HMOX1 de la esquizofrenia

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Abstract

Schizophrenia is a neuropsychiatric disorder that features neural oxidative stress and glutathione (GSH) deficits. Oxidative stress is augmented in brain tissue of GFAP.HMOX1 transgenic mice which exhibit schizophrenia-relevant characteristics. They whey protein isolate, Immunocal® serves as a GSH precursor upon oral administration. In this study, we treated GFAP.HMOX1 transgenic mice daily with either Immunocal (33mg/ml drinking water) or equivalent concentrations of casein (control) between the ages of 5 and 6.5 months. Immunocal attenuated many of the behavioral neurochemical and redox abnormalities observed in GFAP. HMOX1 mice. In addition to restoring GSH homeostasis in the CNS of the transgenic mice, the whey protein isolate augmented GSH reserves in the brains of wild-type animals. These results demonstrate that consumption of whey protein isolate augments GSH stores and antioxidant defenses in the healthy and diseased mammalian brain. Whey protein isolate supplementation (Immunocal) may constitute a safe and effective modality for the management of schizophrenia, an unmet clinical imperative.

Comentarios del Dr. Gutman

El hábil equipo de investigación del Dr. Hyman Schipper en el Instituto de Investigación Médica Lady Davis, en el laboratorio del Hospital General Judío, estudió una especie de ratón que se utiliza en la investigación de la esquizofrenia y encontró altos niveles de estrés oxidativo. En los seres humanos, la esquizofrenia también se ha relacionado con altos niveles de estrés oxidativo y con un bajo nivel de glutatión. El equipo quería ver si estos ratones mostrarían una mejora después de una dieta de Immunocal, en comparación con el grupo de placebo, los ratones alimentados con Immunocal mostraron una mejora bioquímica (niveles más altos de glutatión en el cerebro) y mejoraron los parámetros de comportamiento. El Dr. Schipper señala que la degeneración de las neuronas, el depósito de hierro tóxico y el subsecuente aumento del estrés oxidativo es una característica central de esta enfermedad compartida con el envejecimiento normal, la enfermedad de Alzheimer, la enfermedad de Parkinson y otras enfermedades neurodegenerativas. Sugiere que estos hallazgos ofrecen la evidencia necesaria para proceder a estudios en humanos.

AFR. J. BIOMED. RES. VOL. 20 (SEPTEMBER, 2017); 287- 292

El concentrado de proteína de suero y la dexametasona protegen el cerebelo de ratas de lesiones por radiación gamma

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Abstract

The possible radioprotective effect of Immunocal® (whey protein]) supplement and dexamethasone on gamma-irradiated cerebellar tissue of Wistar rat was investigated in this study. Forty male albino rats were acclimatized and randomized into four groups of 10 animals each. Group I rats served as control; Group II: received 2.5 Gy of gamma-radiation; Group III: received Immunocal® (286mg/kg) for 14 days, then 2.5 Gy gamma rays on day15 of experiment; Group IV: received dexamethasone (1mg/kg) i.p daily for 3 days, then 2.5 Gy gamma rays. All rats were euthanized 14 days post-irradiation. Rat brains were fixed in 10% formalin, processed with routine paraffin wax techniques and stained with Haematoxylin and Eosin. Histomorphometric studies showed that radiation significantly ($p< 0.05$) reduced the thickness of both the molecular and granular layers of the cerebellum when compared with the control group. This reduction was significantly ($p< 0.05$) increased in animals pretreated with Immunocal® and dexamethasone before irradiation. The densities of the Purkinje and outer stellate cells were significantly ($p< 0.05$) reduced in the irradiated animals compared with the control. The Purkinje cells and outer stellate cells were significantly increased ($p< 0.05$) in animals of Radiation + Immunocal® and Radiation + Dexamethasone groups relative to the radiation group. In conclusion, data from the present study showed that pre-treatment with Immunocal® and dexamethasone before exposure to a single dose of 2 Gy of gamma radiation on the 15th day of the experiment, protected rat's cerebellum from gross and histological alterations from radiation injury.

Comentarios del Dr. Gutman

Investigadores nigerianos estudiaron estrategias para reducir la inflamación y los daños cerebrales provocados por la exposición a la radiación. Esto tiene relevancia en el tratamiento del cáncer, ya que muchos tumores cerebrales se tratan con radioterapia. Aunque se hace todo lo posible por concentrar la radiación sólo en el tumor, inevitablemente los tejidos normales sufren daños colaterales. Uno de los tratamientos habituales para estos efectos adversos es el uso de potentes esteroides como la dexametasona. En este estudio, se comparó Immunocal con la dexametasona en cuanto a su capacidad para limitar los daños de la radiación. Immunocal demostró ser igual de eficaz que la medicación con esteroides para aliviar los daños.

FOOD CHEM TOXICOL. 2017 SEP;107(PT A):440-448

Efectos selectivos del concentrado de proteína de suero sobre los niveles de glutatión y la apoptosis en ratas con tumores mamarios

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Abstract

Glutathione (GSH) plays an important role in antioxidant defense and regulation of apoptosis. GSH deficiency is related to many diseases, including cancer, and increased GSH levels in cancer cells are associated with chemotherapy resistance because of resistance to apoptosis. In this study, we investigated the effects of whey protein concentrate (WPC), a precursor of GSH, in rats with mammary tumors induced by treatment with 7,12-dimethylbenz(a)anthracene (DMBA). DMBA treatment results in cellular changes that mimic the initiation and promotion of carcinogenesis of breast tissue. We aimed to examine the possible preventive effects of diets containing whey protein on DMBA-induced mammary tumors in rats. The results indicate that WPC (0.334 g/kg) supplementation significantly increased the liver GSH levels by 92%, and were accompanied by low Bax/Bcl-2 ratio (from 5 to 3) and cleaved caspase-3/procaspase-3 ratio (from 2.4 to 1.2) in DMBA-treated rats. Furthermore, tumor GSH levels were decreased by 47% in WPC-supplemented rats, which resulted in increased Bax/Bcl-2 ratio (from 0.9 to 2) and cleaved caspase-3/procaspase-3 ratio (from 1.1 to 2.7). In conclusion, supplementation with WPC could selectively deplete tumor GSH levels and, therefore, WPC supplementation might be a promising strategy to overcome treatment resistance in cancer therapy.

Comentarios del Dr. Gutman

Siempre subrayo la importancia de los estudios en humanos por encima de los estudios en animales o en laboratorio, pero me impresionó mucho lo que este equipo taiwanés demostró en un modelo animal de cáncer de mama. Uno de los conceptos erróneos que prevalecen en oncología es que el glutatión puede "alimentar" al tumor. Aunque esto se ha demostrado en el cultivo de tejidos, nunca se ha demostrado en organismos vivos. Aquí se ha demostrado lo contrario: el uso de precursores de glutatión en un modelo vivo aumentará los niveles de glutatión en las células normales y, al mismo tiempo, reducirá el glutatión en las células cancerosas. Esto está en consonancia con otros estudios inmunológicos sobre el cáncer.

ELECTRONIC JOURNAL OF METABOLISM & NUTRITION OF CANCER, 3:280-285, 2017

La actividad nutricional de la proteína activa del suero en ratones Nude portadores de tumores pancreáticos

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Abstract

Objective: Active whey protein preserved the active ingredients in cow milk processed with patented low temperature extraction technology. Protein contents up to 90%. In addition, it has many biological functions such as improving the nutrition status and strengthening immunity. It's one of the important components in clinical nutritional therapy. This research is to study the effect potential mechanism and potential of active whey protein on pancreatic carcinoma established in vivo model.

Methods: Xenotransplanted pancreatic carcinoma was established by panc-1 cell line, then divided into 3 groups, 8 mice of each randomly accordingly to the different way of nutritional intervention: standard diet group (SD group), standard diet with soy group (Soy group), standard diet with active whey protein group (ABD group). During the experiment, animals' body condition was observed, weight of nude mice, tumor size and weight were recorded. And, compared the average survival time of mice. Meanwhile, we detected the glutathione levels in the blood and carcinoma.

Results: Weight loss of all mice in the three groups was observed. Weight of mice in ABD group (24.35±1.89) g was significantly higher than SD group (20.04±2.41) g 8 weeks after treatment ($P<0.05$). Volume and weight of mice transplanted tumor in the three groups was no statistical difference. At the end point, compared with SD group and Soy group [(56.00±5.29) d and (51.63±10.54) d, respectively], the average survival time of mice in ABD group ($P<0.05$). The GSH level in the blood of ABD group was significantly higher than SD group and Soy group ($P<0.05$) when the level in the tumor of ABD group was lower but there was no statistical difference.

Conclusions: Active whey protein can prevent the weight loss in transplanted pancreatic mice, prolong the survival time, and this may be associated with preventing and curing cancer cachexia. Key words: whey protein, cancer, nutritional therapy, glutathione.

Comentarios del Dr. Gutman

Este equipo chino injertó tejido de cáncer de páncreas en ratones para examinar el efecto de Immunocal como una intervención. Se utilizaron tres grupos: el primero tenía una dieta estándar; el segundo consumía una dieta estándar complementada con proteína de soya; al tercer grupo se le administró Immunocal (en China llamado "ABD"). Los ratones alimentados con Immunocal tenían mejores niveles de glutatión, sufrían menos pérdida de peso (caquexia por cáncer) y sobrevivieron mucho más tiempo.

FREE RADIC BIOLOGY AND MEDICINE, 2018 AUG 20;124:328-341

El suplemento de proteína de suero rico en cisteína, Immunocal®, preserva el glutatión cerebral y mejora los índices cognitivos, motores e histopatológicos de lesiones cerebrales traumáticas en una especie de ratón de impacto cortical controladot

[1]Ignowski, E, [2]Winter AN, [3]Duval N, [4]Fleming H, [5]Wallace T, [6]Manning E, [7]Koza L, [8]Huber K, [9]Serkova NJ, [10]Linseman DA

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Abstract

Background: Traumatic brain injury (TBI) is a major public health problem estimated to affect nearly 1.7 million people in the United States annually. Due to the often debilitating effects of TBI, novel preventative agents are highly desirable for at risk populations. Here, we tested a whey protein supplement, Immunocal®, for its potential to enhance resilience to TBI. Immunocal® is a non-denatured whey protein preparation which has been shown to act as a cysteine delivery system to increase levels of the essential antioxidant glutathione (GSH). Twice daily oral supplementation of CD1 mice with Immunocal® for 28 days prior to receiving a moderate TBI prevented an ~ 25% reduction in brain GSH/GSSG observed in untreated TBI mice. Immunocal® had no significant effect on the primary mechanical injury induced by TBI, as assessed by MRI, changes in Tau phosphorylation, and righting reflex time or apnea. However, pre-injury supplementation with Immunocal® resulted in statistically significant improvements in motor function (beam walk and rotarod) and cognitive function (Barnes maze). We also observed a significant preservation of corpus callosum width (axonal myelination), a significant decrease in degenerating neurons, a reduction in Iba1 (microglial marker), decreased lipid peroxidation, and preservation of brain-derived neurotrophic factor (BDNF) in the brains of Immunocal®-pretreated mice compared to untreated TBI mice. Taken together, these data indicate that pre-injury supplementation with Immunocal® significantly enhances the resilience to TBI induced by a moderate closed head injury in mice. We conclude that Immunocal® may hold significant promise as a preventative agent for TBI, particularly in certain high risk populations such as athletes and military personnel.

Comentarios del Dr. Gutman

Usando un modelo animal con trauma cerebral leve, el equipo de Dan Linseman en la Universidad de Denver examinó ratones alimentados con Immunocal o con un placebo. Cuando se probaron los marcadores de estrés oxidativo y otros signos de lesión cerebral, los que recibieron Immunocal mostraron una mejora en los niveles de glutatión. También revelaron menos evidencia de lesiones cerebrales microscópicas y, lo más importante, mejoraron la función motora (capacidad de movimiento) y la función cognitiva (capacidad de pensamiento). El equipo sugiere que se hagan más estudios con la esperanza de extender estos beneficios a los atletas, personal militar y otros en riesgo de sufrir un traumatismo craneal.

ELECTRONIC JOURNAL OF METABOLISM & NUTRITION OF CANCER (4)3: 216-221, 2017

Estudio del efecto de la proteína activa del suero en la terapia nutricional de los xenoinjertos para el cáncer de páncreas en ratones Nude

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Abstract

Objective Active whey protein preserved the active ingredients in cow milk processed with patented low temperature extraction technology. Protein contents up to 90%. In addition, It has many biological functions such as improving the nutrition status and strengthening immunity. It's one of the important components in clinical nutritional therapy. This research is to study the effect potential mechanism and potentiof active whey protein on pancreatic carcinoma established in vivo model. **Methods** Xenotransplanted pancreatic carcinoma was established by panc-1 cell line, then divided into 3 groups, 8 mice of each randomly according to the different way of nutritional intervention: standard diet group (SD group), standard diet with soy group (Soy group), standard diet with active whey protein group (ABD group). During the experiment, animals' body condition was observed, weight of nude mice, tumor size and weight were recorded. And, compared the average survival time of mice. Meanwhile, we detected the glutathione levels in the blood and carcinoma. **Results** Weight loss of all mice in the three groups was observed. Weight of mice in ABD group (24.35±1.89)g was significantly higher than SD group (20.04±2.41)g 8 weeks after treatment (P<0.05). Volumn and weight of mice transplanted tumor in the three groups was no statistical difference. At the end point, compared with the SD group and Soy group [(56.00±5.29)d and (51.63±10.54)d, respectively], the average survival time of mice in ABD group(62.13 ± 2.47d) was significantly higher (P<0.05). There was no statistical difference between SD group and Soy group (P>0.05). The GSH level in the blood of ABD group was significantly higher than SD group and Soy group (P<0.05) when the level in the tumor of ABD group was lower but there was no statistical difference. **Conclusions** Active whey protein can prevent the weight loss in transplanted pancreatic mice, prolong the survival time, and this may be associated with preventing and curing cancer cachexia.

Comentarios del Dr. Gutman

Estos científicos de Beijing injertaron tejido de cáncer de páncreas en ratones. Tres grupos de tratamiento fueron seleccionados al azar: 1) dieta normal, 2) dieta estándar con proteína de soya, y 3) dieta estándar con Immunocal (aquí llamada "ABD"). Hubo mejoras estadísticamente relevantes en la supervivencia y la prevención de la pérdida de peso por cáncer en el grupo tratado con Immunocal. Más pruebas "del glutatión que alimenta el cáncer".

CHINA CANCER. (28)6:476-482, 2019

Efectos de la proteína activa del suero en el estado nutricional e inmunológico de los ratones con cáncer de mama triplemente negativo con quimioterapia

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Abstract

Purpose To investigate the effect of active whey protein(ABD) on nutritional and immune status of mice bearing triple-negative breast cancer(TNBC) undergoing chemotherapy.

Methods The triple-negative breast cancer 4T1 cells were inoculated in BALB/c mice. The tumor bearing mice were randomly divided into 4 groups with 6 mice in each group: control group, paclitaxel group, casein + paclitaxel group and ABD+ paclitaxel group. The weight of mice, volume of tumor were observed and measured. The overall survival of mice and glutathione(GSH) levels in blood and tumors were analyzed.

Results Weight of mice in ABD+ paclitaxel group (20.52±1.10)g was significantly higher than those of casein + paclitaxel group (19.03 ±1.76)g and paclitaxel group (18.71±0.86)g (P<0.05) on d31. The tumor sizes in ABD+ paclitaxel group was lower than that in other groups (P<0.05). The overall survival of the ABD+ paclitaxel group was significantly longer than paclitaxel group and casein + paclitaxel group. The GSH levels in tumor tissue of ABD+ paclitaxel group, casein + paclitaxel and paclitaxel group were (34.5±18.0) μmol/L, (55.3±23.8)μmol/L and (54.9±11.7) μmol/Lμrespectively. However,GSH levels in blood of three groups were (19.1±0.7) μmol/L,(13.0±8.8)μmol/L and (15.2±9.7) μmol/L,respectively. There was no significant difference in GSH contents both in blood and tumor tissue among three groups (P>0.05).

Conclusion Whey protein combined with chemotherapy can attenuate weight loss, improve nutritional status, inhibit tumor growth and prolong survival time in mice bearing triple negative breast cancer.

Comentarios del Dr. Gutman

El cáncer de mama fue inducido en ratones. Se seleccionaron al azar cuatro grupos de tratamiento: 1) control (sin tratamiento), 2) Paclitaxel (quimioterapia), 3) Paclitaxel (quimioterapia) con caseína, y 4) Paclitaxel (quimioterapia) con Immunocal (aquí llamado "ABD"). El grupo de Immunocal se desempeñó mejor en términos de pérdida de peso y supervivencia. Más pruebas de la compatibilidad de Immunocal y esta quimioterapia.

ESTUDIOS DE LABORATORIO IN VITRO, ESTUDIOS DE PROBETA, CULTIVOS DE CÉLULAS, ETC.

Comprometerse con un estudio en animales o humanos requiere mucho trabajo de preparación para demostrar si los enormes gastos en tiempo, recursos y esfuerzos valdrán la pena. Esto también es importante para tomar decisiones éticas sobre si los animales vivos (incluidos los humanos) pueden estar en riesgo durante un experimento. Estos estudios de laboratorio ("In-Vitro") a menudo son un requisito para realizar estudios en criaturas vivas ("In-Vivo").

Estos estudios de laboratorio in vitro son de gran interés y, en última instancia, decidirán o dirigirán dónde es posible realizar ensayos adicionales. Sin embargo, debe enfatizarse que los resultados de estos estudios no necesariamente se traducen en aplicación en el "mundo real". Incluso los ensayos clínicos en animales no pueden extender sus conclusiones a lo que sucede en un ser humano vivo. La gran mayoría de las conclusiones hechas en estudios in vitro nunca se aplican a experimentos en humanos.

Sin embargo, los estudios in vivo en animales o humanos se basan absolutamente en los resultados de los experimentos de laboratorio. En las siguientes páginas encontrará los documentos publicados que representan la base de los ensayos clínicos de Immunotec.

PRESENTED AT THE INTERNATIONAL CONFERENCE ON AIDS, AUGUST 7-12, 1994

La actividad anti VIH y anti apoptótica del concentrado de proteína de suero: Immunocal®

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Abstract

Objectives: The in vivo glutathione (GSH) promoting activity of undenatured Whey protein concentrate (WPC) has already been demonstrated. Here we demonstrate the anti HIV and anti Apoptotic activity of a WPC product termed Immunocal and its relation with GSH synthesis.

Methods: Immunocal is produced in linear fashion in order to maintain proteins in a non denatured form and to preserve their glutamyl cysteine residues. We tested the in vitro anti-HIV activity on cord blood mononuclear cells and MT 4 cells by studying each of reverse transcriptase (RT) activity, p24 antigen production, and syncytium formation. GSH was measured by spectrophotometric recycling assay. Apoptosis was evaluated by flow cytometry on PBMC from HIV infected individuals (cells were stained with acridine orange and ethidium bromide) (n = 6).

Results: An anti HIV activity was found at WPC concentrations between 100 micrograms/ml and 500 micrograms/ml. Inhibition of syncytium formation occurred with a IC50 of 150 micrograms/ml. PBMCs cultured with these WPC concentrations (N=3) had a statistically significant increase in GSH synthesis when compared to untreated cells, 9.6 +/- 1.5 vs 5.4 +/- nmoles/10(7) cells, p = 0.01. HIV infected PBMCs cultured in the presence of 100 micrograms/ml of WPC were less prone to die of apoptosis than untreated cells, 15% +/- 2.6 vs 37% +/- 2.4 p <0.001.

Conclusion: Immunocal (WPC) possesses antiviral and anti-apoptotic activities which may be related to its glutathione promoting activity. A clinical trial is currently going on with children with AIDS and wasting syndrome.

Comentarios del Dr. Gutman

Basándose en los prometedores resultados de estudios anteriores con Immunocal, estos prominentes investigadores de la Universidad McGill diseñaron este estudio de células in vitro para determinar si Immunocal podría desencadenar la actividad antiviral al aumentar los niveles de glutatión. La hipótesis fue confirmada, alentando a continuar los estudios en humanos ya existentes sobre el SIDA pediátrico.

ANTICANCER RESEARCH, 16:1095-1100 (1996)

Modulación selectiva in vitro de GSH celular por un aislado de proteína de leche materna humanizada en células normales y un modelo de carcinoma de mama de rata

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Abstract

We report the in vitro selective inhibitory activity of a humanized whey protein concentrate Immunocal™ on growth of mammary carcinoma cells and Jurkat T cells in comparison to normal peripheral blood mononuclear cells. We related this inhibitory activity to a selective depletion of intracellular glutathione synthesis. The use of humanized whey protein concentrate as a food supplementation may have direct implication in clinical trials with adjuvant chemotherapy.

Glutathione accounts for more than 90% of total intracellular non-protein sulfhydryl and is critical in a variety of cellular defense functions including protection from toxic oxygen species and detoxification of various xenobiotics. Tumor cell GSH concentration may be among the determinant of the cytotoxicity of many chemotherapeutic agents, and an increase in GSH concentration appears to be at least one of the mechanisms of acquired drug resistance to chemotherapy.

GSH may be increased by different methods including delivery of L-Cystine, a rare limiting amino acid in GSH synthesis. This is difficult since cysteine is toxic, it is not transported efficiently into cells, and is oxidized spontaneously at neutral pH.

Attempts to cancer treatment based on modulation of GSH concentration in tumor cells must take into consideration the glutathione status and the rate of GSH synthesis in these cells. It is well known that rapid GSH synthesis in tumor cells is associated with high rates of cellular proliferation. Depletion of tumor GSH in vivo decreases the rate of cellular proliferation and inhibits cancer growth. In practice it is difficult to reduce GSH sufficiently in a tumor in vivo without placing the normal tissue at risk.

Numerous studies have demonstrated that GSH can be differently manipulated in normal versus tumor cell line. Dependent upon the method of GSH manipulation protection could be demonstrated in normal but not in tumor cell line.

In this report we demonstrate that it is possible to selectively modulate in vivo GSH synthesis in normal cells compared to cancer cells with a humanized Whey Protein Concentrate (HWPC) and that this selective GSH modulation has an impact on cells proliferation.

Comentarios del Dr. Gutman

Los doctores Baruchel y Viau fueron de los primeros en observar lo que más tarde se llamó "Modulación Selectiva", utilizando precursores de glutatión para mostrar cómo los niveles de glutatión suben y bajan en las células normales y en las cancerosas. Normalmente se observa que las células tumorales contienen grandes cantidades de glutatión, lo que ofrece protección contra la quimioterapia. Surgió la pregunta: "¿Podría el glutatión o sus precursores hacer a estas células cancerosas resistentes al tratamiento?" Este estudio demuestra que cuando las células cancerosas ya tienen un alto contenido de glutatión, " presionarlas" para que produzcan más desencadenantes "inhibición de la retroalimentación negativa", lo que disminuye la producción de glutatión. Las células normales, a menudo bajas en glutatión debido al cáncer, ahora absorben estos precursores, aumentando su propia producción de glutatión e incrementando la resistencia del tejido sano a la quimioterapia. Esto explica el término "Modulación Selectiva", en la que los niveles de glutatión disminuyen en las células cancerosas y aumentan en las células normales, como se demuestra magistralmente en este estudio.

NUTRITION AND CANCER, 2000, VOL 38(2):200-208

Efecto potenciador del aislado de proteína de suero patentado (Immunocal®) en la citotoxicidad del fármaco anticanceroso

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Abstract

To determine the enhancing effect of a whey protein isolate on the cytotoxicity of a potential anti-cancer drug. baicalein, human hepatoma cell line HepG2 was assigned to grow in different media for four days, followed by the investigation of cell growth and apoptosis. Excluding the control group with normal medium, other three treatment media included whey protein isolate (marketed as Immunocal®) medium, baicalein medium, and combined medium containing both Irnmunocal® and baicalein. MTT assay indicated that cells grew in combined medium had a significantly lower survival rate compared to the cells grew in baicalein medium; in contrast, for the cells grew in Immunocal® group, there was no significant difference on survival rate. In the investigation of apoptosis. compared to the cells in baicalein medium, cells in combined medium showed a higher phosphatidylserine exposure, lower rnitochondrial transmembrane potential and nearly 13 times more cells were detected undergoing apoptosis. We also demonstrated that Immunocal® was able to reduce glutathione in HepG2 by 20% to 40% and regulated the elevation of glutathione, which was in response to baicalein. In conclusion, Immunocal® seemed to enhance the cytotoxicity of baicalein by inducing more apoptosis, this increase in apoptotic cells may be in association with the depletion of GSH in HepG2. This is the first study to demonstrate, in vitro, that Immunocal® may function as an adjuvant in cancer treatments.

Comentarios del Dr. Gutman

Tsai y su equipo se cuestionaron si las células cancerosas podían alimentarse de precursores de glutatión y así protegerse de la respuesta inmunológica. Este primer estudio del Immunocal en Taiwán determina claramente, "No, no puede". Al contrario. Cuando Immunocal fue introducido en el laboratorio en las células cancerosas del hígado, los niveles de glutatión en las células realmente disminuyeron. Esto se explica por trabajos anteriores sobre la "inhibición de la retroalimentación negativa" del glutatión en las células tumorales. Además, las células cancerosas expuestas a Immunocal sufrieron un daño mayor que el habitual cuando fueron sometidas a quimioterapia. Estos son argumentos persuasivos para el uso del glutatión en la terapia del cáncer.

FOOD & CHEMICAL TOXICOLOGY, 44:574-578, (2006)

El concentrado de proteína de suero promueve la producción de glutatión (GSH) por la reductasa Gsh en la línea celular PC12 después de la exposición aguda al etanol

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Abstract

Excessive ethanol consumption may increase the production of reactive oxygen species (ROS), which results in the damage of tissues, especially the neurons and glial cells in the central nervous system (CNS). The purpose of this study is to evaluate the effects of whey protein concentrate (WPC) on the glutathione (GSH) status after acute ethanol exposure in the pheochromocytoma (PC12) cell line. In this study, we assayed the cell viability, the percentage of lactate dehydrogenase released (% LDH released), the level of GSH, and the activity of GSH reductase (GRx). The results showed that with the supplement of WPC, the cell viability displayed no significant difference after acute exposure of ethanol in groups with or without ethanol treatment. The ethanol-induced cytotoxicity showed a slight decrease, and the level of GSH showed a significant increase. The activity of GRx significantly increased when 0.1, 10mg/ml of WPC was supplied. In conclusion, these results suggest that WPC in a moderate concentration should be a precursor agent to promote the production of GSH and will enhance the antioxidant capacity in the PC12 cell line.

Comentarios del Dr. Gutman

El alcohol aumenta el estrés oxidativo y los daños causados por los radicales libres y puede provocar la muerte (apoptosis) de estas células. Este estudio de cultivo celular ("tubo de ensayo") realizado en Taiwán, investigó los posibles efectos deletéreos del alcohol en las células humanas. La exposición de una línea celular específica (PC12) a Immunocal aumentó tanto sus parámetros de glutatión como su función antioxidante.

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 56:8141-8147 (2008)

Efectos del concentrado de proteína de suero (WPC por sus siglas en inglés) pretratado con alcohol en el daño oxidativo de las células mononucleares de sangre periférica humana (PBMC por sus siglas en inglés)

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Abstract

Excessive alcohol consumption can induce apoptosis in a variety of tissues and influence the antioxidant status in peripheral blood mononuclear cells (PBMC). This paper investigates the effects of whey protein concentrate (WPC) pretreated in PBMC on the apoptosis and antioxidant status after the treatment of alcohol. The results show that the percentages of apoptotic cells in the alcohol-treated group were higher than those in the group without alcohol treatment. Additionally, there was higher glutathione (GSH) peroxidase (GPx) activity when the PBMC were treated with 300 mg/dL of alcohol. With regards to the activity of GSH reductase (GRx), there was higher activity in the group pretreated with WPC than in the group with the treatment of alcohol only. On the contrary, the levels of GSH were reduced after the treatment of alcohol, but there was a higher level of GSH in the group pretreated with WPC. In this study, it was found that the increased level of GSH in PBMC might not be attributed to the effect of GRx because there was still a higher level of GSH in the group with the treatment of WPC and BCNU (a GRx inhibitor) in this study. The results indicated that PBMC pretreated with WPC might ameliorate alcohol-induced effects such as imbalance of the antioxidant status.

Comentarios del Dr. Gutman

Este estudio de cultivo celular ("tubo de ensayo") fue diseñado en Taiwán para investigar los posibles efectos perjudiciales del alcohol en los glóbulos blancos humanos. El alcohol aumenta el estrés oxidativo y el daño de los radicales libres y puede conducir a la muerte (apoptosis) de estas células. La exposición de estas células a Immunocal aumentó sus parámetros de glutatión y las protegió de los daños.

SCIENTIFIC REPORTS | 7: 15976 | DOI:10.1038/S41598-017-14159-5, 2017

El concentrado de proteína de suero hace que las células MDA-MB-231 sean sensibles a la rapamicina mediante la alteración del estado redox celular y la activación de la señalización GSK3ß/mTOR

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Abstract

Whey protein concentrate (WPC) is an amino acid-rich supplement that has been shown to increase cellular antioxidant capacity. Mammalian target of rapamycin (mTOR) is a crucial regulator of signaling in mammalian cells, and serves as a therapeutic target for triple-negative breast cancer (TNBC). This study was designed to investigate the effect of combining WPC with rapamycin on MDA-MB-231 human breast cancer cells. These cells were found to be insensitive to rapamycin and exhibited higher glutathione (GSH) and reactive oxygen species levels than non-tumorigenic MCF-10A cells. However, for MDA-MB-231 cells, the half maximal inhibitory concentration of rapamycin was lower when this drug was administered in combination with WPC than when used alone. Furthermore, combining WPC with rapamycin depleted GSH levels and reduced Nrf2 nuclear accumulation. In addition, WPC activated GSK3ß/mTOR signaling, and GSK3ß appeared to be involved in the WPC-mediated Nrf2 reduction and mTOR activation. In conclusion, WPC induced rapamycin sensitivity in MDA-MB-231 cells by altering their redox state and activating GSK3ß/mTOR signaling. These results not only suggest a novel therapeutic approach for breast cancer treatment, but also provide insight into the critical pathways affecting the resistance to mTOR inhibition observed in a subgroup of TNBC patients.

Comentarios del Dr. Gutman

Este equipo, que anteriormente ya había realizado estudios sobre Immunocal, continuó con su magnífico trabajo sobre las vías metabólicas bioquímicas implicadas en la progresión del cáncer. Se utilizó una línea celular de cáncer de mama humano para investigar la combinación de Immunocal con Rapamicina (un nuevo agente quimioterapéutico). La combinación demostró ser más eficaz que la Rapamicina por sí sola, ofreciendo una posible estrategia de tratamiento mejorada para el cáncer de mama.

OXIDATIVE MEDICINE AND CELLULAR LONGEVITY, 2017:3103272 DOI.10. 1155

Un suplemento de suero rico en cisteína (Immunocal®) proporciona neuroprotección contra diversos agentes inductores de estrés oxidativo in vitro mediante la conservación del glutatión celular

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Abstract

Oxidative stress is a principal mechanism underlying the pathophysiology of neurodegeneration. Therefore, nutritional enhancement of endogenous antioxidant defenses may represent a viable treatment option. We investigated the neuroprotective properties of a unique whey protein supplement (Immunocal®) that provides an essential precursor (cystine) for synthesis of the endogenous antioxidant, glutathione (GSH). Primary cultures of rat cerebellar granule neurons (CGNs), NSC34 motor neuronal cells, or HT22 hippocampal cells were preincubated in medium containing Immunocal and then subsequently treated with agents know to induce oxidative stress. Immunocal protected CGNs against neurotoxicity induced by the Bcl-2 inhibitor, HA14-1, the nitric oxide donor, sodium nitroprusside, CuCl2, and A1C13. Immunocal also significantly reduced NSC34 cell death due to either H2O2 or glutamate and mitigated toxicity in HT22 cells overexpressing μ-amyloid 1-42. The neuroprotective effects of Immunocal were blocked by inhibition of μ-glutamyl-cysteine ligase, demonstrating dependence on de novo GSH synthesis. These findings indicate that sustaining GSH with Immunocal significantly protects neurons against diverse inducers of oxidative stress. Thus, Immunocal is a nutritional supplement worthy of testing in preclinical animal models of neurodegeneration and in future clinical trials of patients afflicted by these diseases.

Comentarios del Dr. Gutman

Estos neurocientíficos altamente activos de la Universidad de Denver señalan que muchas enfermedades neurodegenerativas comparten dos características: alto estrés oxidativo y bajos niveles de glutatión. Cuando se expone a agentes oxidantes y a daños por radicales libres, el tejido de las células cerebrales cultivado en el laboratorio e incubado en una solución inmunológica se comporta mucho mejor que el cultivo de células sin tratar. Estos prometedores resultados se seguirán estudiando en estudios in vivo.

ARTÌCULOS TEÓRICOS, ARTÌCULOS DE OPINIÓN Y RESEÑAS

Ciencia. Un campo rígido de análisis que busca pruebas. Parece que hay poco espacio para la creatividad y la imaginación, pero todo lo contrario es cierto. La ciencia se basa en la validación de una "teoría" o "hipótesis". Estas ideas a menudo requieren mucha inspiración e ingenio. Abundan las historias sobre grandes científicos que encuentran estas ideas durante los sueños, el descanso o incluso los estados mentales inducidos por las drogas. La "Teoría de la relatividad" de Einstein fue el resultado de "Experimentos de pensamiento" mientras soñaba despierto en su escritorio trabajando en la oficina de patentes.

Las teorías son el combustible para establecer una hipótesis que posteriormente puede ser probada por el "Método Científico". En las próximas páginas encontrará artículos publicados por científicos increíblemente visionarios relacionados con Immunotec que fueron críticos en la búsqueda del establecimiento de ensayos clínicos para este producto.

Los artículos de opinión no siguen el método científico en sí. Están escritos para abordar inquietudes, ideas o controversias que existen en nuestra base de conocimiento actual. Aunque es difícil evitar totalmente la parcialidad en estos documentos, son un esfuerzo para arrojar luz o resolver muchas áreas en cuestión.

Finalmente, los artículos de revisión tienen un gran valor para interpretar las opiniones colectivas de muchos trabajos de investigación que ya han sido publicados. Aunque muchas personas tienen la idea de que hay algo llamado "prueba" que proviene de la investigación, esta certeza absoluta suele ser muy difícil de alcanzar. Uno puede encontrar múltiples "resultados" que parecen apuntar a respuestas que están en completo desacuerdo entre sí. Un artículo de revisión intenta obtener un "consenso" sobre estos temas. Un buen artículo de revisión resaltará que existen estas diferencias y generalmente hará sugerencias sobre qué estrategias de investigación pueden ser necesarias en el futuro para acercarse a la "verdad".

¡Disfruta de este grupo de artículos!

MEDICAL HYPOTHESES, 1988, OCT;27(2):133-40

Rasgos evolutivos en las proteínas de la leche humana

Bounous G1, Kongshavn PA, Taveroff A, Gold P
Montreal General Hospital Research Institute, Quebec, Canada

Abstract

Human milk has the lowest concentration of protein of any mammalian species. Since the rate of growth of the offspring is negatively related to the protein content of the milk, the time required to double the birth weight is greater in the infant than in any other mammal in which it has been measured. Similarly, in weaned animals, a low protein diet increases the time required to reach maximal growth, senescence and natural death. Human milk protein has the highest whey protein to casein ratio than the milk of any other mammalian species. Our previous experiments have shown that mice fed a 20% whey protein diet exhibit increased resistance to Streptococcus pneumoniae and a humoral immune response significantly higher than that of mice fed most of the commercially available animal and plant proteins in nutritionally similar and adequate formula diets. Other studies have demonstrated that mean and maximal longevity of hamsters fed a 20% whey protein diet is increased in comparison with those fed commercial laboratory feed or a supplemented casein diet of similar nutritional efficiency. Thus, the low protein content and the prevalence of whey protein, which are characteristic features of human milk, are both associated with slow body growth and increased longevity. For human infants, mother's milk is the first and, for most, the only food ingested for a considerable period of time. We, therefore, propose that a trace of Nature's design for the offspring and the evolution of the species can be found in mother's milk.

Comentarios del Dr. Gutman

Este es un fascinante trabajo teórico en el que el Dr. Bounous examina la variedad de proteínas de la leche en los mamíferos. Señala que 1) La leche humana tiene la menor concentración de proteínas (lo que posiblemente explica por qué los humanos tardan tanto en llegar a la edad adulta), y 2) La leche humana tiene la mayor concentración de suero en comparación con la caseína. El punto del Dr. Bounous es que la preponderancia del suero en la leche humana puede ayudar a explicar el lento desarrollo de los bebés humanos y la longevidad de la especie humana.

CANCER LETTERS, 57: 91-94, 1991

Las proteínas del suero en la prevención del cáncer

G. Bounous*, G. Batist** and P. Gold***

*Professor of Surgery, McGill University, and Career Investigator of the Medical Research Council of Canada,
**Director, Experimental Therapeutics, Department of Oncology, McGill University,
***Chairman, Department of Medicine, McGill University, and Physician-in-Chief, The Montreal General Hospital

Abstract

Epidemiological and experimental studies suggest that dietary milk products may exert an inhibitory effect on the development of several types of tumors. Some recent experiments in rodents indicate that the antitumor activity of the dairy products is in the protein fraction and more specifically in the whey protein component of milk. We and others have demonstrated that whey protein diets result in increased glutathione (GSH) concentration in a number of tissues, and that some of the beneficial effects of whey protein intake are abrogated by inhibition of GSH synthesis. Whey protein is particularly rich in substrates for GSH synthesis. We suggest that whey protein may be exerting its effect on carcinogenesis by enhancing GSH concentration.

Comentarios del Dr. Gutman

Gerry Batist fue un destacado oncólogo e investigador canadiense, mientras que el Dr. Phil Gold fue jefe de medicina en el Hospital General de Montreal. En este artículo, se unen al Dr. Bounous y sus colegas para revisar la investigación que se llevó a cabo al principio del desarrollo de Immunocal. Identifican los componentes de la proteína del suero responsables de la elevación del glutatión y abren un debate sobre cómo podría utilizarse para combatir el cáncer. Más tarde, el equipo solicitó y recibió patentes internacionales para el uso de Immunocal en el tratamiento del cáncer.

OXIDATIVE STRESS, CELL ACTIVATION AND VIRAL INFECTION
C. PASQUIER ET AL. (EDS) • ©1994 BIRKHÄUSER VERLAG BASEL/SWITZERLAND

Lugar para una terapia antioxidante en la infección por el virus de la inmunodeficiencia humana (VIH)

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[2]McGill University, Department of Medicine; McGill AIDS Centre, Montreal, Quebec, Canada

Abstract

Oxidative stress, a known activator of HIV replication in vitro, has a potential role as a cofactor of HIV disease progression. Arguments supporting the role of oxidative stress as a cofactor in HIV activation are summarized in this review. The role of intracellular antioxidants such as glutathione (GSH), and drugs and nutriceutical agents promoting GSH synthesis, are discussed. The review also includes the early results of nutritional interventions based on a diet enriched with Immunocal®, a whey protein concentrate prepared in a proprietary manner.

Comentarios del Dr. Gutman

Se sabe que el virus del SIDA se desarrolla incluso en un entorno de estrés oxidativo y radicales libres. Esta revisión examina el potencial de Immunocal para suprimir su crecimiento, y constituye hallazgos preliminares en la Universidad McGill con lo que entonces era un novedoso precursor del glutatión.

OXIDATIVE STRESS IN CANCER, AIDS, AND NEURODEGENERATIVE DISEASES
LUC MONTAGNIER ET AL., (ED.) MARCEL DEKKER INC., NEW YORK: 447-461, 1998

Modulación nutricéutica del glutatión con un aislado de proteína de suero de leche materna humanizada, Immunocal™: aplicación en el SIDA y el cáncer

S. Baruchel*, G. Viau*, R. Olivier**, G. Bounous***, M.A. Wainberg****

*McGill University – Montreal Children's Hospital Research Institute, Montreal, Quebec, Canada, **Pasteur Institute Paris, France, ***Montreal General Hospital, Montreal, Quebec, Canada, ****Jewish General Hospital, Lady Davis Institute, Montreal, Quebec, Canada

Abstract

The biological activity of the proteins isolated from cow's milk in Immunocal™ depends on the preservation of those labile proteins which share with the predominant human milk proteins the same extremely rare glutathione (GSH)-promoting components. Cellular GSH depletion has been implicated in the pathogenesis of a number of degenerative conditions and disease states including Parkinson's, Alzheimer's, arteriosclerosis, cataracts, cystic fibrosis, malnutrition, aging, AIDS, and cancer.

This newly discovered nutriceutical modulation of GSH by the use of humanized native milk serum protein isolate of bovine origin in AIDS and cancer may well find other applications in disease where oxidative stress and pathology of GSH metabolism are largely implicated. In a pilot study, this type of whey protein concentrate was found to be well tolerated in children with AIDS and wasting syndrome and was found associated with an improvement of the nutritional status of the patient. Moreover, the GSH promoting activity on the peripheral blood lymphocyte of this protein concentrate was validated in patients with initial low GSH levels. Extensive pharmaco-epidemiological study of GSH metabolism and standardized methods of measurement of intracellular GSH applicable in clinical trials are needed in order to better define the clinical application of this new type of therapy.

Comentarios del Dr. Gutman

Este artículo apareció por primera vez en un libro compilado por el Dr. Luc Montagnier, el descubridor del virus del SIDA y ganador del Premio Nobel de Medicina en 2008. El Dr. Montagnier había estudiado anteriormente trabajos previos sobre pacientes de VIH/SIDA con Immunocal, y los destacó en su discurso de apertura de una conferencia internacional sobre el SIDA en Japón. Un colega cercano que trabaja con él en el Instituto Pasteur de París, el Dr. Richard Olivier, continuó estas investigaciones en colaboración con el equipo original de McGill que estudia Immunocal. De estos autores, Sylvain Baruchel fue un eminente oncólogo pediátrico que estudió Immunocal en el cáncer infantil, y el Dr. Wainberg sirvió varios períodos como presidente de una fundación internacional de investigación sobre el SIDA. Este artículo revisa algunos de los ensayos clínicos que probaron Immunocal en el SIDA y el cáncer.

MEDICAL HYPOTHESES, 1999, 53(4): 347-349

Competencia por los precursores del glutatión entre el sistema inmunológico y el músculo esquelético: Patogénesis del Síndrome de Fatiga Crónica

G. Bounous[1], J. Molson[2]

[1]Former Professor, Department of Surgery, McGill University, and career Investigator of the Medical Research Council of Canada

[2]1994 Quebec Cycling Champion, Road and Time Trial

Abstract

The chronic fatigue syndrome (CFS) is typically associated or follows a recognized or presumed infection. Abnormalities of both humoral and cellular immunity have been demonstrated in a substantial proportion of patients with CFS. The most consistent findings are of impaired lymphocyte responses to mitogen. As an antioxidant, glutathione (GSH) is essential for allowing the lymphocyte to express its full potential without being hampered by oxiradical accumulation. Hence, protracted challenge of the immunocytes may lead to cellular GSH depletion. Because GSH is also essential to aerobic muscular contraction, an undesirable competition for GSH precursors between the immune and muscular systems may develop. It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia.

Comentarios del Dr. Gutman

El Dr. Gustavo Bounous y John Molson se comunicaron con el Dr. Paul Cheney a finales de los 90. El Dr. Cheney, un miembro del equipo que definió el término "Síndrome de Fatiga Crónica", había completado recientemente varios cursos exitosos de tratamientos en sus pacientes con SFC usando Immunocal. Podían ver que la estrategia funcionaba, pero no por qué. Este artículo teórico fue uno de los primeros en ponderar la cuestión.

BESENME VE DIYET DERGISI / J NUTR AND DIET 30(3): 43-48,2001

Funciones terapéuticas de las proteínas del suero (Turquía)

Dr. Emin YILMAZ

Canakkale Onsekiz Mart University. Faculty of Food Engineering. Canakkale. Turkey.

Abstract

Recent studies have indicated that whey proteins show some very important therapeutic functions. The antioxidant properties of these protein isolates are essential for nutrition. Similarly, their protective functions against tumor mutagenesis and cancer are considered significant by medical researchers. Due to the growth factors found in the isolate, they might be used to treat atrophic and inflammatory diseases such as ulcer and colitis. Currently, the challenge lies in the production of these protein isolates without denaturation using most economical technologies. More clinical research is needed.

Comentarios del Dr. Gutman

Un investigador turco, que trabajaba en una importante facultad de ciencias de la alimentación, quería revisar las posibles aplicaciones clínicas de las proteínas del suero de leche en busca de posibles oportunidades para la industria láctea. Como era de esperar, la mayoría de los artículos citados en la revisión eran de científicos de Immunocal, que en ese momento estaban claramente más a la vanguardia que cualquier otro investigador en ese ámbito. El autor, el Dr. Elmin Yilmaz, tenía mucha razón al afirmar que "se necesitaba más investigación", ya que el problema seguía siendo cómo ampliar esta tecnología para su uso comercial. Las tecnologías realmente económicas para producir aislados de proteína de suero sin desnaturalizar siguen siendo difíciles de conseguir.

ANTICANCER RESEARCH 23, 1411-1416 (2003)

El sistema antioxidante

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Abstract

The glutathione (GSH) antioxidant system is the principal protective mechanism of the cell and is a crucial factor in the development of the immune response by the immune cells. Experimental data demonstrate that a cysteine-rich whey protein concentrate represents an effective cysteine delivery system for GSH replenishment during the immune response. Animal experiments showed that the concentrates of whey protein also exhibit anticancer activity. They do this via the GSH pathway, the induction of p53 protein in transformed cells and inhibition of neoangiogenesis.

Comentarios del Dr. Gutman

En este breve artículo teórico, el Dr. Gustavo Bounous y John Molson destacan el papel del glutatión como el antioxidante clave en la respuesta inmunológica sostenida. Revisan algunos trabajos anteriores, en los que se usó Immunocal para desencadenar la actividad anticancerosa.

ANTICANCER RESEARCH 24, 553-554 (2004)

Patogénesis molecular y prevención del cáncer de próstata

G. Bounous, D. Beer

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Abstract

Studies in laboratory animals indicate inhibition of chemically-induced carcinoma by cystine-rich diets enhancing the cysteine-GSH antioxidant system. The progression of carcinoma of the prostate is also inhibited by these diets, which were later found to raise the level of GSH in the prostate epithelium of man. New data presented at the July 13, 2003 meeting of the American Association for Cancer Research indicates that higher levels of total cysteine in plasma may predict a reduced risk for breast cancer. This prospective investigation was conducted among 32,000 women in the Nurses Health study. The previously reported prostate cancer data appears then not to be strictly gender-related as the antioxidant role of the cysteine – GSH system may also apply to breast cancer prevention.

Comentarios del Dr. Gutman

En esta discusión teórica, el Dr. Bounous sugiere que así como los niveles altos de cisteína disminuyen el riesgo de desarrollar cáncer de mama, la protección también puede extenderse al cáncer de próstata. En una investigación posterior, su equipo informó de la mejora de los valores de PSA (un análisis de sangre para el cáncer de próstata) utilizando Immunocal.

PHILOSOPHICAL TRANSCATIONS OF THE ROYAL SOCIETY B: BIOLOGICAL SCIENCES, 360, 2355-2372 (2005)

Estrés oxidativo y envejecimiento: ¿El envejecimiento es un síndrome de deficiencia de cisteína?

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Abstract

Reactive oxygen species (ROS) are constantly produced in biological tissues and play a role in various signaling pathways. Abnormally high ROS concentrations cause oxidative stress associated with tissue damage and dysregulation of physiological signals. There is growing evidence that oxidative stress increases with age. It has also been shown that the life span of worms, flies and mice can be significantly increased by mutations, which impede the insulin receptor signaling cascade. Molecular studies revealed that the insulin-independent basal activity of the insulin receptor is increased by ROS and downregulated by certain antioxidants. Complementary clinical studies confirmed that supplementation of the glutathione precursor cysteine decreases insulin responsiveness in the fasted state. In several clinical trials, cysteine supplementation improved skeletal muscle functions, decreased the body fat/lean body mass ratio, decreased plasma levels of the inflammatory cytokine tumour necrosis factor alpha (TNF-alpha), improved immune functions, and increased plasma albumin levels. As all these parameters degenerated with age, these findings suggest: (i) that loss of youth, health and quality of life may be partly explained by a deficit in cysteine and (ii) that the dietary consumption of cysteine is generally suboptimal and everybody is likely to have a cysteine deficiency sooner or later.

Comentarios del Dr. Gutman

En este artículo teórico, el especialista en antienvejecimiento Wulf Droge llama la atención sobre la teoría aceptada de que el estrés oxidativo y el daño de los radicales libres son los principales culpables del proceso de envejecimiento. Señala que estudios anteriores han demostrado cómo el precursor del glutatión cisteína revirtió con éxito los síntomas del envejecimiento como la masa muscular, el aumento de la inflamación, el compromiso inmunológico y otros parámetros. Sugiere que la juventud y la calidad de vida se pierden en parte debido a la disminución de los niveles de cisteína y glutatión que están bien documentados en el envejecimiento.

PEDIATRIC BLOOD CANCER, 50:447-450 (2008)

Comité de Nutrición del Grupo de Oncología Infantil (COG por sus siglas en inglés)

Paul C. Rogers, MB ChB, MBA[1] Steven J. Melnick, MD, PhD[2], Elena J. Ladas, MS[3]
Jacqueline Hamilton, MD[4] Jacques Baillargeon, PhD[5] and Nancy Sacks, MS[6]

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Abstract

Children's Oncology Group (COG) Nutrition Committee was established to further the knowledge of nutrition in children with cancer by education and conduct of clinical trials. A survey of COG institutions revealed lack of conformity in evaluation and categorization of nutritional status, and criteria for nutritional intervention. The Committee subsequently established specific categories of malnutrition (Underweight and Overweight) based on ideal body weight or body mass index. An algorithm was developed as a guideline for nutritional intervention as well as references and resources for determining estimated needs. The Committee embarked on concepts for clinical trials of nutritional interventions. The first pilot study, evaluating the feasibility of using an immunoneutraceutical precursor for glutathione production, has been completed. The study showed weight gain and improvement in glutathione status. A pilot trial of proactive enteral feeding for patients at high risk of malnutrition has commenced. The Committee believes that nutrition is relevant to all aspects of cancer control. The paucity of nutritional investigation in children with cancer needs to be rectified. Key words: cancer, children; nutrition.

Comentarios del Dr. Gutman

El "Grupo de Oncología Infantil" es una organización norteamericana que examina la eficacia de la nutrición en el tratamiento del cáncer pediátrico y en los ensayos clínicos. Este artículo informa sobre su primer experimento piloto. Los niños alimentados con Immunocal experimentaron un aumento en los niveles de glutatión. Y lo que es más importante, aumentaron de peso, un factor de supervivencia crucial. Este informe sirvió como una buena plataforma de lanzamiento para estudios posteriores.

ANTIOXIDANTS & REDOX SIGNALING, 10:661-675 (2008)

La señalización de receptores de insulina aberrantes y la homeostasis de aminoácidos como causa principal del estrés oxidativo en el envejecimiento?

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[2]Department of Anatomy & Developmental Biology, University of Heidelberg, Mannheim, Germany

Abstract

The mechanisms leading to the increase in free-radical-derived oxidative stress in "normal aging" remained obscure. Here we present our perspective on studies from different fields which reveal a previously unnoticed vicious cycle of oxidative stress. The plasma cysteine concentrations during starvation in the night and early morning hours (the postabsorptive state) decreases with age. This decrease is associated with a decrease in tissue concentrations of the cysteine derivative and quantitatively important antioxidant glutathione. The decrease in cysteine reflects changes in the autophagic protein catabolism which normally ensures free amino acid homeostasis during starvation. Autophagy is negatively regulated by the insulin receptor signaling cascade, which is enhanced by oxidative stress in the absence of insulin. This synopsis of seemingly unrelated processes reveals a novel mechanism of progressive oxidative stress in which decreasing antioxidant concentrations and increasing basal (postabsorptive) insulin receptor signaling activity compromise not only the autophagic protein catabolism but also the activity of FOXO transcription factors, i.e. two functions which were found to have an impact on lifespan in several animal models of aging. In addition, the aging-related decrease in glutathione level is likely to facilitate certain "secondary" disease-related mechanisms of oxidative stress. Studies on cysteine supplementation show therapeutic promise.

Comentarios del Dr. Gutman

Los doctores Droge y Kinsherf son autoridades reconocidas en el campo del envejecimiento, el estrés oxidativo y el antienvejecimiento. En este artículo revisan la evidencia de que el daño de los radicales libres afecta a la señalización de la insulina, lo que a su vez conduce a la pérdida de músculo y proteína. Promueven la idea de que uno de los mecanismos subyacentes del envejecimiento es la disminución de los niveles de glutatión y cisteína.

PEDIATRIC BLOOD CANCER, 2008, 50:490-493

Aportando pruebas a la medicina complementaria y alternativa en niños con cáncer: enfoque en las terapias relacionadas con la nutrición

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Abstract

Children with cancer frequently use complementary and alternative medicine (CAM), especially in conjunction with conventional therapy. Dietary supplements are a commonly used CAM modality, with the prevalence of supplement use ranging from 35% to 50% of children with cancer in surveys completed in the United States. Less is known about the use of dietary supplements in developing countries. The evidence for some dietary supplements providing some benefit to children with cancer is reviewed. Preliminary studies have shown that antioxidant status may affect chemotherapy tolerance in children with acute lymphoblastic leukemia. Other supplements, including TRAUMEEL S®, glutamine, vitamin E, Immunocal®, colostrum, and probiotics, may help to reduce gastrointestinal toxicities of chemotherapy and radiation. However, more definitive evidence is needed. Most dietary supplements have not been tested adequately to determine their safety and efficacy, with even less understood about their potential interactions with conventional chemotherapy and radiation. With the greater use of dietary supplements by patients with cancer, increasing scientific attention is being paid to the investigation of these therapies. But research on dietary supplements is complex and usually more difficult than that on conventional medications. Strong research designs are critical in obtaining information that will ultimately influence clinical practice and public awareness.

Comentarios del Dr. Gutman

Este trabajo fue publicado en una importante revista sobre leucemia y linfoma infantiles que analiza la utilidad de los productos naturales (medicina complementaria y alternativa o tratamientos de medicina complementaria y alternativa) en pacientes con este grupo de cánceres de la sangre. Algunos de estos productos parecen mitigar los efectos secundarios de la quimioterapia, entre ellos el Immunocal. Los autores señalan que este campo requiere más estudios antes de que sea totalmente aceptado por la comunidad médica. Immunotec ha publicado desde entonces más trabajos en esta área, impulsando la aceptación de Immunocal como una terapia complementaria.

RECENT PATENTS ON CENTRAL NERVOUS SYSTEM DRUG DISCOVERY, 2012, DEC;7(3):230-5

Immunocal® y la preservación del glutatión como una nueva estrategia neuroprotectora para los trastornos degenerativos del sistema nervioso

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Abstract

Oxidative stress and glutathione (GSH) depletion are both recognized as significant contributors to the pathogenesis of many devastating neurodegenerative diseases. In particular, mitochondrial dysfunction leads to the aberrant production and accumulation of reactive oxygen species (ROS) which are capable of oxidizing key cellular proteins, lipids, and DNA, ultimately triggering cell death. In addition to other roles that it plays in the cell, GSH functions as a critical scavenger of these ROS. Therefore, GSH depletion exacerbates cell damage due to free radical generation. Strategies that increase or preserve the levels intracellular GSH have been shown to act in a neuroprotective manner, suggesting that augmentation of the available GSH pool may be a promising therapeutic target for neurodegeneration. This review discusses the capacity of a cysteine-rich, whey protein supplement (Immunocal®) to enhance the de novo synthesis of GSH in neurons, and highlights its potential as a novel therapeutic approach to mitigate the oxidative damage that underlies the pathogenesis of various neurodegenerative diseases. Additionally, this review discusses various patents from 1993 to 2012 both with Immunocal® and other methods that modulate GSH in neurodegeneration.

Comentarios del Dr. Gutman

En este documento se revisaron estudios anteriores de Immunocal, así como las patentes concedidas para el uso de Immunocal en el aumento del glutatión. La reducción del glutatión es una característica clave de muchas enfermedades neurodegenerativas, incluyendo la enfermedad de Alzheimer, la enfermedad de Parkinson, la esclerosis lateral amiotrófica y otras. Los autores sugieren que esta estrategia podría ser una intervención de gran importancia, y que debería ser investigada.

RECENT PATENTS ON CENTRAL NERVOUS SYSTEM DRUG DISCOVERY, 2012, DEC: 7(1)

Editorial: antioxidantes terapéuticos para enfermedades neurodegenerativas

Linseman DA

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Research Service, Veterans Affairs Medical Center, Denver, Colorado, USA

Abstract

The aberrant production of reactive oxygen species (ROS) within a cell can cause significant oxidative damage to key cellular proteins, lipids, and DNA. Harmful free radical species like ROS can be generated intrinsically via inadvertent "leakage" from the mitochondrial electron transport chain or by oxidant-generating enzymatic systems like NADPH oxidase, xanthine oxidase, glucose oxidase, or nitric oxide synthase. Alternatively, noxious free radicals can be generated by extrinsic sources such as toxins or reactive inflammatory cells. Regardless of their source, ROS and other free radical species must be scavenged by intracellular antioxidant systems to protect the cell from oxidative damage and consequent cell death. To this end, the cell has developed a large repertoire of antioxidant defense mechanisms that are normally able to keep ROS in check; however, during many disease states these antioxidant defenses are often overwhelmed and the cell succumbs to oxidative stress. This certainly appears to be the case in many types of neurodegenerative disease including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, to name a few. For each of these disorders, oxidative stress is a significant factor in the neuronal death underlying disease pathogenesis. In addition, oxidative stress is hypothesized to play a substantial role in aging which is a major risk factor for neurodegeneration. Thus, it is not surprising that strategies either to bolster endogenous antioxidant defenses or to provide exogenous free radical scavengers are currently under intense investigation as potential therapies for neurodegeneration.

Comentarios del Dr. Gutman

La revista en la que aparece este editorial publica novedosas estrategias para tratamientos neurológicos. El artículo fue escrito por el investigador Dr. Dan Linseman, quien ha explorado extensamente el sistema inmunológico y los vínculos entre el glutatión y los trastornos neurodegenerativos. En este editorial sugiere que estrategias como esta deberían recibir mayor atención para futuras investigaciones.

CHINA CANCER. (24)12:1026-1030, 2015

Avances en la aplicación del concentrado de proteína de suero en el tratamiento de los tumores malignos

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Abstract

As a safe and effective cysteine carrier, whey protein concentrate (WPC) effectively promote the body's glutathione synthesisμthereby elevating glutathione level in serum and tissue and enhancing lymphocyte proliferation and phagocytosis, as well as T helper cells and cytotoxic activity of natural killer T cells, which finally improve the immune system. Second, as quality nitrogen source, WPC significantly improve the negative nitrogen balance of patients, stimulate muscle protein synthesis to avoid or slow down the development of the cachexia and the resulting adverse reactions. During the process of the integrated anti-tumor treatment, the application of whey protein concentrates for malignancies may improve the patients nutritional and immune status, reduce the stress reaction of anti-tumor treatments (surgery, radiation and chemotherapy), and reduce the risk of infectious complications as well as prevent or slow down smooth muscle loss and improve the quality of life.

Comentarios del Dr. Gutman

Este documento chino revisa la aplicación de la proteína del suero en el tratamiento del cáncer. Un desafortunado error de traducción se refiere al suero como un "concentrado" cuando en realidad la mayoría de los estudios revisados utilizaban aislados de suero. Concluyen que la literatura sugiere posibles mejoras en el estado nutricional, la función inmunológica, las mediciones de la calidad de vida, el mantenimiento del peso y los efectos secundarios de la quimioterapia y la radioterapia.

JOURNAL OF NUTRITIONAL ONCOLOGY, NOVEMBER 15, 2016, VOLUME 1, NUMBER 1

El potencial terapéutico del aumento del glutatión en pacientes con cáncer que reciben quimioterapia o radioterapia

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Abstract

The majority of cancer patients receiving conventional medical therapy receive chemotherapy, radiotherapy, surgery or palliative support. Nutritional support is increasingly recognized as vital to successful treatment. Glutathione (GSH) is a naturally-occurring tripeptide in human cells that serves many important functions, including antioxidant regulation, detoxification, protein synthesis and repair, immune modulation, and redox signaling. Altering glutathione levels has been demonstrated to have significant effects in chemotherapy/radiotherapy outcomes as well as influence on retarding cachexia. This review article summarizes some of the most notable findings, suggesting that up-regulation of glutathione through nutritional intervention has a potential to be integrated into a holistic approach to cancer treatment.

Comentarios del Dr. Gutman

Una de las preguntas más comunes que recibo tanto de los médicos como de los pacientes, es si "el glutatión 'alimenta' las células cancerosas" y si podría "proteger" las células cancerosas de la quimioterapia y la radioterapia. Estas preguntas son el resultado de muchos estudios que muestran que esto puede suceder en cultivos celulares y en un " tubo de ensayo". Hay que destacar que los estudios de laboratorio no son un reflejo de lo que ocurre en un ser humano vivo. No he podido encontrar ni un solo estudio realizado en seres humanos en el que el aumento del glutatión haya promovido el crecimiento del cáncer o haya intensificado el cáncer contra el tratamiento. Por el contrario, muchos estudios han demostrado justo lo contrario: que el aumento del glutatión es una estrategia que conviene utilizar en el tratamiento del cáncer. En este articulo explico el por qué, basándome en toda la literatura disponible.

CLINICAL NUTRITION, 2018 JULY 9, Pii:S0261-5614(18)31201-9

La prehabilitación trimodal para la cirugía colorrectal atenúa las pérdidas posquirúrgicas en la masa corporal magra: un análisis conjunto de ensayos controlados aleatorios

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Abstract

Background and Aims: Preservation of lean body mass is an important cancer care objective. The capacity for prehabilitation interventions to modulate the lean body mass (LBM) of colorectal cancer patients before and after surgery is unknown.

Methods: A pooled analysis of two randomized controlled trials of trimodal prehabilitation vs. trimodal rehabilitation at a single university-affiliated tertiary center employing Enhanced Recovery After Surgery (ERAS) care was conducted. The prehabilitation interventions included exercise, nutrition, and anxiety-reduction elements that began approximately four weeks before surgery and continued for eight weeks after surgery. The rehabilitation interventions were identical to the prehabilitation interventions but were initiated only after surgery. Body composition, measured using multifrequency bioelectrical impedance analysis, was recorded at baseline, pre-surgery, 4 and 8 weeks after surgery. The primary outcome was change in LBM before and after colorectal surgery for cancer. A mixed effects regression model was used to estimate changes in body mass and body composition over time controlling for age, sex, baseline body mass index (BMI), baseline six-minute walk test (6MWT), and postoperative compliance to the interventions.

Results: Pooled data included 76 patients who followed prehabilitation and 63 patients who followed rehabilitation (n = 139). Neither group experienced changes in preoperative LBM. Compared to rehabilitated patients, prehabilitated patients had significantly more absolute and relative LBM at four and eight-weeks post-surgery in models controlling for age, sex, baseline BMI, baseline 6MWT, and compliance to the postoperative intervention.

Conclusion: Trimodal prehabilitation attenuated the post-surgical LBM loss compared to the loss observed in patients who received the rehabilitation intervention. Patients who receive neither intervention (i.e., standard of care) would be likely to lose more LBM. Offering a prehabilitation program to colorectal cancer patients awaiting resection is a useful strategy to mitigate the impact of the surgical stress response on lean tissue in an ERAS setting, and, in turn, might have a positive impact on the cancer care course.

Comentarios del Dr. Gutman

En el presente documento se examinan una serie de estudios de prehabilitación. Se utilizó el Immunocal como componente nutricional de una intervención trimodal (nutrición, ejercicio y apoyo psicológico). El documento concluye que los pacientes que reciben prehabilitación se recuperan mejor que los que reciben atención estándar.

NEURAL REGENERATION RESEARCH, 2019, doi:10.4103

Los precursores del glutatión protegen al cerebro de los traumas

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Abstract

In the United States, approximately one-third of all injury-related deaths are due to traumatic brain injury (TBI). Anyone is at risk for TBI; however, the risk is higher for athletes in contact sports, military personnel, children and the elderly. TBI is characterized by a mild, moderate, or severe mechanical force to the head which can be further classified as blast, blunt, or ballistic. The sheer mechanical force of the impact to the head results in the primary injury including diffuse axonal injury, internal bleeding, swelling, and neuronal cell death. Secondary injury occurs over time, often weeks to months post TBI, and is characterized by neuroinflammation, blood-brain-barrier disruption, oxidative stress, mitochondrial dysfunction, neuronal apoptosis, and other deleterious effects in the brain (Khatri et al., 2018). Recent research indicates that secondary injury from TBI may be considered a risk factor for neurodegenerative diseases occurring later in life, such as Alzheimer's disease and chronic traumatic encephalopathy. A key molecular mechanism that contributes to secondary injury after TBI is free radical damage which is induced by the aberrant production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Comentarios del Dr. Gutman

Esta reseña escrita por el neurocientífico de la Universidad de Denver, Dan Linseman y su equipo, examina la forma en que los radicales libres y el estrés oxidativo aumentan el daño cerebral después de un trauma físico. El Dr. Linseman se centra en el papel protector del glutatión en el daño cerebral traumático. Ha escrito numerosos artículos sobre el glutatión, incluyendo estudios en vivo en animales, explorando el Immunocal como una posible solución.

NUTR CANCER. 2021 DEC 28;1-14.

Efecto del suplemento de proteína de suero de leche en los resultados postoperatorios en pacientes con cáncer: revisión sistemática y metanálisis (PROSPERO 2020: CRD42020188666)

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Abstract

Whey protein has several biochemical characteristics which make it an ideal nutritional supplement in cancer. This meta-analysis aims to evaluate the effects of whey on perioperative outcomes in cancer. A systematic review was conducted as per the Preferred Reporting of Systematic Reviews and Meta-analysis (PRISMA) guidelines. The primary outcome was postoperative complications. Secondary outcomes included 6-minute walk test, length of stay (LOS), and thirty-day readmission. Of the ten trials, six supplemented whey to meet protein requirements of around 1.2 mg/kg/day, and four supplemented whey variably. A synthesis of ten trials with 643 patients showed significantly decreased postoperative complications in the whey supplemented (22%) group as compared to the control (32%) (OR 0.61, 95% CI 0.41–0.90; P = 0.01). Analysis of six trials showed that patients supplemented with whey had greater functional walking capacity before surgery (MD 23.76 meters, 95% CI 4.05–43.47; participants = 377; P = 0.02) and after 4 weeks of surgery (MD 45.76, 95% CI 14.19–77.33; participants = 366; P = 0.004). Thirty-day readmissions and LOS showed no differences. Risk of bias varied between the trials and evidence was moderate to low. Whey protein supplementation improved the perioperative functional capacity and significantly reduced postoperative complications in patients with cancer.

Comentarios del Dr. Gutman

Los términos "revisión sistemática" y "metanálisis" requieren una definición. Una "revisión sistemática" requiere una búsqueda exhaustiva de todos los artículos de investigación disponibles sobre un tema en concreto. Esto puede ser toda una odisea, dependiendo de la cantidad de artículos disponibles. Antes de que Internet fuera la herramienta que representa hoy en día, una revisión de este tipo podía llevar una gran cantidad de tiempo. Un "metanálisis" es el proceso de "agrupar" los resultados de diferentes ensayos y analizarlos en su conjunto. Cuando se hace correctamente, puede ser una forma eficaz de solidificar una tesis o una perspectiva general. En este estudio, se hicieron ambas cosas, validando de nuevo la estrategia de utilizar la proteína de suero de leche para mejorar los resultados postoperatorios (postquirúrgicos) de los pacientes con cáncer. Dada la preponderancia de los artículos escritos sobre Immunocal ante esta situación, no es de extrañar que gran parte de la revisión y el metanálisis utilizaran datos de Immunocal.

ESTUDIOS HUMANOS

Existen muchos tipos de estudios en humanos, todos con diferentes matices y, lo que es más importante, diferentes niveles de importancia. Aquí hay algunos tipos de diversos artículos publicados, con niveles crecientes de importancia y relevancia:

REPORTES DEL CASO

Ocasionalmente se trata a un paciente que muestra un proceso enfermedad o un desenlace muy inusual. Debido a que estas situaciones son raras, a menudo se eliminan ó editan y la descripción del caso se envía para su publicación. Si los autores de la revista consideraron que el "informe" del caso agrega un valor significativo en el avance de nuestro conocimiento, se aprueba su entrada en la revista. Los informes de casos pueden referirse a un solo individuo o, a menudo, a un grupo de pacientes que comparten características o resultados similares. Aunque estos informes no tienen relevancia estadística, son una ventana a lo que puede estar "sucediendo" y pueden ayudar a dar dirección para futuros estudios.

ESTUDIOS PILOTO

Antes de dedicar grandes cantidades de tiempo, esfuerzo y recursos a amplios estudios en humanos, a menudo es prudente hacer una prueba pequeña que dará una mejor idea del éxito potencial de una prueba más grande. En el proceso de acceder a fondos o permisos éticos para realizar grandes estudios, a menudo estos estudios piloto son necesarios para mostrar una "prueba de concepto". Debido a que el número de sujetos a menudo es demasiado reducido para lograr "relevancia estadística", carecen del poder para ser tan convincentes como un gran ensayo, donde se pueden obtener estadísticas significativas. Por ejemplo, si un tratamiento es exitoso el 30% del tiempo (esto es realmente bastante común para muchos medicamentos), se necesita una gran cantidad de personas para asegurarse de que los resultados encontrados no sean solo "casuales". Los estudios piloto son un paso importante para ganar la confianza (y a menudo la autoridad) para realizar un gran ensayo en humanos.

ESTUDIOS NO CEGADOS

El "efecto placebo" es real. Los pacientes que "toman" algo a menudo creen que, debido a que están recibiendo una intervención, mejorarán. Se ha demostrado durante mucho tiempo que si la creencia es lo suficientemente fuerte, de hecho pueden ocurrir cambios positivos. Hay muchos factores involucrados más allá del alcance de esta discusión para explicar este fenómeno, el lector puede explorarlo por otros medios.

Del mismo modo, los investigadores que usan un medicamento o una metodología que están convencidos de que esta intervención es válida, pueden hacer inconscientemente observaciones tendenciosas o manipulaciones sutiles para "probar" que sus teorías son correctas. Esto puede no hacerse intencionalmente, pero, de nuevo, hay muchos que simplemente "hacen trampa".

El concepto de "cegamiento" implica que los pacientes o los investigadores, o ambos, no saben si el sujeto está recibiendo la intervención real o el placebo. Esto ofrece cierta protección contra el efecto placebo o la parcialidad del investigador. Sin embargo, un estudio no cegado tiene peso si se realiza de manera adecuada y ética. Son mucho más simples de hacer que un estudio "doble ciego" (ver más abajo).

Hay muchas otras variaciones en el diseño del estudio; estudio simple ciego; estudio de casos y controles; análisis retrospectivo y más. La descripción de todo esto es demasiado compleja para considerarla para una discusión completa en este documento.

Immunotec ha llevado a cabo una buena cantidad de estas diferentes metodologías de estudio. Son el penúltimo paso antes de completar un estudio doble ciego.

ESTUDIOS CIEGOS

Aquí pasamos a lo que se considera el "estándar de oro" de los ensayos en humanos. Ni el investigador ni el sujeto saben si el tratamiento que cada uno recibe es real o placebo. Por supuesto, esta es una explicación simplificada, hay diferentes matices que pueden ocurrir como un "estudio de 3 brazos" o "estudio de 4 brazos", donde varios grupos diferentes se combinan en un estudio, y otras variaciones. El otro término que verá en gran uso es "aleatorizado". Esto significa que los sujetos, todos de un grupo similar de individuos, son seleccionados al azar para recibir placebo o tratamiento. Esto es importante para garantizar una homogeneidad imparcial en los dos grupos. Finalmente, el término "estadísticamente relevante" es crítico para describir si de hecho un grupo de tratamiento ha mostrado alguna diferencia con respecto al placebo. Las dos medidas más comunes de relevancia estadística que verá son los índices "p" o "probabilidad". Cuando lee "p <0.05", esto significa que la probabilidad de que ocurra una casualidad en los números es inferior al 5%. Un valor p de p <0.01 significa que puede estar 99% seguro de que los resultados obtenidos son correctos.

Ahora debería tener la idea de que el 100% de "prueba" rara vez existe. Un estudio que se describe como "probado" realmente significa que muestra con "gran probabilidad" que los resultados son significativos. ¿Y qué hacer cuando dos estudios similares muestran resultados completamente opuestos? ¿Uno dice "sí" y el otro un claro "no"? Esto es un reflejo de la fragilidad del método científico. Es extremadamente difícil llegar al experimento "perfecto". El diseño del estudio, la selección de pacientes, la metodología estadística, la hipótesis adecuada, las técnicas de medición e incluso las presiones financieras pueden afectar el resultado.

Le insto a mantener una mente abierta y crítica al leer cualquier estudio. ¡Y una mente aún más crítica al leer las opiniones de otra persona sobre un estudio! Esto es un ejercicio maravilloso y sólo dará como resultado la ampliación de su conocimiento y conciencia.

REPORTES DE CASOS CON IMMUNOCAL EN HUMANOS

CHEST, 2000, MARCH; 117(3):914-6

Tratamiento de la enfermedad obstructiva de las vías respiratorias con un suplemento de proteína donante de cisteína: informe de un caso

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Abstract

Oxidant/antioxidant imbalance can occur in obstructive airways disease, as a result of ongoing inflammation. Glutathione plays a major role in pulmonary antioxidant protection. As an alternative or complement to anti-inflammatory therapy, augmenting antioxidant protection could diminish the effects of inflammation. We describe a case of a patient with obstructive lung disease, responsive to corticosteroids, with low whole blood glutathione levels. Following one month of supplementation with a whey-based oral supplement, designed to provide glutathione precursors, whole blood glutathione levels and pulmonary function significantly and dramatically increased. The potential for such supplementation in pulmonary inflammatory conditions deserves further study.

Comentarios del Dr. Gutman

El estudio me interesaba especialmente porque el sujeto del estudio era una de mis propias pacientes, una madre soltera que ejercía la abogacía. Después de la exposición a la radiación para el tratamiento del linfoma de Hodgkin cuando era más joven, desarrolló "fibrosis pulmonar", que le dejó tantas cicatrices en el pulmón que quedó confinada a su casa y dependiente de una máscara de oxígeno. Cuando empezó a tomar Immunocal pudo reanudar gran parte de su estilo de vida anterior. La referí al Dr. Lands, un especialista en pulmones. Uno por uno, él le quitó los medicamentos de su régimen diario para determinar lo que realmente la ayudaba a sentirse mejor. Dos semanas después de que le quitó Immunocal, tuvo que ser ingresada en urgencias. El Immunocal fue reincorporado y sus pruebas de función pulmonar mejoraron tan dramáticamente que su caso fue presentado en Grand Rounds en el Royal Victoria Hospital de la Universidad McGill en Montreal, lo que provocó la redacción del artículo.

ANTICANCER RESEARCH 20, 4785-4792, 2000

El Concentrado de Proteína de Suero (WPC por sus siglas en inglés) y la modulación del glutatión en el tratamiento del cáncer

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Abstract

The glutathione (GSH) antioxidant system is foremost among the cellular protective mechanisms. Depletion of this small molecule is a common consequence of increased formation of reactive oxygen species during increased cellular activities. This phenomenon can occur in the lymphocytes during the development of the immune response and in the muscular cells during strenuous exercise. It is not surprising that so much research has been done, and is still being done on this small tripeptide molecule. Whey protein concentrate has been shown to represent an effective and safe cysteine donor for GSH replenishment during GSH depletion in immune deficiency states. Cysteine is the crucial limiting amino acid for intracellular GSH synthesis. Animal experiments showed that the concentrates of whey proteins also exhibit anti-carcinogenesis and anticancer activity. They do this via their effect on increasing GSH concentration in relevant tissues, and may have anti-tumor effect on low volume of tumor via stimulation of immunity through the GSH pathway. It is considered that oxygen radical generation is frequently a critical step in carcinogenesis, hence the effect of GSH on free radicals as well as carcinogen detoxification, could be important in inhibiting carcinogenesis induced by a number of different mechanisms. Case reports are presented which strongly suggest an anti-tumor effect of a whey protein dietary supplement in some urogenital cancers. This non toxic dietary intervention, which is not based on the principles of current cancer chemotherapy, will hopefully attract the attention of laboratory and clinical oncologists.

Comentarios del Dr. Gutman

El Dr. Gustavo Bounous descubrió Immunocal. En este artículo revisa el sistema antioxidante del glutatión y revisa algunos trabajos anteriores de Immunocal en deficiencia inmunológica y cáncer. También reporta los beneficios de Immunocal para los pacientes de cáncer. Pide que se hagan estudios más amplios, los cuales fueron completados más tarde.

ESTUDIOS PILOTO CON IMMUNOCAL EN HUMANOS

CLINICAL INVESTIGATIVE MEDICINE, 16:204-209, 1993

Las proteínas de suero como suplemento alimenticio en personas seropositivas al VIH

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Abstract

On the basis of numerous animal experiments, a pilot study was undertaken to evaluate the effect of undenatured, biologically active, dietary whey protein in 3 HIV-seropositive individuals over a period of 3 months. Whey protein concentrate was prepared so that the most thermosensitive proteins, such as serum albumin which contains 6 glutamylcysteine groups, would be in undenatured form. Whey protein powder dissolved in a drink of the patient's choice was drunk cold in quantities that were increased progressively from 8.4 to 39.2 g per day. Patients took whey proteins without adverse side effects. In the 3 patients whose body weight had been stable in the preceding 2 months, weight gain increased progressively between 2 and 7 kg, with 2 of the patients reaching ideal body weight. Serum proteins, including albumin, remained unchanged and within normal range, indicating that protein replenishment per se was not likely the cause of increased body weight. The glutathione content of the blood mononuclear cells was, as expected, below normal values in all patients at the beginning of the study. Over the 3-month period, GSH levels increased and in one case rose by 70% to reach normal value. The increase in body weight observed in these patients did not correlate with increase in energy or protein intake.

In conclusion, these preliminary data indicate that, in patients who maintain an adequate total caloric intake, the addition of "bioactive" whey protein concentrate as a significant portion of total protein intake increases body weight and shows elevation of glutathione (GSH) content of mononuclear cells toward normal levels. This pilot study will serve as a basis for a much larger clinical trial.

Comentarios del Dr. Gutman

Este pequeño estudio fue el primer ensayo de Immunocal en humanos. Después de haber realizado con éxito experimentos en animales con SIDA/VIH, el equipo del Hospital General de Montreal se sintió lo suficientemente confiado como para comenzar los ensayos clínicos colaborando con los investigadores de McGill. El permiso para experimentar en humanos está estrictamente regulado por juntas de revisión, comités de ética y agencias gubernamentales, y el acceso a estos pacientes con SIDA en estado avanzado se concedió sólo porque su pronóstico era poco favorable. El equipo del Dr. Bounous documentó un aumento de peso significativo en todos estos individuos, que de otra manera perderían músculo, dejando abierta la puerta para realizar más estudios. Estos pacientes seriamente comprometidos también reportaron un aumento en los niveles de glutatión, en un caso por encima del 70%. Aunque se trataba de un ensayo pequeño, atrajo mucha atención y aseguró fondos para más investigaciones.

ANTICANCER RESEARCH 15, 2643-2650, 1995

El uso de un concentrado de proteína de suero en el tratamiento de pacientes con carcinoma metastásico: un estudio clínico de fase I-II

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Abstract

Glutathione (GSH) concentration is high in most tumor cells and this may be an important factor in resistance to chemotherapy. Previous in-vitro and animal experiments have shown a differential response of tumor versus normal cells to various cysteine delivery systems. More specifically, an in-vitro assay showed that at concentrations that induce GSH synthesis in normal human cells, a specially prepared whey protein concentrate, Immunocal™, caused GSH depletion and inhibition of proliferation in human breast cancer cells. On the basis of this information five patients with metastatic carcinoma of the breast, one of the pancreas and one of the liver were fed 30 grams of this whey protein concentrate daily for six months. In six patients the blood lymphocyte GSH levels were substantially above normal at the outset, reflecting high tumor GSH levels. Two patients (#1, #3) exhibited signs of tumor regression, normalization of haemoglobin and peripheral lymphocyte counts and a sustained drop of lymphocyte GSH levels towards normal. Two patients (#2, #7) showed stabilization of the tumor, increased haemoglobin levels. In three patients (#4, #5, #6) the disease progressed with a trend toward higher lymphocyte GSH levels. These results indicate that whey protein concentrate might deplete tumor cells of GSH and render them more vulnerable to chemotherapy.

Comentarios del Dr. Gutman

Este fue uno de los primeros estudios clínicos de Immunocal en humanos, realizado antes de que el producto fuera ampliamente conocido e incluso antes del lanzamiento oficial de Immunotec. Un amplio estudio en humanos en esta etapa habría sido prematuro, por lo que el equipo comenzó con estudios más pequeños para primeramente atender las preocupaciones de seguridad y confirmar el método de investigación. Todos los pacientes se encontraban en etapas avanzadas de cáncer de mama, hígado o páncreas y los investigadores obtuvieron la aprobación ética para tratarlos. Durante tres meses, a cada paciente se le administraron 30 gramos diarios de HMS90 (nombre que se le dio inicialmente al Immunocal). Los tumores de dos pacientes se redujeron, los tumores de otros dos se estabilizaron y el recuento de glóbulos rojos de otros dos mejoró. Este estudio fue demasiado pequeño para establecer evidencia estadística confiable, sin embargo, permitió que posteriormente se realizaran estudios de mayor envergadura.

JOURNAL OF THE AMERICAN NEUTRACEUTICAL ASSOCIATION, VOL. 11, NO. 1, (2008)

Tolerancia cero del aislamiento de la proteína del suero rico en cisteína en el autismo: un estudio piloto

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Abstract

Purpose: To examine the tolerability of non-denatured whey protein isolate (NWPI) in children with autism. Many children with autism are low in glutathione and have higher levels of oxidative stress. NWPI can raise glutathione levels and reduce oxidative stress. However, anecdotal reports suggest that NWPI may be problematic in children with autism because it contains cysteine and other sulfurated amino acids.

Methods: A 6-week open-label trial was conducted, supplementing 10 children with autism or autism spectrum disorder (ASD), 3-15 years of age, with NWPI (Immunocal®). To measure possible side effects, procedures that examined the frequency, intensity, and types of side effects, as well as behavioral measures, were completed at baseline, and at days 3, 14, 30 and 45.

Results: Seven of the ten children took the supplement over the six-week trial and tolerated it well. Two children discontinued after two weeks due to possible side effects: one due to gastrointestinal disturbance and one due to being less responsive to parents. Another child discontinued due to difficulty of administering the product.

Conclusion: This study suggests that NWPI can be used as a supplement for this small population of children with autism without high rates of side effects, which means that further studies to determine its safety and efficacy in larger populations might yield the same promising result. Larger studies are planned to determine its efficacy in raising glutathione levels.

Comentarios del Dr. Gutman

Soy uno de los autores de este artículo. Para cuando lo escribí, se me habían acercado los padres de muchos niños autistas que afirmaban que sus síntomas habían mejorado con el Immunocal. Sin embargo, sin pruebas clínicas que apoyen estas afirmaciones, me negué a compartirlas. En 2004, el equipo de Jill James en Arkansas demostró que más del 80% de los niños autistas sufrían niveles anormalmente bajos de glutatión. Este fue mi punto de partida. Me puse en contacto con Janet Kern en Texas, una investigadora del Trastorno del Espectro Autista (TEA), para colaborar en un ensayo clínico con Immunocal. Hubo algunas dudas iniciales, ya que a los niños autistas se les suele advertir que "eviten los productos lácteos" porque podrían exacerbar los síntomas. De hecho, el responsable es la única proteína de la leche que no se encuentra en Immunocal, la caseína. Un pequeño estudio piloto pronto demostró que era seguro, y también observamos mejoras en el comportamiento. El número de personas reclutadas para el estudio fue insuficiente para establecer la importancia estadística, pero abrió la puerta a estudios posteriores más grandes.

JOURNAL OF CLINICAL AND AESTHETIC DERMATOLOGY, 2013, 6(10):23-26)

Mejoria de la psoriasis en pacientes que utilizan el aislado de proteína de suero no desnaturalizado que incrementa el glutatión: estudio piloto

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Abstract

Background: Psoriasis is a common autoimmune disease with enhanced systemic inflammation and heightened levels of oxidative stress. Glutathione is the major antioxidant in human cells. Objectives: To determine if a nondenatured bioactive whey protein isolate previously demonstrated to increase glutathione levels can clinically improve patients with psoriasis vulgaris.

Methods: A single site prospective, non-blinded trial. Seven patients with psoriasis were recruited to take a nondenatured bioactive whey protein isolate, 20g orally per day, in addition to their current treatments, if any. Psoriasis Area and Severity Index scores and photographs were taken at baseline and monthly for three months.

Results: Patients with psoriasis were found to have a beneficial clinical improvement, whether they were on existing topical therapy, narrowband ultraviolet B, or no other treatment. Conclusion: The positive preliminary outcomes from this pilot study suggest a randomized, double-blind, clinical trial would be worthwhile in evaluating whether this protein isolate would result in statistically significant improvement for patients with psoriasis.

Comentarios del Dr. Gutman

Un pequeño grupo de pacientes psoriásicos en el área de Washington fue alimentado con Immunocal para ver qué beneficios clínicos podrían ser medidos en una puntuación estándar de severidad de la psoriasis. También compararon fotografías de la piel afectada. Los pacientes mejoraron en todos los casos, abriendo la puerta a estudios más grandes en el futuro.

ESTUDIOS NO CIEGOS CON IMMUNOCAL EN HUMANOS

JOURNAL OF MEDICINCE, 2000, 31(5-6):283-302

Tratamiento de la Hepatitis Crónica con Proteína de Suero (no calentada)

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Abstract

In an open study, the clinical efficacy of whey protein (Immunocal: cysteine content; 7.6-fold that of casein) isolated from fresh milk and purified without being heated was evaluated based on liver function test, immunological parameters, plasma or lymphocyte GSH concentrations and hepatitis virus markers in 25 patients with chronic hepatitis B or C. Immunocal (12 g as protein) food (mousse) was given twice a day, in the morning and evening, for 12 weeks (test period). Casein (12 g as protein) food (mousse) was given for 2 weeks prior to the start of -supplement with Immunocal food (induction period) and for 4 weeks after the end (follow-up period). The effects of Immunocal food on various clinical parameters were examined at 4-week intervals for 18 weeks to evaluate the efficacy of Immunocal. As a result, serum ALT activity decreased in 6 of 8 patients with chronic hepatitis B 12 weeks after the start of supplement with Immunocal food. Plasma GSH concentrations were increased in 5 of the 8 patients. Serum . concentrations of lipid peroxides significantly decreased 8 weeks after Immunocal food. Serum IL-2 levels began to increase 8 weeks and remained high even after supplement with Immunocal -food had ended. Furthermore, NK activity was significantly increased. However, an item correlating with reduced serum ALT activity could not be clarified. In 17 patients with chronic hepatitis C, there wore no significant Immunocal-related changes in liver function test or immunological parameters. These findings suggest that long-term supplement with Immunocal alone may be effective for patients with chronic hepatitis B, and a further clinical study that long-term combination therapy with Immunocal and other agents including interferon may be effective for those with chronic hepatitis C should be performed.

Comentarios del Dr. Gutman

Al principio de su desarrollo, varias compañías farmacéuticas consideraron la posibilidad de adquirir Immunocal. Una de ellas fue el gigante japonés Otsuka Pharmaceuticals. Lo que interesaba al Dr. Watanabe, al Dr. Kondo y a los otros autores era la hepatitis. En este estudio reportan una mejoría en la función del hígado y niveles elevados de glutatión en pacientes con hepatitis B en comparación con el placebo.

INTERNATIONAL JOURNAL OF FOOD SCIENCES AND NUTRITION, 2006; 57(3/4): 204211

Efecto de la proteína del suero para modular la respuesta inmune en niños con asma atópica

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Abstract

Background: Levels of glutathione (GSH) in antigen-presenting cells promote a T-helper type 2 (Th2) cytokine response in mice. We have previously demonstrated that we can increase intracellular GSH levels in healthy young adults using a whey-based oral supplement (HMS90TM). We hypothesized that such supplementation in children with atopic asthma, a Th2 cytokine disease, would improve lung function and decrease atopy.

Methods: Eleven children (six females, five males; mean9/standard deviation age, 12.69/3.6 years; baseline forced expired volume in 1 sec (FEV1), 82.49/15.4% predicted), underwent spirometry, methacholine provocation testing, and blood analysis for serum IgE and lymphocyte GSH before and after 1 month of supplementation (10 g twice daily).

Results: Initially the IgE was 16899/1596 mg/l (normal range 5/240 mg/l) and lymphocyte GSH was 1.759/0.48 mM (normal range 1.559/0.33 mM). IgE significantly decreased to 13799/ 1329 mg/l (PB/0.05) following supplementation. Although no significant changes in lymphocyte GSH or FEV1 were found for the group as a whole, the two patients with significant increases in lymphocyte GSH concentrations were the only two to demonstrate reductions in methacholine provocation doses (provocative concentration causing a 20% fall in FEV1).

Conclusions: These results suggest a modest impact of whey protein supplementation on the cytokine response in atopic asthma. Supplementation for longer periods, or with more potent whey-based supplements, currently under development, may prove more beneficial.

Comentarios del Dr. Gutman

Este equipo de investigación de la Universidad McGill había demostrado anteriormente el éxito en el aumento de glutatión en adultos sanos usando "HMS90" una forma anterior del Immunocal. Creían que elevar la GSH en niños con asma atópica (alérgica) sería útil ya que la inflamación era una parte importante de este tipo de patología. Los niños cuyo nivel de glutatión subió demostraron una mejoria en sus pruebas de función pulmonar.

JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY 24:1045-1050 (2009)

Estudio piloto abierto de la suplementación de aislado de proteína de suero rico en cisteína para pacientes con esteatohepatitis no alcohólica

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Abstract

Background and Aims: Glutathione (GSH) depletion contributes to liver injury and development of steatohepatitis. Undenatured cysteine-rich whey protein isolate has been clinically proven to raise GSH in several patient groups. The aim of this study was to evaluate the effect of oral supplementation with whey protein on patients with nonalcoholic steatohepatitis (NASH).

Methods: In an open-labeled clinical trial, 38 patients (18 male, 20 female; mean age 48 ± 14 years) with NASH confirmed by computed tomography measurements and liver biochemistries were given with a daily dose of 20g whey protein isolate for 12 weeks.

Results: A significant reduction in alanine aminotransferase (ALT) (64 ± 72 vs 46 ± 36, P=0.016) and aspartate aminotransferase (AST) (45 ± 49 vs 33 ± 18, P=0.047) were observed. Plasma glutathione and total antioxidant capacity increased significantly at the end of study (53 ± 11 vs 68 ± 11, P< 0.05 and 1.26 ± 0.10 vs 2.03 ± 0.10, P< 0.05). Liver attenuation index improved from -13.4 ± 11.1 to -9.7 ± 13.1 (P = 0.048). Hepatic macrovesicular steatosis decreased significantly after 12 weeks of supplementation (33.82 ± 12.82 vs 30.66 ± 15.96, P=0.046). Whey protein isolate was well tolerated. No serious adverse events were observed.

Conclusions: The results indicate that oral supplementation of cysteine-rich whey protein isolate leads to improvements in liver biochemistries, increased plasma GSH, total antioxidant capacity and reduced hepatic macrovesicular steatosis in NASH patients. The results support the role of oxidative stress in the pathogenesis of this disease.

Comentarios del Dr. Gutman

La EHNA (Esteatohepatitis no alcohólica, comúnmente llamada "hígado graso") es un trastorno hepático que se encuentra en pacientes que no abusan del alcohol. Los pacientes con EHNA suelen ser diagnosticados cuando los análisis de sangre de rutina de la función hepática (LFT) revelan un deterioro de la función hepática. Las personas son más propensas a padecer EHNA cuando tienen sobrepeso, son diabéticos o sufren de síndromes metabólicos o similares. En este estudio, un grupo de pacientes no ciego (sin control de placebo) fue alimentado con Immunocal durante tres meses. Los análisis de sangre compararon su estado inicial (de referencia) de glutatión, su estado antioxidante, las tomografías computarizadas y (lo más importante) las pruebas de función hepática con los mismos parámetros después del tratamiento. Todos los pacientes mostraron mejoria.

EAR NOSE THROAT J. 2010 SEP;89(9):422-33.

Los efectos del aumento del glutatión en la pérdida de audición neurosensorial

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Abstract

Previous research has demonstrated the benefits of antioxidant treatment in the prevention of hearing loss in animals. Our study tested the effects of an undenatured whey protein supplement rich in glutathione on human patients with hearing loss. Over an average of 36 months, 30 patients with hearing loss and who had data sufficient for analysis were treated with a glutathione supplement and were compared with 30 retrospective controls selected from the same otologic patient population. Patients were followed using regular hearing tests. Linear regression analysis was used to determine whether study group, baseline audiometric score, time followed, and autoimmune etiology modified the rate of hearing loss. Treatment with the glutathione supplement failed to modify significantly the progression of hearing loss in the treated population. The baseline audiometric score was most predictive of the final audiometric score ($p < 0.0005$). Although glutathione supplementation was not shown to be helpful in slowing hearing loss in the patients studied, our research model proved valid as it demonstrated an overall decline in hearing in both the treated and control groups over time of sufficient magnitude to permit detection of a treatment effect if a substantial effect had occurred. We suggest that this model be applied to future studies investigating the effects of antioxidants on hearing loss.

Dr. Gutman's Comments

Este equipo de investigadores especialistas en nariz y garganta era consciente de que el tratamiento con antioxidantes podía ser útil para prevenir la pérdida de audición en los animales. Se propusieron comprobar si también lo era en los seres humanos. Aunque los resultados no alcanzaron un significado estadístico, la tendencia era tal que sugirieron que se hicieran estudios más completos como seguimiento.

JOURNAL OF WOUND CARE, 2019 JUL 1;28 (SUP7):S16-S23. DOI: 10.12968/JOWC.2019.28.SUP7.S16

Suplemento de proteína de suero no desnaturalizado rico en cisteína en los resultados de las úlceras por presión de los pacientes: un estudio de etiqueta abierta

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Abstract

Objective: The prevalence and costs associated with treating pressure ulcers (PU) are at high levels. Frequently, PUs heal slowly or not at all, which may be due to the patient's catabolic state which may include protein energy malnutrition. The objective of this open label clinical trial was to improve healing rates by providing patients with a patented, high-quality protein containing all essential amino acids to ensure positive nitrogen balance. An additional benefit of this protein is the delivery of bioavailable cysteine (cystine) to promote glutathione (GSH) synthesis which supports immune function and heightens antioxidant defences.

Methods: Patients with category II, III and IV PUs were fed 20g BID whey protein dietary supplement for 16-120 days, without change in ongoing 'best practice' PU management and their progress recorded.

Results: A total of 10 patients were recruited, with an average age of 77 years. Most had shown no improvement in healing for ≥2 months before treatment and usually had other complications including chronic obstructive pulmonary disease (COPD), diabetes and various cardiovascular diseases. There were a total of 23 PUs, with some patients having more than one. Of these, 44% (n=10) showed complete resolution 83% (n=19) had better than 75% resolution over the observation period. Healing rates ranged from 16.9-0.2cm2/month (healed PUs) and 60.0-1.6cm2/month for resolving PUs.

Conclusion: By providing the necessary amino acids to rebuild tissues and bioactive cysteine (cystine) to promote synthesis of intracellular GSH and positive nitrogen balance, improvement in PUs healing was achieved.

Comentarios del Dr. Gutman

Después de escuchar anécdotas del campo de que Immunocal estaba teniendo efectos beneficiosos en ciertas lesiones de la piel incluyendo úlceras de presión (escaras), se decidió realizar un estudio oficial. Las úlceras de decúbito se llaman "úlceras por presión" porque se producen en pacientes que están acostados en la cama durante períodos prolongados y la piel que está bajo presión por el peso del paciente comienza a descomponerse. Esto es extremadamente angustioso y requiere enormes recursos para su cuidado. Este trabajo muestra que una simple intervención dietética usando Immunocal puede aliviar mucho sufrimiento.

ESTUDIOS CIEGOS CON IMMUNOCAL EN HUMANOS

JOURNAL OF APPLIED PHYSIOLOGY, 87: 1381-1385, 1999

El efecto de la suplementación con un donante de cisteína en el rendimiento muscular

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Abstract

Oxidative stress contributes to muscular fatigue. Glutathione (GSH) is the major intracellular antioxidant, whose biosynthesis is dependent upon cysteine availability. We hypothesized that supplementation with a whey-based cysteine donor (Immunocal (HMS90)) designed to augment intracellular GSH, would enhance performance. Twenty healthy young adults (10 m) were studied pre- and 3 months post-supplementation with either Immunocal (20 gm/day) or casein placebo. Muscular performance was assessed by whole leg isokinetic cycle testing, measuring Peak Power and 30-sec Work Capacity. Lymphocyte GSH was used as a marker of tissue GSH. There were no baseline differences (age, ht, wt, % ideal wt, Peak Power, 30-sec Work Capacity). Follow-up data on 18 subjects (9 Immunocal, 9 placebo) were analyzed. Both peak power [13 +/- 3.5 (SE) %, P < 0.02] and 30-s work capacity (13 +/- 3.7%, P < 0.03) increased significantly in the Immunocal group, with no change (2 +/- 9.0 and 1 +/- 9.3%) in the placebo group. Lymphocyte GSH also increased significantly in the Immunocal group (35.5 +/- 11.04%, P < 0.02), with no change in the placebo group (-0.9 +/- 9.6%). This is the first study to demonstrate that prolonged supplementation with a product designed to augment antioxidant defenses resulted in improved volitional performance.

Comentarios del Dr. Gutman

El Dr. Larry Lands de la Universidad McGill concibió este estudio después de escuchar repetidos informes sobre la mejora del rendimiento de los atletas que tomaban Immunocal. Como científico, buscó evidencia para validar estas afirmaciones. A los adultos jóvenes y atléticos se les dio un placebo o Immunocal. Todos se sometieron al mismo programa de entrenamiento físico, tres meses después, cuando se midió la fuerza y resistencia muscular, sus indicadores de rendimiento (fuerza y resistencia) habían mejorado en un 10-15%, una ventaja sustancial en los deportes competitivos. Al mismo tiempo, los niveles de glutatión en esta población sana subieron un significativo 35%. Estudios posteriores sobre el rendimiento muscular e Immunocal han reforzado estos resultados.

JOURNAL OF CYSTIC FIBROSIS, VOL 2, ISSUE 4, DECEMBER 2003

Mejora del estado del glutatión en pacientes adultos jóvenes con fibrosis quística complementada con proteína de suero

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Abstract

The lung disease of cystic fibrosis is associated with a chronic inflammatory reaction and an over abundance of oxidants relative to antioxidants. Glutathione functions as a major frontline defense against the build-up of oxidants in the lung. This increased demand for glutathione (GSH) in cystic fibrosis may be limiting if nutritional status is compromised. We sought to increase glutathione levels in stable patients with cystic fibrosis by supplementation with a whey-based protein. Methods: Twenty-one patients who were in stable condition were randomly assigned to take a whey protein isolate (Immunocal, 10 g twice a day) or casein placebo for 3 months. Peripheral lymphocyte GSH was used as a marker of lung GSH. Values were compared with nutritional status and lung parameters. Results: At baseline there were no significant differences in age, height, weight, percent ideal body weight or percent body fat. Lymphocyte GSH was similar in the two groups. After supplementation, we observed a 46.6% increase from baseline ($P<0.05$) in the lymphocyte GSH levels in the supplemented group. No other changes were observed. Conclusion: The results show that dietary supplementation with a whey-based product can increase glutathione levels in cystic fibrosis. This nutritional approach may be useful in maintaining optimal levels of GSH and counteract the deleterious effects of oxidative stress in the lung in cystic fibrosis.

Comentarios del Dr. Gutman

La fibrosis quística es una enfermedad grave y crónica que aparece a una edad temprana. Los pulmones suelen ser los más afectados. Están crónicamente inflamados, y se desarrolla una mucosidad espesa dentro de las vías respiratorias que obstruye su función y conduce a una mayor inflamación e infección. Se sabe desde hace mucho tiempo que en la fibrosis quística se espera una disminución de los niveles de glutatión. En este estudio canadiense se utilizó Immunocal para elevar con éxito los niveles de glutatión en 32 adultos jóvenes con fibrosis quística. Los investigadores observaron un aumento del 45 al 50% en los niveles de glutatión de los glóbulos blancos.

MEDICINE & SCIENCE IN SPORTS & EXERCISE, VOL. 37, NO. 9, PP. 1468-1473, 2005

Efectos del suplemento del donante de cisteína en la broncoconstricción inducida por el ejercicio

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Abstract

Purpose Reactive oxygen/nitrogen species (ROS/RNS) in resident airway cells may be important in bronchoconstriction following exercise. Glutathione (GSH) is a major lung antioxidant and could influence pathological outcomes in individuals with exercise-induced bronchoconstriction (EIB). This study examined the effects of supplementation with undenatured whey protein (UWP) in subjects exhibiting airway narrowing following eucapnic voluntary hyperventilation (EVH), a surrogate challenge for diagnosis of EIB. UWP is a cysteine donor that augments GSH production.

Methods In a randomized, double-blind, placebo-controlled study, 18 EIB-positive subjects (age: 25.2 ±9.01 yr; weight: 77.3 ±18.92 kg; height: 1.7 ±0.09 m) with post-EVH falls of ± 10% in FEV received 30 g UWP (TX) or casein placebo (PL)/d. Subjects performed 6-min EVH challenges before and after 4 and 8 wk of supplementation. Exhaled nitric oxide (eNO) was measured serially before spirometry and at 1-wk intervals. Spirometry was performed pre- and 5, 10, and 15 min postchallenge.

Results Subjects exhibited significant mean improvement in postchallenge falls in FEB from 0 wk (-2.6 ±12.22%) with TX at 4 (-18.9 ±12.89%, P±0.05) and 8 wk (-16.98 ±11.61%, P± 0.05) and significant mean reduction in post-EVH peak falls in FEF from 0 wk (-40.6 ±15.28%) with TX at 4 (-33.1 ±17.11%, P ±0.01) and 8 (-29.7 ±17.42%, P±0.05) wk. No changes in FEV or FEF were observed in the PL group at any time point. Mean eNO for PL and TX groups at 0, 4, and 8 wk (46.8 ± 31.33, 46.5 ±35.73, 49.3 ±37.12 vs 35.2 ±26.87, 29.1 ±17.26, 34.7 ±21.11 ppb, respectively) was not significantly different.

Conclusions UWP may augment pulmonary antioxidant capacity and be therapeutically beneficial in individuals exhibiting EIB, as postchallenge pulmonary function improved with supplementation. The lack of significant change in eNO suggests that the pulmonary function improvements from UWP supplementation are independent of eNO.

Comentarios del Dr. Gutman

Este interesante estudio realizado sobre jugadores de hockey universitario, por lo demás sanos, abordó el tema de los jóvenes atletas que sufren de asma inducida por el ejercicio, secundaria a la exposición a los gases de escape del motor de los Zambonis (vehículos de limpieza de pistas de hielo). Se observa una tasa de asma más alta de lo esperado en los jugadores de hockey sobre hielo que en los atletas de la misma edad que practican otros deportes. Los jugadores asmáticos fueron asignados al azar a un grupo Immunocal o a un grupo de placebo. Después de 4 semanas, las pruebas de función pulmonar fueron significativamente mejores en el grupo Immunocal que en el grupo de control (placebo). Esta diferencia fue aún mayor después de 8 semanas. El mensaje de este estudio no sólo fue que el asma mejoró con Immunocal, sino que Immunocal puede ofrecer protección contra la contaminación del aire que resulta de los gases de escape de los motores de combustión.

ANTIOXIDANTS & REDOX SIGNALING, 10:395-402, (2008)

La proteína rica en cisteína invierte la pérdida de peso en pacientes con cáncer de pulmón que reciben quimioterapia o radioterapia

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Abstract

Oxidative stress plays a role in the tumor-cytotoxic effect of cancer chemotherapy and radiotherapy and also in certain adverse events. In view of these conflicting aspects, a double-blind trial over 6 months has been performed to determine whether a cysteine-rich protein (IMN1207) may have a positive or negative effect on the clinical outcome if compared with casein, a widely used protein supplement low in cysteine. Sixty-six patients with Stage IIIB-IV non-small cell lung cancer were randomly assigned to IMN1207 or casein. Included were patients with a previous involuntary weight loss of ≥3%, Karnofsky status ≥70, and an estimated survival of > 3 months. Thirty-five lung cancer patients remained on study at six weeks. Overall compliance was not different between treatment arms (42-44% or 13g/day). The patients treated with the cysteine-rich protein had a mean increase of 2.5% body weight while casein-treated patients lost 2.6% (P=0.049). Differences in secondary end points included an increase in survival, hand grip force and quality of life. Adverse events were mild or moderate. Further studies will have to show whether the positive clinical effects can be confirmed and related to specific parameters of oxidative stress in the host.

Comentarios del Dr. Gutman

Este estudio histórico fue el primero en abordar directamente la pregunta: "¿Elevar el glutatión protege a las células cancerosas de la quimioterapia?" Los estudios de laboratorio habían demostrado que las células cancerosas pueden usar el glutatión para resistir la quimioterapia. Sin embargo, esto se había demostrado en estudios de probeta solamente, no en cuerpos vivos. Sólo un estudio definitivo en humanos revelaría si esto se traduce en una situación de la vida real. Dirigido por el eminente inmunólogo Wulf Droge, un equipo de investigadores canadienses inició un estudio doble ciego, controlado por placebo, con los máximos estándares de calidad en los principales centros de tratamiento del cáncer de todo el país. Los pacientes con cáncer de pulmón que recibían quimioterapia o radioterapia fueron alimentados con Immunocal o un placebo. Los pacientes seleccionados ya mostraban un significativo desgaste muscular (caquexia), lo que significa una enfermedad avanzada. Se estimó que todos sobrevivieron no más de 3 meses. A diferencia de los experimentos de probeta, el Immunocal no "protegió" el cáncer. Por el contrario, los pacientes alimentados con Immunocal en realidad aumentaron su masa muscular (reversión de la caquexia) - un resultado muy raro de la intervención nutricional. Además, sus mediciones de calidad de vida mejoraron significativamente. Finalmente, las estadísticas de supervivencia fueron igualmente impresionantes. Después de un año, el 80% de los pacientes alimentados con Immunocal sobrevivieron, mientras que menos de la mitad del grupo de placebo seguía vivo.

JOURNAL OF NUTRITION, HEALTH & AGING, 2015, 19(5):531-6s

Efecto de la suplementación de proteína de suero rica en cisteína (Immunocal®) en combinación con el entrenamiento de resistencia en la fuerza muscular y la masa corporal magra en sujetos ancianos no discapacitados: un estudio aleatorio, doble ciego y controladoy

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Abstract

Objectives: The purpose of the present study was to examine the effect of a cysteine-rich whey protein (Immunocal®) supplementation in combination with resistance training on muscle strength and lean body mass (LBM) in elderly individuals. We hypothesized that the cysteine-rich whey protein (Immunocal®) group would experience a greater increase in muscle strength and lean body mass versus the control group (casein). Design: Randomized double-blind controlled intervention study. Setting: Institut de Recherches Cliniques de Montréal in Montréal, Canada. Participants: Ninety-nine non-frail elderly subjects were recruited. Intervention: Participants were randomly assigned into two groups. The experimental group received a cysteine-rich whey protein isolate (Immunocal®) (20g/day) and the control group received casein (20g/day) during a 135-day period. In addition, both groups performed the same resistance training program (3 times per week). Measurements: Body composition (DXA) and muscle strength (leg press) were measured. Results: Of the 99 recruited participants, 84 completed the 135-day study period. Of these, 67 subjects (33 in the casein group and 34 in the Immunocal® group) complied and used at least 80% of the study product and completed at least 80% of their training sessions. Results in this selected group show an increase in all three muscle strength variables (absolute, normalized by BW and by LBM) by 31.0%, 30.9% and 30.0%, respectively in the casein group as well as 39.3%, 39.9% and 43.3% respectively in the Immunocal® group after the intervention ($p<0.05$). The increases in muscle strength favored Immunocal® versus casein by approximately 10% when expressed in kg per kg BW and in kg per kg LBM ($p< 0.05$) No significant changes were found between pre-and-post intervention in both groups for total LBM. Conclusions: Our findings showed increases in muscle strength in both groups after resistance training, however, significant additional increases were observed in muscle strength with the addition of a cysteine-rich whey protein (Immunocal®) versus casein.

Comentarios del Dr. Gutman

El Dr. Karelis, la Dra. Rabasa-Lhoret y sus equipos de investigación en Montreal (Canadá) realizaron un ensayo clínico controlado sobre Immunocal en una población de ancianos no discapacitados. Este fue el primer ensayo de Immunocal con la participación de un gran número de sujetos de edad avanzada; un grupo consumió Immunocal, el otro una proteína de leche llamada caseína. Ambos grupos siguieron el mismo programa de entrenamiento de resistencia tres veces por semana. El grupo de Immunocal comparado con el grupo de la caseína demostró un aumento estadísticamente significativo en la fuerza muscular de alrededor del 10%. Estos datos tan favorables llevaron a Immunotec a garantizar una nueva afirmación de salud de que Immunocal "aumenta la fuerza muscular" por parte de la Dirección de Productos de Salud Natural del Ministerio de Salud de Canadá (NHPD por sus siglas en inglés).

JOURNAL OF THE NEUROLOGICAL SCIENCES 367, (2016) 162-170

Efectos bioquímicos y clínicos de la suplementación de proteína de suero en la enfermedad de Parkinson

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Abstract

Background: Parkinson's Disease (PD) is an oxidative stress-mediated degenerative disorder. Elevated plasma homocysteine (Hcy) is frequently found in the levodopa-treated PD patients, is associated with disease progression and is a marker of oxidative stress. Whey protein is a rich source of cysteine, and branched-chain amino acids (BCAA). It has been shown that supplementation with Whey protein increases glutathione synthesis and muscle strength.

Objectives & Methods: In this study, we conducted a placebo-controlled, double-blind study (NCTO1662414) to investigate the effects of undenatured Whey protein isolate supplementation for 6 months on plasma glutathione, plasma amino acids, and plasma Hcy in PD patients. Clinical outcome assessments included the unified Parkinson's disease rating scale (UPDRS) and striatal L-3,4-dihydroxy-6-(18) F-fluorophenylalanine (FDOPA) uptake were determined before and after supplementation. 15 patients received Whey protein, and 17 received Soy protein, served as a control group.

Results: Significant increases in plasma concentration of reduced glutathione and the ratio of reduced to oxidized glutathione were found in the Whey-supplemented patients but not in a control group. This was associated with a significant decrease of plasma levels of Hcy. The plasma levels of total glutathione were not significantly changed in either group. Plasma BCAA and essential amino acids (EAA) were significantly increased in the Whey-supplemented group only. The UPDRS and striatal FDOPA uptake in PD patients were not significantly ameliorated in either group. However, significant negative correlation was observed between the UPDRS and plasma BCAA and EAA in the pre-supplemented PD patients.

Conclusion: This study is the first to report that Whey protein supplementation significantly increases plasma reduced glutathione, the reduced to oxidized glutathione ratio, BCAAs and EAAs in patients with PD, together with a concomitant significant reduction of plasma Hcy. However, there were no significant changes in clinical outcomes. Long-term, large randomized clinical studies are needed to explore the benefits of whey protein supplementation in the management of PD patients.

Comentarios del Dr. Gutman

Un equipo internacional de investigadores contribuyó a este ensayo doble ciego controlado por placebo en pacientes con la enfermedad de Parkinson. A cada participante se le dio Immunocal o un aislado de proteína de soya. Las mediciones de glutatión mejoraron en el grupo de Immunocal. Los investigadores consideraron que un estudio más amplio proporcionaría pruebas de la mejora clínica.

ELECTRONIC JOURNAL OF METABOLISM & NUTRITION OF CANCER (6)3: 346-350, 2019

Los bioactivos de ABD alivian la mielosupresión inducida por la quimioterapia

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Abstract

Objective To explore the effect of ABD Bioactives on myelosuppression alleviation in lung cancer patients during chemotherapy.
Methods 44 lung cancer patients who received chemotherapy were randomly divided into an intervention group and a control group. 22 lung cancer patients in the intervention group received ABD Bioactives for adjuvant therapy. 22 lung cancer patients were treated conventionally. The difference of myelosuppression was compared between the two groups.
Results 43 patients completed chemotherapy as planned, and 1 patient from the control group terminated chemotherapy due to severe myelosuppression. Myelosuppression of the intervention group was significantly alleviated ($P < 0.05$). The incidence of myelosuppression of III ~ IV was significantly lower ($P < 0.05$), and the inhibition of leukocytes, granulocytes, and platelets was significantly alleviated ($P < 0.05$, $P < 0.05$, $P < 0.05$) compared with the control group. The myleosuppression induced by paclitaxel + platinum-based agents, pemetrexed + platinum-based agents was significantly alleviated ($P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$) compared with the control group.
Conclusion ABD Bioactives can alleviate chemotherapy-induced myelosuppression in lung cancer patients, especially reduce the incidence of myelosuppression of III ~ IV, increase the levels of leukocytes, granulocytes, and platelets and reduce the toxicity of platinum-based agents paclitaxel, antimetabolite.

Comentarios del Dr. Gutman

Este estudio en humanos se realizó en pacientes con cáncer de pulmón. 44 pacientes fueron divididos al azar en grupos de control (tratamiento estándar) o de intervención (Immunocal añadido). (Immunocal se llama "ABD Bioactives" en China). Uno de los principales efectos adversos potenciales de la quimioterapia es una depresión de la función inmunológica. La medida que se utiliza con más frecuencia para medir la salud del sistema inmunológico es el número de glóbulos blancos, un grupo de células denominadas "mielocitos," con subgrupos como los leucocitos, los granulocitos, etc. "Mielosupresión" es la condición en la que estos glóbulos blancos (que son los soldados de primera línea del sistema inmunológico) son reducidos en número, lo que conduce a un estado inmunológico debilitado. Immunocal tuvo éxito en la mejora de esta condición, un problema importante en el éxito o fracaso de la quimioterapia.

FRONTIERS IN PSYCHIATRY. 2021 VOL. 12, ARTICLE 669089, 1-15.

Aumento de la capacidad antioxidante en niños con autismo: Estudio controlado aleatorio y doble ciego con proteína de suero rica en cisteína

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Abstract

Previous studies indicate that children with autism spectrum disorder (ASD) have lower levels of glutathione. Nutritional interventions aim to increase glutathione levels suggest a positive effect on ASD behaviors, but findings are mixed or non-significant. A commercially available nutritional supplement comprising a cysteine-rich whey protein isolate (CRWP), a potent precursor of glutathione, was previously found to be safe and effective at raising glutathione in several conditions associated with low antioxidant capacity. Therefore, we investigated the effectiveness of a 90-day CRWP intervention in children with ASD and examined whether intracellular reduced and oxidized glutathione improvements correlated with behavioral changes. We enrolled 46 (of 81 screened) 3–5-year-old preschool children with confirmed ASD. Using a double-blind, randomized, placebo-controlled design, we evaluated the effectiveness of daily CRWP (powder form: 0.5 g/kg for children < 20kg or a 10-g dose for those >20kg), compared with placebo (rice protein mimicking the protein load in the intervention group), on glutathione levels and ASD behaviors assessed using different behavioral scales such as Childhood Autism Rated Scale, Preschool Language Scale, Social Communication Questionnaire, Childhood Behavioral Checklist and the parent-rated Vineland Adaptive Behavior Scale, 2nd edition (VABS-II). Forty children (CRWP, 21; placebo, 19) completed the 90-day treatment period. Improvements observed in some behavioral scales were comparable. However, the VABS-II behavioral assessment, demonstrated significant changes only in children receiving CRWP compared to those observed in the placebo group in the composite score (effect size 0.98; $p = 0.03$). Further, several VABS-II domain scores such as adaptive behavior ($p = 0.03$), socialization ($p = 0.03$), maladaptive behavior ($p = 0.04$) and internalizing behavior ($p = 0.02$) also indicated significant changes. Children assigned to the CRWP group showed significant increases in glutathione levels ($p = 0.04$) compared to those in the placebo group. A subanalysis of the VABS-II scale results comparing responders (>1 SD change from baseline to follow up) and non-responders in the CRWP group identified older age and higher levels of total and reduced glutathione as factors associated with a response. CRWP nutritional intervention in children with ASD significantly improved both glutathione levels and some behaviors associated with ASD. Further studies are needed to confirm these results.

Comentarios del Dr. Gutman

Este estudio fue un gran paso tras la publicación de mi estudio piloto original sobre Immunocal y el autismo. El auspicioso equipo de investigación sobre el autismo en Florida, dirigido por la Dra. Ana Castejón, se propuso evaluar si el uso de Immunocal puede lograr dos cosas: 1) elevar el glutatión, y 2) mejorar los resultados de conducta en los niños con autismo. Demostraron que ambas cosas son ciertas. Determinar los resultados exactos de los análisis de sangre del glutatión era una cosa, pero medir parámetros multifacéticos del comportamiento requería mucho tiempo y grandes recursos: este estudio tardó diez años en publicarse. Los estudios más significativos suelen requerir que la investigación sea aún más significativa. En este caso, parecía haber dos respuestas distintas, cuyas mejoras eran más notorias en niños: a) mayores, y; b) que sus niveles de glutatión eran muy bajos. Al haber hecho el estudio en pacientes de 3 a 5 años, esto sugirió que debería estudiarse un grupo de mayor edad y que podrían ser necesarias dosis más altas de Immunocal. Los estudios de seguimiento están pendientes.

ESTUDIOS CIEGOS DE PREHABILITACIÓN CON IMMUNOCAL EN HUMANOS

ANESTHESIOLOGY, 2014, 121:937-47

Prehabilitación versus rehabilitación es un ensayo de control aleatorio en pacientes que se someten a una resección colorrectal por cáncer

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Abstract

Background: The preoperative period (prehabilitation) may represent a more appropriate time than the postoperative period to implement an intervention. The impact of prehabilitation on recovery of functional exercise capacity was thus studied in patients undergoing colorectal resection for cancer.

Methods: A parallel-arm single-blind superiority randomized controlled trial was conducted. Seventy-seven patients were randomized to receive either prehabilitation (n=38) or rehabilitation (n = 39). Both groups received a home-based intervention of moderate aerobic and resistance exercises, nutritional counseling with protein supplementation, and relaxation exercises initiated either 4 weeks before surgery (prehabilitation) or immediately after surgery (rehabilitation), and continued for 8 weeks after surgery. Patients were managed with an enhanced recovery pathway. Primary outcome was functional exercise capacity measured using the validated 6-min walk test. Results: Median duration of prehabilitation was 24.5 days. While awaiting surgery, functional walking capacity increased (≥20m) in a higher proportion of the prehabilitation group compared with the rehabilitation group (53 vs. 15%, adjusted P= 0.006). Complication rates and duration of hospital stay were similar. The difference between baseline and 8-week 6-min walking test was significantly higher in the prehabilitation compared with the rehabilitation group (+23.7 m [SD, 54.8] vs. -21.8m [SD, 80.7]; mean difference 45.4 m [95% CI, 13.9 to 77.0]). A higher proportion of the prehabilitation group were also recovered to or above baseline exercise capacity at 8 weeks compared with the rehabilitation group (84 vs. 62%, adjusted P=0.049).

Conclusions: Meaningful changes in postoperative functional exercise capacity can be achieved with a prehabilitation program

Comentarios del Dr. Gutman

Mientras los investigadores buscan mejorar la recuperación de los pacientes de cáncer de colon de la cirugía, este ensayo de control aleatorio comparó las ventajas de la prehabilitación con las de la rehabilitación. Usando una dieta con Immunocal, el programa de prehabilitación fue significativamente mejor en la restauración del rendimiento muscular que cualquier otro método post-quirúrgico.

JOURNAL OF THE ACADEMY OF NUTRITION AND DIETETICS 2015

Prehabilitación con suplemento de proteína de suero en la capacidad de ejercicio funcional perioperatorio en pacientes sometidos a resección colorrectal por cáncer: Ensayo piloto doble ciego aleatorio controlado por placebo

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Abstract

Background: A previous comprehensive prehabilitation program, providing nutrition counseling with whey protein supplementation, exercise, and psychological care, initiated 4 weeks before colorectal surgery for cancer, improved functional capacity before surgery and accelerated functional recovery. Those receiving standard of care deteriorated. The specific role of nutritional prehabilitation alone on functional recovery is unknown.

Objective: This study was undertaken to estimate the impact of nutrition counseling with whey protein on preoperative functional walking capacity and recovery in patients undergoing colorectal resection for cancer.

Design: We conducted a double-blinded randomized controlled trial at a single university-affiliated tertiary center located in Montreal, Quebec, Canada. Colon cancer patients (n=48) awaiting elective surgery for nonmetastatic disease were randomized to receive either individualized nutrition counseling with whey protein supplementation to meet protein needs or individualized nutrition counseling with a nonnutritive placebo. Counseling and supplementation began 4 weeks before surgery and continued for 4 weeks after surgery.

Main Outcome Measure: The primary outcome was change in functional walking capacity as measured with the 6-minute walk test. The distance was recorded at baseline, the day of surgery, and 4 weeks after surgery. A change of 20 m was considered clinically meaningful.

Results: The whey group experienced a mean improvement in functional walking capacity before surgery of +20.8m, with a standard deviation of 42.6m and the placebo group improved by +1.2 (65.5) m (P=0.27). Four weeks after surgery, recovery rates were similar between groups (P=0.81).

Conclusion: Clinically meaningful improvements in functional walking capacity were achieved before surgery with whey protein supplementation. These pilot results are encouraging and justify larger-scale trials to define the specific role of nutrition prehabilitation on functional recovery after surgery.

Comentarios del Dr. Gutman

Uno de los primeros ensayos de control aleatorios y a doble ciego para examinar los beneficios de la prehabilitación con Immunocal en la dieta fue dirigido por el Dr. Carli en la Universidad McGill en Montreal. Incluso en este pequeño ensayo, los pacientes que se sometían a una cirugía de cáncer de intestino se beneficiaron con resultados significativos, alimentando el interés en estudios más amplios.

ACTA ONCOLOGICA, 2017, FEBRUARY;56(2):295-300

La prehabilitación multimodal mejora la capacidad funcional antes y después de la cirugía colorrectal para el cáncer: una experiencia de cinco años de investigación

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Abstract

Background: Multimodal prehabilitation is a preoperative conditioning intervention in form of exercise, nutritional assessment, whey protein supplementation, and anxiety-coping technique. Despite recent evidence suggesting that prehabilitation could improve functional capacity in patients undergoing colorectal surgery for cancer, all studies were characterized by a relatively small sample size. The aim of this study was to confirm what was previously found in three small population trials.

Material and Methods: Data of 185 participants enrolled in a pilot single group study and two randomized control trials conducted at the McGill University Health Center from 2010 to 2015 were reanalyzed. Subjects performing trimodal prehabilitation (exercise, nutrition, and coping strategies for anxiety) were compared to the patients who underwent the trimodal program only after surgery (rehabilitation/control group). Functional capacity was assessed with the six-minute walk test (6MWT), a measure of the distance walked over six minutes (6MWD). A significant functional improvement was defined as an increase in 6MWD from baseline by at least 19 m. Changes in 6MWD before surgery, at four and eight weeks were compared between groups.

Results: Of the total study population, 113 subjects (61%) underwent prehabilitation. Changes in 6MWD in the prehabilitation group were higher compared to the rehabilitation/control group during the preoperative period {30.0 [standard deviation (SD) 46.7] m vs. -5.8 (SD 40.1) m, $p < 0.001$}, at four weeks [-11.2 (SD 72) m vs. -72.5 (SD 129) m, $p < 0.01$], and at eight weeks [17.0 (SD 84.0) m vs. -8.8 (SD 74.0) m, $p = 0.047$]. The proportion of subjects experiencing a significant preoperative improvement in physical fitness was higher in those patients who underwent prehabilitation [68 (60%) vs. 15 (21%), $p < 0.001$].

Conclusion: In large secondary analysis, multimodal prehabilitation resulted in greater improvement in walking capacity throughout the whole perioperative period when compared to rehabilitation started after surgery.

Comentarios del Dr. Gutman

El equipo del Dr. Carli revisó cinco años de ensayos de prehabilitación en pacientes de cirugía de cáncer para volver a examinar las estadísticas resultantes. Combinando la evidencia de varios ensayos más pequeños en este análisis más grande resultó en una mayor importancia estadística y una mayor confianza en los resultados.

SUPPORT CARE CANCER, 2017, JAN;25(1):33-40

El programa de prehabilitación de cuatro semanas es adecuado para modificar los comportamientos de ejercicio y mejorar la capacidad funcional preoperatoria de caminar en pacientes con cáncer colorrectal

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Abstract

Purpose: High complication rates following colorectal surgery render many patients unable to fully regain functional capacity, thus seriously compromising quality of life. The aim of this study was to assess whether a 4-week trimodal prehabilitation program (exercise, nutritional supplementation, and counseling on relaxation techniques), implemented during the preoperative period, is sufficient to modify exercise behaviors and improve functional capacity of elderly patients scheduled for colorectal cancer surgery.

Methods: Patients were assigned to either a prehabilitation (PREHAB; n = 57) or matched time control group (CTRL; n = 59). Over the 4-week period prior to surgery, patients in PREHAB participated in a trimodal prehabilitation program. Patients in CTRL received the same program but only postoperatively. The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire was used to measure physical activity levels, while the 6-min walk test (6MWT) was used for assessment of functional walking capacity. Measurements were collected at baseline and at the time of surgery.

Results: Over the preoperative period, patients in PREHAB significantly increased the amount of moderate- and vigorous-intensity physical activities that they performed. PREHAB patients also demonstrated a greater improvement in 6MWT compared to CTRL. At the time of surgery, a greater proportion of patients in PREHAB met current physical activity guidelines, as compared to CTRL.

Conclusions: These findings highlight the positive effects of a trimodal prehabilitation program on patients' physical activity levels and functional walking capacity and demonstrate that modifying exercise behaviors and improving physical function within the 4-week preoperative period are an achievable goal.

Comentarios del Dr. Gutman

El equipo del Dr. Carli alimentó con Immunocal a los pacientes que se preparaban para la cirugía de cáncer de intestino, y mostraron que esta prehabilitación mejoró su rendimiento físico y los niveles de actividad física posteriores. Estos importantes indicadores de recuperación ayudan a determinar cuándo los pacientes pueden ser dados de alta de forma segura y recuperar su independencia.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION SURGERY,
2018 SEPT 5 DOI:10.1001/JAMASURG.2018. 1645

Efecto de la prehabilitación del ejercicio y la nutrición en la capacidad funcional en la cirugía del cáncer esofagogástrico: un ensayo clínico aleatorio

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Abstract

Importance: Preserving functional capacity is a key element in the care continuum for patients with esophagogastric cancer. Prehabilitation, a preoperative conditioning intervention aiming to optimize physical status, has not been tested in upper gastrointestinal surgery to date.

Objective: To investigate whether prehabilitation is effective in improving functional status in patients undergoing esophagogastric cancer resection.

Design, Setting, and Participants: A randomized clinical trial (available-case analysis based on completed assessments) was conducted at McGill University Health Centre (Montreal, Quebec, Canada) comparing prehabilitation with a control group. Intervention consisted of preoperative exercise and nutrition optimization. Participants were adults awaiting elective esophagogastric resection for cancer. The study dates were February 13, 2013, to February 10, 2017.

Main Outcomes and Measures: The primary outcome was change in functional capacity, measured with absolute change in 6-minute walk distance (6MWD). Preoperative (end of the prehabilitation period) and postoperative (from 4 to 8 weeks after surgery) data were compared between groups.

Results: Sixty-eight patients were randomized, and 51 were included in the primary analysis. The control group were a mean (SD) age, 68.0 (11.6) years and 20 (80%) men. Patients in the prehabilitation group were a mean (SD) age, 67.3 (7.4) years and 18 (69%) men. Compared with the control group, the prehabilitation group had improved functional capacity both before surgery (mean [SD] 6MWD change, 36.9 [51.4] vs −22.8 [52.5] m; P < .001) and after surgery (mean [SD] 6MWD change, 15.4 [65.6] vs −81.8 [87.0] m; P < .001).

Conclusions and Relevance: Prehabilitation improves perioperative functional capacity in esophagogastric surgery. Keeping patients from physical and nutritional status decline could have a significant effect on the cancer care continuum.

Comentarios del Dr. Gutman

Este ensayo clínico aleatorio del equipo del Dr. Carli probó un programa de prehabilitación de dos puntas (ejercicio y nutrición) en pacientes antes de la cirugía de estómago y esófago. Los que estaban en el programa se recuperaron mejor de la cirugía que los que estaban en el tratamiento estándar.

ACTA ONCOLOGICA, 2018, JUNE;57(6) :849-859

Evaluación del programa de prehabilitación multimodal supervisado en pacientes con cáncer que se someten a una resección colorrectal: ensayo de control aleatorio

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Abstract

Background Prehabilitation has been previously shown to be more effective in enhancing postoperative functional capacity than rehabilitation alone. The purpose of this study was to determine whether a weekly supervised exercise session could provide further benefit to our current prehabilition program, when comparing to standard post-surgical rehabilitation.

Methods A parallel-arm single-blind randomized control trial was conducted in patients scheduled for non-metastatic colorectal cancer resection. Patients were assigned to either a once weekly supervised prehabilitation (PREHAB+, n = 41) or standard rehabilitation (REHAB, n = 39) program. Both multimodal programs were home-based program and consisted of moderate intensity aerobic and resistance exercise, nutrition counseling with daily whey protein supplementation and anxiety-reduction strategies. Functional exercise capacity, as determined by the 6-minute walk test distance (6MWD), was the primary outcome. Exercise quantity, intensity and energy expenditure was determined by the CHAMPS questionnaire.

Results Both groups were comparable for baseline walking capacity and included a similar proportion of patients who improved walking capacity (>20 m) during the preoperative period. After surgery, changes in 6MWD were also similar in both groups. In PREHAB+, however, there was a significant association between physical activity energy expenditure and 6MWD ($p < .01$). Previously inactive patients were more likely to improve functional capacity due to PREHAB+.

Conclusions The addition of a weekly supervised exercise session to our current prehabilitation program did not further enhance postoperative walking capacity when compared to standard REHAB care. Sedentary patients, however, seemed more likely to benefit from PREHAB+. An association was found between energy spent in physical activity and 6MWD. This information is important to consider when designing cost-effective prehabilitation programs.

Comentarios del Dr. Gutman

En los pacientes que se someten a una cirugía de cáncer de intestino, este ensayo de control aleatorio examina los beneficios de la prehabilitación utilizando Immunocal como una intervención dietética.

SUPPORT CARE CANCER 2018 Aug;26(8):2717-2723

Maximizar la adherencia del paciente a la prehabilitación: ¿Qué dicen los pacientes?

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Abstract

Purpose Multimodal prehabilitation programs (exercise, nutrition, and anxiety reduction) have been shown to be successful for enhancing patients' physical function prior to surgery, although adherence remains a challenge. Given the short pre-operative period, maintaining adherence is critical to maximize program effectiveness. This study was designed to better understand patients' perspectives of prehabilitation and to identify factors related to program adherence.

Methods A qualitative descriptive study was conducted based on 52 cancer patients enrolled in a prehabilitation program at the Montreal General Hospital, Montreal, Canada. Data was collected with a structured questionnaire designed to evaluate the program.

Results Patients enjoyed their experience in prehabilitation, especially the exercise program and training sessions. The primary motivating factor for participation was to be physically prepared for the surgery. The most challenging exercise component was resistance training, while the most enjoyed was the aerobic training. Approximately 50% of patients were interested in group fitness classes as opposed to supervised individual training sessions for reasons related to social support. The preferred methods for exercise program delivery were home-based and one supervised exercise session per week. The biggest barrier to participation was related to transportation.

Conclusions These findings highlight the need to make prehabilitation programs more patient-centered. This is critical when designing more effective therapeutic strategies tailored to meet patients' specific needs while overcoming program nonadherence.

Comentarios del Dr. Gutman

Este trabajo fue el resultado de una encuesta realizada a pacientes que habían sido sometidos a un programa de prehabilitación multimodal para el tratamiento del cáncer. Esto incluyó estrategias como el ejercicio, la intervención dietética y la asesoría psicológica. La intervención dietética fue Immunocal. Los elementos del programa fueron examinados en un esfuerzo por hacer que los pacientes se adhirieran más estrechamente y cumplieran con las instrucciones.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION SURGERY
2018 Dec 1;153(12):1081-1089

Efecto de la prehabilitación del ejercicio y la nutrición en la capacidad funcional en la cirugía del cáncer esofagogástrico: un ensayo clínico aleatorio

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Abstract

Importance Preserving functional capacity is a key element in the care continuum for patients with esophagogastric cancer. Prehabilitation, a preoperative conditioning intervention aiming to optimize physical status, has not been tested in upper gastrointestinal surgery to date. OBJECTIVE To investigate whether prehabilitation is effective in improving functional status in patients undergoing esophagogastric cancer resection.

Design, Setting, and Participants A randomized clinical trial (available-case analysis based on completed assessments) was conducted at McGill University Health Centre (Montreal, Quebec, Canada) comparing prehabilitation with a control group. Intervention consisted of preoperative exercise and nutrition optimization. Participants were adults awaiting elective esophagogastric resection for cancer. The study dates were February 13, 2013, to February 10, 2017.

Main Outcomes and Measures The primary outcomewas change in functional capacity, measured with absolute change in 6-minute walk distance (6MWD). Preoperative (end of the prehabilitation period) and postoperative (from 4 to 8 weeks after surgery) data were compared between groups.

Results Sixty-eight patients were randomized, and 51 were included in the primary analysis. The control group were a mean (SD) age, 68.0 (11.6) years and 20 (80%) men. Patients in the prehabilitation group were a mean (SD) age, 67.3 (7.4) years and 18 (69%) men. Compared with the control group, the prehabilitation group had improved functional capacity both before surgery (mean [SD] 6MWD change, 36.9 [51.4] vs −22.8 [52.5] m; P < .001) and after surgery (mean [SD] 6MWD change, 15.4 [65.6] vs −81.8 [87.0]m; P < .001).

Conclusions and Relevance Prehabilitation improves perioperative functional capacity in esophagogastric surgery. Keeping patients from physical and nutritional status decline could have a significant effect on the cancer care continuum.

Comentarios del Dr. Gutman

En una estrategia de prehabilitación bimodal, en la que los pacientes de cáncer eran tratados previamente con optimización nutricional y ejercicio. Estos pacientes con cáncer de estómago o esófago fueron seleccionados al azar para someterse a la prehabilitación o al tratamiento estándar. La optimización nutricional utilizó Immunocal como una intervención activa. Al grupo de prehabilitación le fue mucho mejor en la recuperación de su cirugía.

EUROPEAN UROLOGY FOCUS. 2019 Jun 8:S2405-4569 (19)30153-1

Prehabilitación multimodal para mejorar la capacidad funcional después de una cistectomía radical: un ensayo controlado aleatorio

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Abstract

Background In patients with bladder cancer, poor functional status has remarkable deleterious effects on postoperative outcome and prognosis. Conditioning intervention initiated before surgery has the potential to reduce functional decline attributable to surgery. Nonetheless, evidence is lacking in patients undergoing radical cystectomy.

Objective To determine whether a preoperative multimodal intervention (prehabilita- tion) is feasible and effective in radical cystectomy. Design, setting, and participants: This study, conducted at an academic tertiary health care institution, enrolled adult patients scheduled for radical cystectomy. From August 2013 to October 2017, 70 patients were randomized: 35 to multimodal prehabilitation (prehab group) and 35 to standard care (control group).

Intervention Multimodal prehabilitation was a preoperative conditioning intervention including aerobic and resistance exercise, diet therapy, and relaxation techniques.

Outcome measurements and statistical analysis Primary outcome was perioperative change in functional capacity, measured with the distance covered during a 6-min walk test (6MWD), assessed at baseline, before surgery, and at 4 and 8 wk after surgery. Data were compared using robust mixed linear models for repeated measures. Results and limitations: Preoperative change in 6MWD compared with baseline was not significantly different between groups (prehab group 40.8 [114.0] m vs control group 9.7 (108.4) m, p = 0.250). However, at 4 wk after surgery, a significant difference in functional capacity was detected (6MWD, prehab group –15.4 [142.5] m vs control group –97.9 [123.8] m, p = 0.014). No intervention-related adverse effects were reported.

Conclusions Data suggested that multimodal prehabilitation resulted in faster functional recovery after radical cystectomy. Patient summary: After major cancer surgery, people usually feel week and tired, and have less energy to perform activities of daily living. In this study, we showed that using the time before surgery to promote exercise and good nutrition could fasten recovery after the surgical removal of the bladder.

Comentarios del Dr. Gutman

El equipo del Dr. Franco Carli hizo un estudio de control aleatorio en pacientes con cáncer de vejiga que recibieron una cistectomía total (extirpación de la vejiga). Un grupo recibió una prehabilitación antes de la cirugía que consistió en ejercicio, optimización nutricional usando Immunocal, y técnicas de relajación para aliviar la ansiedad. Cuando se comparó con un grupo que recibía una terapia estándar, el grupo de prehabilitación tuvo como resultado una recuperación más rápida y pudo recuperar su fuerza y energía para volver a la vida normal.

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Prehabilitación multimodal para mejorar la capacidad funcional después de una cistectomía radical: un ensayo controlado aleatorio

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Abstract

Background & aims Preservation of lean body mass is an important cancer care objective. The capacity for prehabilitation interventions to modulate the lean body mass (LBM) of colorectal cancer patients before and after surgery is unknown. **Methods** A pooled analysis of two randomized controlled trials of trimodal prehabilitation vs. trimodal rehabilitation at a single university-affiliated tertiary center employing Enhanced Recovery After Surgery (ERAS) care was conducted. The prehabilitation interventions included exercise, nutrition, and anxietyreduction elements that began approximately four weeks before surgery and continued for eight weeks after surgery. The rehabilitation interventions were identical to the prehabilitation interventions but were initiated only after surgery. Body composition, measured using multifrequency bioelectrical impedance analysis, was recorded at baseline, pre-surgery, 4 and 8 weeks after surgery. The primary outcome was change in LBM before and after colorectal surgery for cancer. A mixed effects regression model was used to estimate changes in body mass and body composition over time controlling for age, sex, baseline body mass index (BMI), baseline six-minute walk test (6MWT), and postoperative compliance to the interventions. NCT02586701 & NCT01356264. **Results** Pooled data included 76 patients who followed prehabilitation and 63 patients who followed rehabilitation (n ¼ 139). Neither group experienced changes in preoperative LBM. Compared to rehabilitated patients, prehabilitated patients had significantly more absolute and relative LBM at four and eight-weeks post-surgery in models controlling for age, sex, baseline BMI, baseline 6MWT, and compliance to the postoperative intervention. **Conclusion** Trimodal prehabilitation attenuated the post-surgical LBM loss compared to the loss observed in patients who received the rehabilitation intervention. Patients who receive neither intervention (i.e., standard of care) would be likely to lose more LBM. Offering a prehabilitation program to colorectal cancer patients awaiting resection is a useful strategy to mitigate the impact of the surgical stress response on lean tissue in an ERAS setting, and, in turn, might have a positive impact on the cancer care course.

Comentarios del Dr. Gutman

El equipo del Dr. Franco Carli hizo un estudio de control aleatorio en pacientes con cáncer de vejiga que recibieron una cistectomía total (extirpación de la vejiga). Un grupo recibió una prehabilitación antes de la cirugía que consistió en ejercicio, optimización nutricional usando Immunocal, y técnicas de relajación para aliviar la ansiedad. Cuando se comparó con un grupo que recibía una terapia estándar, el grupo de prehabilitación tuvo como resultado una recuperación más rápida y pudo recuperar su fuerza y energía para volver a la vida normal.

HEALTH PSYCHOLOGY 2019 Oct;38(10):900-909

Depresión y estado funcional en pacientes de cáncer colorrectal en espera de cirugía: impacto de un programa de prehabilitación multimodal

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Abstract

Objective Depression and poor functional status (FS) frequently co-occur. Though both predict adverse surgical outcomes, research examining preoperative functional performance (FP; self-reported) and functional capacity (FC; performance-based) measures in depressed cancer patients is lacking. Prehabilitation, a preoperative intervention including exercise, nutrition, and stress-reduction, may improve FC; however, whether depressed patients benefit from this intervention remains unknown. The primary objectives were to (a) assess differences in FP and FC and (b) explore the impact of prehabilitation on FC in individuals with depressive symptoms versus those without.

Method A secondary analysis was conducted on 172 colorectal cancer patients enrolled in three studies comparing prehabilitation with a control group (rehabilitation). Measures were collected at 4 weeks pre- and 8 weeks postoperatively. FP, FC, and psychological symptoms were assessed using the 36-Item Short Form Health Survey, Six-Minute Walk Distance (6MWD), and Hospital Anxiety and Depression Scale (HADS), respectively. Subjects were divided into three groups according to baseline psychological symptoms: no psychologicalsymptoms (HADS-N), anxiety-symptoms (HADS-A), or depressive-symptoms (HADS-D). Main objectives were tested using analyses of variance, chi-square tests, and multivariate logistic regression.

Results At baseline, HADS-D reported lower FP, had shorter 6MWD, and a greater proportion walked 400 m. Prehabilitation was associated with significant improvements in 6MWD in HADS-D group but not in HADS-N or HADS-A groups.

Conclusion Poorer FS was observed in subjects with depressive symptoms, and these subjects benefited most from prehabilitation intervention. Future research could examine whether severity of depression and co-occurrence of anxiety differentially impact FS and whether prehabilitation can improve psychological symptoms and quality of life.

Comentarios del Dr. Gutman

Este trabajo examinó los posibles beneficios psicológicos de un programa de prehabilitación en pacientes con cáncer de colon que se someten a una cirugía. Se centró en la combinación de los resultados de tres estudios aleatorios anteriores sobre estos pacientes, sus niveles de depresión y cómo esto puede haber afectado a su resultado. Los pacientes que tuvieron prehabilitación (ejercicio prequirúrgico, optimización de la dieta con Immunocal, y asesoramiento psicológico) mostraron una mayor mejoria en las puntuaciones de depresión que los grupos comparables que no recibieron cuidados prehabilitativos.

La supervisión médica del estilo de vida saludable del paciente con cáncer (MCL por sus siglas en inglés) mejora la rehabilitación postoperatoria

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Abstract

Objective to explore the effect of medical supervision for cancer (chronic disease) patients' healthy lifestyle (Mcl) on the postoperative rehabilitation of tumor patients. **Methods** fifty patients with solid tumor were randomly assigned into the intervention group or the control group. Twenty-five patients in the intervention group were given mcl during perioperative period, while another 25 cancer patients with the same disease background were subjected to routine clinical treatments. Hospital stay, postoperative complications, nutritional risk screening, nutritional assessment, main laboratory values and quality of life of two groups were compared.

Results All 50 patients completed the operation as planned. The differences in hospital stay, postoperative complication incidence rate, nutritional assessment and KPS score were statistically significant between two groups (P<0.05). The values of leukocyte, lymphocyte, hemoglobin, platelet of two groups have no statistically significant difference (P>0.05). The emotional function, nausea and vomiting, loss of appetite, insomnia and diarrhea in the intervention group were significantly improved compared with the control group (P<0.05). PG-SGA score is correlated with total protein, prealbumin and albumin levels (P<0.05).

Conclusions MCL can shorten the hospital stay, reduce the incidence of postoperative complications, improve nutritional status, enhance serum total protein, prealbumin and albumin levels, improve emotional function, reduce the incidence of nausea and vomiting, appetite loss, insomnia and diarrhea.

Comentarios del Dr. Gutman

En una serie de conferencias de prehabilitación presentadas en China por el Dr. Franco Carli y por mí, los chinos siguieron esta estrategia. En esta variante, los pacientes fueron ubicados en un programa de modificación de dieta y estilo de vida (MCL por sus siglas en inglés), que incluía a Immunocal como agente de intervención. Seleccionados al azar para recibir el tratamiento estándar o el MCL, el grupo MCL mostró una mejoria en la estancia hospitalaria, complicaciones postoperatorias, estado nutricional y síntomas físicos como náuseas, vómitos, anorexia, diarrea y bienestar emocional

JOURNAL OF AMERICAN MEDICAL ASSOCIATION SURGERY 2020 Jan 22;155(3):233-42

Efecto de la prehabilitación multimodal vs. la rehabilitación postoperatoria en las complicaciones postoperatorias de 30 días para pacientes delicados que se someten a una resección de cáncer colorrectal: un ensayo clínico aleatorio

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Abstract

Importance Research supports use of prehabilitation to optimize physical status before and after colorectal cancer resection, but its effect on postoperative complications remains unclear. Frail patients are a target for prehabilitation interventions owing to increased risk for poor postoperative outcomes.

Objective To assess the extent to which a prehabilitation program affects 30-day postoperative complications in frail patients undergoing colorectal cancer resection compared with postoperative rehabilitation.

Design, Setting, and Participants This single-blind, parallel-arm, superiority randomized clinical trial recruited patients undergoing colorectal cancer resection from September 7, 2015, through June 19, 2019. Patients were followed up for 4 weeks before surgery and 4 weeks after surgery at 2 university-affiliated tertiary hospitals. A total of 418 patients 65 years or older were assessed for eligibility. Of these, 298 patients were excluded (not frail [n = 290], unable to exercise [n = 3], and planned neoadjuvant treatment [n = 5]), and 120 frail patients (Fried Frailty Index,2) were randomized. Ten patients were excluded after randomization because they refused surgery (n = 3), died before surgery (n = 3), had no cancer (n = 1), had surgery without bowel resection (n = 1), or were switched to palliative care (n = 2). Hence, 110 patients were included in the intention-to-treat analysis (55 in the prehabilitation [Prehab] and 55 in the rehabilitation [Rehab] groups). Data were analyzed from July 25 through August 21, 2019.

Interventions Multimodal program involving exercise, nutritional, and psychological interventions initiated before (Prehab group) or after (Rehab group) surgery. All patients were treated within a standardized enhanced recovery pathway.

Main Outcomes and Measures The primary outcome included the Comprehensive Complications Index measured at 30 days after surgery. Secondary outcomes were 30-day overall and severe complications, primary and total length of hospital stay, 30-day emergency department visits and hospital readmissions, recovery of walking capacity, and patient-reported outcome measures.

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JOURNAL OF AMERICAN MEDICAL ASSOCIATION SURGERY 2020 Jan 22;155(3):233-42

Efecto de la prehabilitación multimodal vs. la rehabilitación postoperatoria en las complicaciones postoperatorias de 30 días para pacientes delicados que se someten a una resección de cáncer colorrectal: un ensayo clínico aleatorio

[1]Carli F, [1]Bousquet-Dion G, [1]Awasthi R, [2]Elsherbini N, [3]Liberman S, [4]Boutros M, [3]Stein B, [3]Charlebois P, [4]Ghitulescu G, [4]Morin N, [5]Jagoe T, [6]Scheede-Bergdahl C, [1]Minnella EM, [3]Fiore JF Jr.

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Abstract

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Results Of 110 patients randomized, mean (SD) agewas 78 (7) years; 52 (47.3%)were men and 58 (52.7%)werewomen; 31 (28.2%) had rectal cancer; and 87 (79.1%) underwent minimally invasive surgery. Therewas no between-group difference in the primary outcome measure, 30-day Comprehensive Complications Index (adjusted mean difference, –3.2; 95%CI, –11.8 to 5.3; P = .45). Secondary outcome measureswere also not different between groups.

Conclusions and Relevance In frail patients undergoing colorectal cancer resection (predominantly minimally invasive) within an enhanced recovery pathway, a multimodal prehabilitation program did not affect postoperative outcomes. Alternative strategies should be considered to optimize treatment of frail patients preoperatively.

Comentarios del Dr. Gutman

Después de haber publicado una gran cantidad de estudios que muestran los beneficios de las estrategias de prehabilitación, este ensayo no logró mejorar los resultados en estos pacientes tan delicados. Al tener una edad media de 78 años, parece que en este grupo tan frágil de pacientes de cirugía oncológica habría que ajustar las modificaciones del programa de prehabilitación vigente para que se adapte mejor a este grupo demográfico.

THE ANNALS OF THORACIC SURGERY, 2020. DEC 13;S0003-4975(20)32108-1, 10-25

Prehabilitación multimodal para la cirugía del cáncer de pulmón: Un ensayo aleatorio controlado

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Abstract

Background: To determine whether a multimodal prehabilitation program enhances post- operative functional recovery compared to multimodal rehabilitation.
Methods: Patients scheduled for non-small cell lung cancer resection were randomized to two groups receiving home-based moderate intensity exercise, nutritional counseling with whey protein supplementation and anxiety reducing strategies, either for four weeks before (PREHAB, n=52) or 8 weeks after surgery (REHAB, n=43). Functional capacity (FC) was measured by the six-minute walk test (6MWT) at baseline, immediately prior to surgery, four and eight weeks after surgery. All patients were treated according to Enhanced Recovery Pathway (ERP) guidelines.
Results: There was no difference in FC at any time point during the perioperative period between the two multimodal programs. By eight weeks after surgery, both groups returned to baseline FC and a similar proportion of patients (over 75%) in both groups had recovered to their baseline.
Conclusions: In patients undergoing surgical resection for lung cancer within the context of ERP, multimodal prehabilitation initiated four weeks prior to surgery is as effective in recovering FC as multimodal rehabilitation.

Comentarios del Dr. Gutman

Para seguir ampliando la bibliografía que establece la eficacia de la prehabilitación en la cirugía del cáncer, el equipo del Dr. Carli descubrió que, en este ensayo en particular, la prehabilitación era igual a la rehabilitación en la mejora de la capacidad funcional de los pacientes. Se seguirán llevando a cabo más estudios.

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Capacidad funcional de los pacientes prediabéticos: efecto de la prehabilitación multimodal en pacientes sometidos a resección de cáncer colorectal

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Abstract

Background: Prehabilitation is the process of increasing functional capacity (FC) before surgery. Poor glycemic control is associated with worse outcomes in patients undergoing surgery. Therefore, prediabetic patients could particularly benefit from prehabilitation.

Methods: This is a pooled analysis of individual patient data from three multimodal prehabilitation trials in colorectal cancer surgery. Following a baseline assessment using the 6-minute walking test (6MWT), subjects were randomized to multimodal prehabilitation or to a control group. Participants were reassessed 24 h before surgery and 4 weeks after surgery. Prediabetes (PreDM) was defined as HbA1c 5.7%-6.4%. Multivariable logistic regression was used to adjust for potentially confounding variables.

Results: Participation in a prehabilitation program was the most important predictive factor of clinical improvement in FC prior to surgery (Adjusted OR 2.42, 95% CI 1.18, 4.94); prediabetes was not a statistically significant predictor of improvement in FC after adjustments for covariates. Prehabilitation attenuated the loss of FC in unadjusted analyses after surgery in prediabetic patients (PreDM Control: median change -6 m [IQR -50-20] vs PreDM Prehab: median change +25 m [IQR -20-53], p = 0.045). Adjusted analyses also suggested the protective effect against loss of FC after surgery was stronger in prediabetic patients (PreDM Prehab vs PreDM Control: OR 5.5, 95% CI: 1.2-25.8; Normo Prehab vs Normo Control: OR 1.5, 95% CI: 0.53-4.52).

Conclusions: Multimodal prehabilitation favored clinical recovery of FC after surgery in CRC patients, especially prediabetic patients.

Dr. Gutman's Comments

Una vez establecidos los beneficios de la prehabilitación en pacientes operados de cáncer colorrectal, el equipo de la Universidad McGill quiso definir mejor en qué subcategorías de pacientes podría tener especial importancia la estrategia. En este trabajo, se centraron en los pacientes prediabéticos. Se sabe que este grupo demográfico tiene un mayor riesgo de sufrir tanto la cirugía como sus complicaciones. El uso de la prehabilitación, que incluía Immunocal como intervención nutricional, demostró una clara mejora en la recuperación clínica.

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Acta Oncolgica
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Anesthesiology
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Cancer Letters
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Oxidative Stress In Cancer, Aids, And Neurodegenerative Diseases
Oxidative Stress, Cell Activation And Viral Infection
Pediatric Blood Cancer
Philosophical Transactions of The Royal Society B: Biological Sciences
Recent Patents on Central Nervous System Drug Discovery
Scientific Reports
Support Care Cancer
The Annals of Thoracic Surgery
Tumor Biology

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